Universidad Europea

TRABAJO DE FIN DE GRADO

Grado en Odontología

SPECIAL CONSIDERATIONS AND SPECIFIC PRECAUTIONS IN DENTAL HYPERTENSIVE PATIENTS

Madrid, curso 2020/2021

Número identificativo 141

Abstract

Introduction: Hypertension is defined as a systolic blood pressure over 140mmHg or a diastolic blood pressure above 90mmHg. It presents with social, environmental, and genetic risk factors and is classified according to severity or causal factors. Hypertension produces an increased risk of cardiovascular complications, with many pharmacological treatments causing oral complications or interactions with common drugs.

Objectives: To review risk factors and treatment options of hypertension and how these will influence pharmacological and nonpharmacological considerations that must be made when treating patients.

Materials and Methods: Systematic search and review of trusted scientific databases, analysing 41 articles pertaining to hypertension, its aetiology, classification, treatment, drug interactions and specific considerations for patients.

Discussion: Xerostomia and dysgeusia are shared oral side effects of all antihypertensives reviewed. Lichenoid reactions are a common side effect of diuretics and beta blockers. Notably calcium channel blockers are linked to the appearance of gingival hyperplasia. ACE Inhibitors and angiotensin II blockers are associated with angioedema. Vasoconstrictors have an exacerbating effect on hypertension. A maximum dose of 0.36-0.54mg of epinephrine poses little risk to hypertensive patients. When using epinephrine with beta blockers, increased hypertension, hypertensive crisis, and bradycardia may occur. Using epinephrine with diuretics may cause the potential development of arrhythmias. NSAIDs cause increased sodium and water retention, producing increases in blood pressure. The effectiveness of all antihypertensives reviewed is reduced due to the contradictory effects of NSAIDs. Pre-

sedation of anxious patients may be indicated with use of Benzodiazepines or Nitrous oxide. Increased haemorrhagic risk can be controlled through local haemostatic agents and monitoring of blood pressure throughout treatment.

Conclusion: Patients must be evaluated individually and precautions such as control and education of risk factors, use of vasoconstrictor with local anaesthesia, complications associated with NSAIDs or even possible need of pre-sedation, should be taken when indicated.

Resumen

Introducción: La hipertensión se define como una presión arterial sistólica superior a 140 mmHg o diastólica superior a 90 mmHg. Se presenta debido a factores de riesgo sociales, ambientales y genéticos y se clasifica según su gravedad o factores causales. La hipertensión produce un mayor riesgo de complicaciones cardiovasculares, y muchos tratamientos farmacológicos provocan complicaciones orales o interacciones con fármacos habituales.

Objetivos: Revisar los factores de riesgo y las opciones de tratamiento de la hipertensión, y cómo estos influyen en las soluciones farmacológicas y no farmacológicas que se deben tener en cuenta al tratar a los pacientes.

Materiales y Métodos: Búsqueda y revisión sistemática de bases de datos científicas, analizando 41 artículos relacionados con la hipertensión, su etiología, clasificación, tratamiento, interacciones médicas y consideraciones específicas para los pacientes.

Discusión: La xerostomía y la disgeusia son efectos secundarios orales compartidos por todos los antihipertensivos revisados. Las reacciones liquenoides son un efecto secundario común

de los diuréticos y los betabloqueantes. En particular, los bloqueadores de los canales de calcio están relacionados con la aparición de hiperplasia gingival. Los inhibidores de la ECA y los bloqueadores de la angiotensina II están asociados con el angioedema. Los vasoconstrictores tienen un efecto agravante sobre la hipertensión. Una dosis máxima de 0,36-0,54 mg de epinefrina presenta un riesgo mínimo para los pacientes hipertensos. Cuando se usa epinefrina con betabloqueantes, puede ocurrir un aumento de la hipertensión, crisis hipertensiva y bradicardia. El uso de epinefrina con diuréticos puede provocar el desarrollo potencial de arritmias. Los AINE provocan un aumento de la retención de sodio y agua, lo que produce un aumento de la presión arterial. La eficacia de todos los antihipertensivos revisados se reduce debido a los efectos contradictorios de los AINE. La sedación previa de pacientes ansiosos podria ser tratada con benzodiazepinas u óxido nitroso. El aumento del riesgo hemorrágico se puede controlar mediante agentes hemostáticos locales y monitorización de la presión arterial durante todo el tratamiento. Conclusión: Los pacientes deben ser evaluados individualmente y se deben tomar precauciones como el control y educación de los factores de riesgo, el uso de vasoconstrictor con anestesia local, las complicaciones asociadas con los AINE o incluso la posible necesidad de sedación previa cuando esté indicado.

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Introduction

Hypertension is considered one of the leading causes of cardiovascular mortality worldwide and one of the most ubiquitous pathologies, affecting 1.3 billion people globally according to the most recent World Health Organisation figures (1,2). The most common definition of hypertension is clarified by the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure in 2003 (JNC 7) as a systolic blood pressure of over 140 mmHg or a diastolic blood pressure of above 90 mmHg. These values have been selected as studies have shown that patients with blood pressure above these values exhibit a greater risk for cardiac complications (3). These patients also will exhibit a beneficial outcome when taking antihypertensive medications. (4)

According to the systolic and diastolic values of a patient, their hypertensive condition is classified into the following categories: Normal Blood Pressure as systolic <120 mmHg and diastolic <80 mmHg, Prehypertension as systolic 120-139 mmHg or diastolic 80-89 mmHg, Stage 1 Hypertension as systolic 140-159 mmHg or diastolic 90-99 mmHg and Stage 2 Hypertension as systolic ≥160 mmHg or diastolic ≥100 mmHg (2). The Prehypertension category was recently added to the existing classification as it was shown that those patients with an elevated blood pressure value within these parameters exhibit a higher risk of developing hypertension.

Stages of hypertension	Range for systolic and diastolic blood pressure
Normal blood pressure	Systolic <120 mmHg and diastolic <80 mmHg
Prehypertension	Systolic 120–139 mmHg or diastolic 80–89 mmHg
Stage 1 hypertension	Systolic 140–159 mmHg or diastolic 90–99 mmHg
Stage 2 hypertension	Systolic ≥160 mmHg or diastolic ≥100 mmHg
Hypertensive urgency	Severe hypertension (diastolic pressure usually >120 mmHg); no end-organ damage
Hypertensive emergency	Severe hypertension (diastolic pressure usually >120 mmHg); end-organ damage
"White coat" hypertension	Elevated blood pressure secondary to fear and anxiety from a health care provider

Table 1. Classification of Hypertension according to JNC7 (2)

As you can see from **Table 1** additional subcategories are outlined according to the classification of JNC7, such as hypertensive crisis. This is defined as when a patient is exhibiting a blood pressure value systolic >180 mmHg or diastolic >120 mmHg. This subcategory can be further divided into two types: hypertensive urgency and hypertensive emergency. Hypertensive urgency is defined as severe hypertension with values of systolic >180 mmHg or diastolic >120 mmHg but does not cause end organ damage, whilst hypertensive emergency will lead to end organ damage (2).

White coat hypertension is defined as when a patient presents with a higher than normal blood pressure value within the dental office and clinical setting compared to a "normal" lower value when outside of the dental clinic. This diagnosis can be confirmed using an at home blood pressure monitoring system or 24-hour ambulatory monitoring with values <130/80 mmHg. It is not yet proven that White Coat Hypertension leads to an increased cardiovascular risk in dental patients, with some studies showing that its cardiovascular risk can be approximated to that of normal blood pressure, yet we can assume that an increased blood pressure of a patient in the dental setting can lead to implications in various fields such as haemostasis (3,4,5).

<u>Primary vs Secondary</u>

Classification based on the pathophysiology and aetiology is commonly used in medicine and divides patients into those with primary or essential hypertension and secondary hypertension.

Primary hypertension is defined as repeated increased blood pressure levels without any known causative factors or evidence of an organic cause. (2,4) This type is the most frequent,

accounting for 90-95% of all hypertension cases (4) and is widely accepted as a combined result of environmental and genetic factors (6,7). Unlike secondary hypertension, this type is incurable but can be managed with changes in lifestyle, modifications of prevalent risk factors a patient may exhibit, and the use of antihypertensive medication. (6) The most predominant environmental factors include a sedentary lifestyle, obesity, habits such as high alcohol consumption or smoking, high sodium and high cholesterol diet, Age (>55yrs for men and >65yrs for women), and family history of cardiovascular disease (4,6,7). According to the Seventh Report on the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure 2004 (JNC6), other environmental factors leading to essential hypertension also include high levels of stress, use of contraceptives, menopause, race, reduced nephron number, diabetes, dyslipidaemia, personality/depression, Hypovitaminosis D, low education and socioeconomic status. (2,8). These social factors such as race, education and socioeconomic status can likely be attributed to differing diets, attitudes to healthcare, provision of healthcare and inequality in healthcare related information, regarding specific communities (2,8).

Genetic mutations can lead to Primary/Essential hypertension, through affectation of sodium levels due to increased activity of the endocrine and sympathetic nervous system leading to an increased release of sodium which in turn leads to elevated blood pressure levels (6). Affectation of other facets such as catecholamines, insulin levels and cell membrane function also in turn leads to increased blood pressure levels, whilst one of the most important systems affected is the Renin-Angiotensin-Aldosterone system (4,6). This system controls body fluid volume and electrolyte balance which will affect the blood pressure, neuronal and endocrinal control of the cardiovascular system (9). Angiotensin II is responsible for vasoconstriction and

release of aldosterone once it binds to its specific receptors. In turn, aldosterone decreases renal perfusion leading to an increase in water retention and increased renal absorption of sodium (6,9). When genetic mutations associated with this system occurs, it can lead to an increase in levels of angiotensin II and therefore a higher blood level in vasoconstricted vessels (6).

Secondary hypertension is elevated blood pressure levels in response to an underlying disease, medical condition, or a reaction to medications. Unlike primary hypertension this has identifiable organic causes. (2,4,10). This form of hypertension theoretically can be cured by removing the causative medication or treating the underlying medical condition (6).

The most common causative factor leading to secondary hypertension is renal disease, as the reduced renal function leads to fluid accumulation in vasculature which leads to an increase in blood pressure. The conditions below have all been found to have associations with secondary hypertension.

Renal Factors: chronic renal failure, nephritis, papillary necrosis, renal vascular disease, renin secreting tumours, renal vascular stenosis, polycystic kidney disease, renal infarction, and infection (2,4,11)

Endocrinal factors: Diabetes mellitus, Cushing syndrome, pheochromocytoma, myxoedema, acromegaly, thyroid and parathyroid Hyperfunction (2,4)

Cardiovascular Factors: coarctation of the aorta, Takayasu's, arterial stenosis (2,4,11)

Medications: corticosteroids, cyclosporine, contraceptives, NSAID, sympathomimetic drugs, some antidepressants, and oestrogens. (6,11). The most common drugs leading to secondary

hypertension are NSAIDs, whose actions decrease production of prostaglandins. Prostaglandins play a key role in vasodilation and sodium excretion. Considering their prevalence in the day to day life of many patients and the use in dentistry to manage pain, the link between hypertension and NSAIDs is especially pertinent (6). Other factors contributing to secondary hypertension include sleep apnoea, alcohol consumption, drug abuse, polyarthritis, hypercalcemia, and pregnancy toxaemia (2,4,7).

Treatment of Hypertension

For successful treatment of secondary hypertension, one must understand that treating the underlying medical condition or adjustment of the causative drug will lead to a reduction in blood pressure and successful treatment of hypertension (10). To treat essential hypertension on the other hand, the dentist must understand that it is a condition with multiple aetiologies (genetic, environmental, and pathological) and risk factors and therefore no single patient is identical in their response to treatment.

All patients regardless of aetiology of the condition should be given the same lifestyle advice and modifications in order to decrease blood pressure (6,10). High sodium intake, sedentary lifestyle and being overweight are all environmental factors that can be modified to lower blood pressure and decrease risk of hypertension. Common non-pharmacological recommendations include;

- increased activity and exercise in day to day lifestyle
- decrease in sodium intake and adjustment of diet, especially focusing on limiting sweets, sugary beverages, and red meat (6,10)
- promoting the consumption of fruits, vegetables, grains, poultry, and fish (10)

- decrease in alcohol consumption and smoking (4,6)
- removal or avoidance of stress causing factors in daily lifestyle (6)

When non-pharmacological measures have not decreased the blood pressure of a patient, pharmacological measures can be employed. This includes treatments with diuretics, beta blockers, calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers and alpha blockers (2). Treatment through medication may involve taking a combination of these medications and a dentist must be aware of the dose, side effects and common drug interactions of each of these agents (2).

To understand how these aforementioned antihypertensive drugs interact with commonly used drugs and products in dentistry, one must understand how each drug works and the physiological actions they take to decrease the blood pressure of the patient.

Diuretics – These drugs work by increasing the amount of sodium, chloride and water that is excreted by the body through the inhibition of reabsorption by the kidneys (2,12). This action, in turn, leads to a decrease in blood volume, cardiac output and therefore blood pressure (12,13). With this decrease in blood volume and cardiac output, it prompts the renin-angiotensin-aldosterone system and the sympathetic nervous system to increase sodium and water retention once again. This will lead to an increase in extracellular fluid volume and therefore blood volume, but the blood pressure of the patient will not increase to levels before starting the treatment with thiazide diuretics, as there is a decrease in peripheral vascular resistance (2,12)

Beta Blockers – The action of these drugs is to bind to the beta receptors found both in the heart and body, beta-1 receptors are found in the heart and beta-2 receptors found in the

lungs (2,13). They work by decreasing the heart rate of patients and the strength of the contractions of the heart, through their actions as competitive antagonists (14). Beta blockers bind to beta receptors in which catecholamines such as adrenaline and noradrenaline also bind, therefore acting as competition. Catecholamines such as these are responsible for increasing heart rate and contractions of the heart (14). Beta blockers can present as both selective, which only bind to beta-1 receptors on the heart and avoid binding to beta-2 receptors, or non-selective which can bind to both beta-1 and beta-2 receptors, therefore leading to the stimulation of the receptors on the lungs and affectation of smooth muscle cells (2,13,14). In patients that present with pulmonary problems or breathing difficulty, selective beta blockers may present with an advantage (13,14). When using beta blockers over a prolonged period of time, patients can also present with a secondary mechanism of decreased blood pressure in which peripheral vascular resistance is decreased, yet this is not a direct action of this drug (14).

Calcium Channel Blockers – As the name suggests, calcium channel blockers bind to calcium channels in blood vessels and stop the entry of calcium, into both the blood vessels and the smooth muscle cells (10,2,13). By preventing the entry of calcium, it allows relaxation of the smooth muscle in vasculature, therefore leading to vasodilation and therefore a decrease in blood pressure (10,2). Within this class of drugs, we find two main subcategories, dihydropyridine and non-dihydropyridine. The former are more selective on smooth muscle cells and vasodilation whilst the latter have a more cardiac focused effect (2,15). Non-dihydropyridine calcium channel blockers have a negative chronotropic and ionotropic effect, meaning they decrease heart rate and contractability of the heart, leading to a decrease in blood pressure (2,13,15).

ACE Inhibitors - As mentioned previously, the renin-angiotensin-aldosterone system plays a key role in the regulation of blood pressure in patients. This specific set of drugs lower the blood pressure of the patient by preventing the conversion of angiotensin I to angiotensin II (10,13). Angiotensin II is responsible for vasoconstriction, increase in cardiac output and the production of aldosterone, which in turn is the compound responsible for retainment of both sodium and water, thereby producing an increase in blood pressure due to an increase in blood volume (10,16). By preventing this formation of angiotensin II and aldosterone, ACE inhibitors have been proven to lower blood pressure in hypertensive patients (10,13).

Angiotensin II Blockers – Much like the action of beta blockers, angiotensin II blockers act as competitive agonists for the angiotensin II receptors in vascular smooth muscle cells, therefore not allowing the vasoconstrictive effects to take place. This action leads to a vasodilatory effect and a reduction in peripheral resistance, therefore lowering blood pressure. (2,10,17).

Alpha Blockers – Alpha blockers work by binding to the alpha-adrenergic receptors found in smooth muscle cells of vasculature (2). They act by impeding vasoconstricting sympathetic transmitting compounds such as norepinephrine from binding to the receptors and therefore lead to vasodilation and a reduction in peripheral vascular resistance leading to a lower blood pressure (2,13).

Objectives

Primary Objective: To understand the different stages and classifications of Hypertension, including the risk factors and treatment options of this pathology, and how these will influence day to day practice in dentistry and the special considerations that must be made when treating these patients.

Specific Objectives:

- To outline the common oral side effects of antihypertensives and interactions between antihypertensive treatments and commonly used drugs in dentistry.
- To briefly outline the special considerations that must be taken when performing invasive or surgical treatment of a hypertensive patient e.g. use of vasoconstrictor and haemostatic measures

Methodology

By completing a systematic search and review from the following trusted scientific databases: PubMed, Medline, Mendeley, Cochrane Library, Scopus and Web of Science using keywords such as “arterial hypertension”, “hypertension”, “hypertensive”, “oral cavity”, “dental health”, “dentistry”, “antihypertensive interactions” “antihypertensive therapy” “antihypertensive complications” etc. Various search filters and parameters were applied to these scientific databases to find the most relevant articles. For example, primarily articles from the last 10 years were utilised but age was not considered as an exclusion criteria. To begin research, only review articles were compiled and used to give a brief overview of the condition. Specific articles outlying points of considerations that must be taken for a hypertensive dental patient were then utilised e.g. drug interactions, oral side effects, haemostatic measures, and prescription cautions. After compiling the aforementioned articles, a total of 41 articles were analysed and reviewed for this paper.

Discussion

Side Effects of Antihypertensive Drugs

As a dentist, when treating a patient that is suffering from hypertension, arguably the most crucial aspect of the interaction is a clear and thorough clinical and medical history being taken. In order to treat a patient successfully and safely, the dentist must be well informed of the nature, severity, and stability of any conditions the patient may have suffered from in the past or is currently suffering from. When taking the history, it is important to gauge the functional capacity of the patient and the emotional status of the patient.

The first consideration one must take, when treating a hypertensive individual, is the medication they may be taking to treat their hypertension. A dentist must have basic knowledge and familiarity with common hypertensives and understand the common side effects of each drug both orally and systemically.

1. Diuretics – Chlorthalidone, Hydrochlorothiazide, Indapamide, Metolazone (4,10)

Common side effects of prolonged use of diuretics can include hypokalaemia, hyperlipidaemia, constipation, hyperglycaemia, muscle cramps, headache, increased perspiration, and increased urination.

The most common oral side effects associated with this medication include xerostomia (dry mouth), which in turn are likely to have dental implications such as increased risk of development of caries, oral candidiasis and burning mouth syndrome, as well as problems which deglutition, mastication and phonation. (2,4,10,13). Problems associated with the retention of a prosthesis must also be considered with this condition (3). When presented

with a patient displaying the sign and symptoms associated with a dry mouth, the dentist must consider treatment with parasympathomimetic drugs such as Pilocarpine or Cevimeline in order to increase salivary production once more (3,4). After prescription, the dentist must revise with the patient at a later date to confirm the cessation of symptoms or consider a consultation with the physician of the patient to switch antihypertensive drugs.

In a study performed by the department of Oral Medicine and Radiology at Narayana Dental College in India, 100 patients were split into a control group and a test group, taking oral diuretics. The following parameters were analysed: total volume of saliva, saliva pH, buffering capacity, sodium, potassium, chloride, and protein levels (18). The study found that the set of patients taking diuretics had a highly significant difference in salivary flow rate both stimulated and unstimulated, salivary pH and buffering capacity, periodontal index, plaque index and a moderate significant difference in DMFT (Decayed, Missing or Filled Teeth). The study concluded that patients taking diuretics have a decreased salivary flow rate stimulated and unstimulated, pH, buffering capacity and sodium and chloride levels and also present with a higher prevalence of xerostomia, periodontitis, and decay (18).

A relationship between use of diuretics and the appearance of lichenoid reactions has also been proven and whilst clinically similar to Lichen Planus, the distinguishable presence of Wickham's Striae cannot be identified (4,19). Treatment of this may be to cease use of the antihypertensive drug in question and switch to another, or if this is not possible treatment with topical corticosteroids. In cases such as this the dentist must consider a consultation with the prescribing physician (4).

2. Beta Blockers – Metoprolol, Atenolol, Nebivolol, Bisoprolol (2)

   Nonselective Beta Blockers - Carvedilol, Propranolol, Nadolol, Sotalol (2)

Similar to diuretics, beta blockers can also present with oral side effects such as xerostomia i.e. dry mouth and the presence of lichenoid reactions (2). Unlike diuretics, beta blockers have been found to cause dysgeusia or taste changes in their users, whilst it has been postulated that these taste changes may be as a result of decreased salivary production associated with prolonged use of beta blockers. One study researching the relationship between beta blockers and the perception of taste concluded that participants using beta blockers did present with a decrease in unstimulated salivary flow, but this did not stimulate dysgeusia (20). Hypothesises have been made in which the variance in the perception of taste can be attributed to metal ion content within the saliva, for example magnesium (3).

3. Calcium Channel Blockers – Amlodipine, Felodipine, Nifedipine, Isradipine, Nicardipine, Nisoldipine (2,10)

Calcium channel blockers present with oral side effects such as xerostomia and changes in taste (2,13). The most notable side effect a dentist must consider when presented with a patient taking calcium channel blockers is the possible development of gingival hyperplasia or enlargement (2,3,4,13,17). According to studies, the occurrence of gingival growth occurs in 1.7-38% of cases (2,13), with the most common cause to be use of Nifedipine (2). As previously mentioned there are 2 classes of calcium channel blockers, dihydropyridine and non-dihydropyridine and whilst it is a much more common side effect of the former class, there are cases documented in which non-dihydropyridine calcium channel blockers have caused gingival hyperplasia (3).

With this condition the patient will present with swollen and enlarged, painful and bleeding gums, and whilst a good oral hygiene regimen from the patient may help to avoid its development (4) the most advised treatment is gingival surgery to help resolve the pain and haemorrhaging such as gingivectomy, laser gingivectomy or flap surgery (21). However, studies have shown a 34% rate of recurrence 18 months after periodontal surgery if the patient has not discontinued use of the responsible drug (21). In order to fully and correctly treat this condition without risk of recurrence, the dentist should consult with the physician of the patient to stop use of the calcium channel blocker and switch to another drug, or adjust the dose of the drug (13,4,21). Non-surgical treatment options are mainly those that help reduce any inflammatory factors that could exacerbate the condition. These include control and reinforcement of correct oral hygiene techniques of the patient, proper root debridement if necessary and adjustment of plaque retentive sources such as open contact points or furcation defects etc (21).

4. ACE Inhibitors – Captopril, Ramipril, Enalapril, Lisinopril, Benazepril, Fosinopril, Moexipril, Perindopril, Quinapril (2,10)

Like most antihypertensive medication, ACE Inhibitors present with xerostomia, but its side effects can also include a change in taste (dysgeusia), ageusia and ulceration (2,4). The most outstanding side effects of this medication is the dry cough associated with it and the development of angioedema (17). Angioedema can be clarified as the well delimited oedema of the subcutaneous or submucosal layers of the skin commonly in the face and neck area and is mediated by bradykinin or mast cell or mast cell mediators (22,23). Both the dry cough and the angioedema are likely explained by the increase in peptides and bradykinin (17). The formation of angioedema occurs as bradykinin causes vasodilation and increased vascular

permeability and is usually broken down by Angiotensin Converting Enzyme (ACE). As the name suggest ACE Inhibitors reduce the degradation of bradykinin and Substance P, another vasodilator, leading to an accumulation of these compounds. As a consequence of this, there is increased extravasation of fluid into the subcutaneous and submucosal layers of the skin leading to potentially life-threatening angioedema (22). Treatments of this condition are still up for debate to this day, as there is no single pharmacological treatment that has been proven to rectify drug induced angioedema, although the most commonly prescribed treatments are antihistamines, steroids or epinephrine, to varying degrees of success. In life threatening situations in which there is no response to a pharmacological approach, tracheal intubation will be considered (22). A dentist must consider this side effect and look for any signs of this and consult with the physician immediately to ascertain the best course of action.

5. Angiotensin II Blockers – Losartan, Valsartan, Irbesartan, Candesartan, Telmisartan, Olmesartan, Eprosartan, Azilsartan (2,10)

The side effects of this class of drugs are similar to those of ACE inhibitors, in which they also can lead to xerostomia, loss of taste and angioedema (2,13). Unlike ACE inhibitors, the action of this set of drugs is not mediated by kinins, hence there is no accumulation of bradykinin and is therefore thought to have a far lower risk of angioedema (17,24). Whilst this is the accepted case for angiotensin receptor blockers, there lacks enough evidence to prove there is truly no effect on bradykinin levels, in fact a previous study analysing bradykinin levels in patients taking Losartan found that those taking the angiotensin II blocker did display increased levels of bradykinin, but further evidence and studies are lacking (24). Dysgeusia is another side effect of this drug. Studies have shown that angiotensin receptor blockers such

as Losartan show an association with loss of taste, whilst patients taking Candesartan and Valsartan display a diminution in taste sensitivity or some other taste changes (25).

6. Nonselective Alpha Blockers - Phenoxybenzamine, Phentolamine

   Selective Alpha Blockers – Prazosin, Terazosin, Doxazosin (2)

The most common side effect of alpha blockers is xerostomia or dry mouth, and this can be attributed to the effect alpha adrenoreceptor antagonists have on the salivary glands. In a study comparing the effect of alpha adrenoreceptor agonists such as Prazosin, Silodosin and Tamsulosin, it was concluded that these medications not only have an inhibitory effect on salivary glands, but also some alpha blockers such as Silodosin are highly specific and effective in its inhibition of salivary glands (26). The likely cause of this condition is due to the presence of alpha-1 adrenoreceptors found in the submandibular glands of human, whose activation leads to the secretion of fluid and electrolytes yet when they are blocked by selective alpha blockers, this will lead to a diminished salivary flow and dry mouth in patients (26).

Considerations of the Use of Vasoconstrictor

Local anaesthesia with or without a vasoconstrictor is one of the most used drugs by dentists throughout the world and when presented with a patient suffering from hypertension, the dentist must consider how best to anaesthetise the patient according to their blood pressure requirements. In order for pain to be transmitted by a neuron, a threshold level must be reached in order to propagate an action potential. Local anaesthetics work by blocking the sodium channels that are present in the cell membranes of neurons, consequently preventing the movement of sodium throughout the cell, meaning an action potential cannot be reached and pain is therefore not felt by the patient (27).

The most common examples of local anaesthesia used in dentistry are included below:

Lidocaine 2%	- Lasting 30-45 minutes
Lidocaine 2% + Epinephrine	- Lasting 180-300 minutes
Mepivicaine 3%	- Lasting 90-120 minutes
Mepivicaine 2% + Epinephrine	- Lasting 120-240 minutes
Prilocaine 4%	- Lasting 60-240 minutes, depending on the use of infiltrative or block technique

Figure 2. Common local anaesthetics and effective working time (28).

The use of vasoconstrictors with local anaesthesia presents with multiple benefits for the dentist, one of which is outlined in **Figure 2**. The local anaesthetic, when used in conjunction with a vasoconstrictor, the most common of which is epinephrine, has a much lower absorption level in the area of the injection therefore leading to a longer lasting effective time of the anaesthetic (2,13). This in turn also leads to a decrease in the risk of toxicity of the agent of the patient due to the slower absorption rate and due to the vasoconstrictive ability of epinephrine. Haemostasis aid is an added benefit.

Vasoconstrictors within anaesthesia can pose a risk of exacerbating hypertension, angina pectoris, arrythmias or myocardial infarction when used on a cardiovascular impaired patient or a patient that presents with uncontrolled hypertension (2). When presented with a patient displaying blood pressure values >180/100, invasive, non-emergency treatment should be avoided, and in the situation where they may be presenting hypertensive symptoms such as headache, chest pain or shortness of breath, the physician of the patient should be contacted (1,3,13). Studies have shown that in patients with controlled hypertension and blood pressure boundaries within safe limits, the use of anaesthesia without vasoconstrictor is not

contraindicated and the treatment plan may continue. In those individuals which present with uncontrolled hypertension, yet within safe treatment boundaries, it was shown that epinephrine did not lead to any considerable increase in pulse or blood pressure when a dental extraction was performed on hypertensive patients (1). The use of epinephrine 1:100,000 in anaesthesia, with a maximum dose of 0.36-0.54mg showed slight cardiovascular changes in hypertensive patients but did not confirm any significant risk was posed, therefore this is considered the maximum dose of epinephrine to give to a hypertensive patient, equating to 2-4 cartridges of anaesthesia, depending on the concentration (1, 2, 13, 29). Whenever possible when treating a patient with hypertension, the use of anaesthesia with a vasoconstrictor should be avoided and only used for invasive procedures in which the benefits of the vasoconstrictor such as the effective duration or hemostasia are required. For non-invasive procedures such as restorations of teeth without pulp involvement or bleeding risk, an anaesthesia without vasoconstrictor is recommended. The dentist must consider the proper technique when performing the injection and avoid injection into blood vessels to avoid rapid absorption of epinephrine (13). The dentist must consider avoiding the use of extra epinephrine, when it is not required, for example the use of Epinephrine-soaked retraction cords can lead to figurative “overdose” and pose cardiovascular risks for the patient (2,3,13).

When considering the use of a vasoconstrictor such as epinephrine on patient with hypertension the dentist must also be aware of the specific and possible drug interactions that may occur with common antihypertensives. The most common antihypertensive drug interaction with a vasoconstrictor is that between beta blockers and epinephrine, and can have severe consequences leading to increased hypertension, hypertensive crisis, and bradycardia (1,30,31). Epinephrine is commonly known to have a vasoconstrictive effect due

to the binding of it to alpha-1 receptors found in smooth muscle cells of vasculature, but it also has a lesser known vasodilatory effect on other vessels as it binds to the beta-2 adrenergic receptors in skeletal muscle. This opposing effect it has on itself helps to regulate the vasoconstrictive effects it performs and is also one of the major advantages it has over other vasoconstrictors that can be used such as norepinephrine or levonordefrin (30,31). Non-selective beta blockers such as Propranolol block both beta-1 and beta-2 receptors therefore not allowing the potentiating vasodilatory effect of epinephrine to occur, and leading to both hypertension and activation of the baroreceptor reflex of the body leading to reflex bradycardia (2, 31). In a study in which patients undergoing hypertensive treatment with non-selective beta-adrenergic blockers, in this case Pindolol, and undergoing dental treatment with the use of anaesthesia with epinephrine, the study showed that in the group taking non-selective beta blockers, there was a clear significant increase in both systolic and diastolic blood pressure and a decreased heart rate, whilst the group not taking antihypertensive medication displayed a decrease in systolic and diastolic pressure and a decrease in peripheral vascular resistance (31,32).

Another notable interaction between epinephrine and an antihypertensive drug is with the use of diuretics. Thiazide and loop diuretics lead to loss of potassium through the urine with their use, so possible side effects can include hypokalaemia and metabolic acidosis, whilst loop diuretics are considered “potassium sparing” and therefore have the opposing side effects of hyperkalaemia (33). Epinephrine as a stand-alone compound can cause hypokalaemia itself, due to the binding of epinephrine to the beta-2 adrenoreceptors found in skeletal muscle, it will cause a movement of potassium intracellularly and lead to hypokalaemia of the patient

(34). The hypokalaemia effect of diuretics can be exacerbated by the use of epinephrine and thereby cause the development of arrhythmias in patients (2).

Interactions Between Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Antihypertensive Drugs

Non-steroidal anti-Inflammatory drugs, commonly referred to as NSAIDs are widely prescribed by dentists worldwide in order to aid the patient in the management of pain and inflammation for any conditions they may present or after an invasive treatment or surgery such as a dental extraction. The most frequently prescribed NSAIDs prescribed by a dentist include Ibuprofen, Aspirin or Naproxen. NSAIDs are able to reduce pain of patients by preventing the formation of prostaglandins, through the inhibition of COX-1 and COX-2 enzymes, which are involved in the production of pain and inflammation. Through this inhibition of these enzymes the patient is able to control the pain, but non-dental associated side effects can occur (35). We can classify these drugs into 2 main categories, those that inhibit COX-1 enzyme and those that inhibit COX-2 enzyme. The NSAIDs associated with the inhibition of COX-1 enzyme are linked to the development of gastrointestinal side effects (35), this is most likely due to the large presence of this enzyme in gastrointestinal epithelium (36). Selective Inhibition of COX-2 enzymes leads to an increase in risk of cardiovascular events especially in those patients with pre-existing cardiovascular conditions, for example hypertension (35). Through the action of NSAIDs, formation of prostaglandins is inhibited due to the inhibition of the COX enzymes. This leads to an increased retainment of sodium and therefore water, consequently leading to an increase in blood pressure (37). Also, patients with hypertension present an amplified risk of blood pressure increase, when compared to

non-hypertensive patients, as shown in a study performed in 2011, in which it presented an increase of 1.1mm Hg in the blood pressure of non-hypertensive patients and a much more significant increase of values up to 14.3mm Hg for systolic blood pressure and 2.3mm Hg for diastolic blood pressure, in patients previously suffering from hypertension (38).

The dentist must take this knowledge into consideration when presented with a hypertensive patient in need of pain and inflammation relief. In a systematic review of 32 randomized controlled trials, which included 3626 participants, the blood pressure of patients was monitored, and it was concluded that Ibuprofen displayed the greatest occurrence in new hypertensive cases (39). As Ibuprofen is one of the most common medications prescribed by the dentist, a dentist must consider the inherent risk of increasing the blood pressure of the patient and weigh this against the anti-inflammatory and analgesic benefits of the drug. At all times recommended doses must be followed and in cases in which the dentist deems it necessary, advice should be given to all patients about the inherent risk of increasing blood pressure and advice regarding continuous monitoring of their blood pressure should be given.

The appearance of adverse interactions between antihypertensives and NSAIDs must be considered by the dentist also when prescribing pain and inflammatory relieving drugs. The effectiveness of diuretics, beta blockers, calcium channel blockers, ACE inhibitors and angiotensin II blockers are all reduced due to the contradictory effect of NSAIDs. As previously mentioned NSAIDs inhibit the formation of COX enzymes and therefore prostaglandin. Prostaglandins are not only responsible for the formation of pain, inflammation, and fever, but also have a renal vasodilatory effect, lower vascular resistance and increases the circulation of blood through the kidney. By inhibiting prostaglandins, vascular resistance is

raised and there is lower renal perfusion which in turn leads to an increase in the retention of sodium and therefore fluid. This increased retention of fluid leads to an opposing hypertensive effect on patients thereby negating the blood pressure lowering effect of the medication (30,37).

According to a 2014 article by The British Dental Journal, NSAIDs exhibit 3 different types of adverse reactions with Diuretics: nephrotoxicity, opposing the hypotensive effect of the agent or greatening the danger of developing a cardiac arrhythmia due to hyperkalaemia (30). Proving this antagonistic effect of NSAIDs, a study in which patients were given Ibuprofen or a placebo for a 4-week period in conjunction with the use of Hydrochlorothiazide, a common diuretic, was performed. Results of this study outlined a significant increase in blood pressure of 4.2-4.7mm Hg in those patients taking Ibuprofen, such increases were not visible in those taking the placebo (40).

Another trial comparing the effect of Ibuprofen, Nabumetone and Celecoxib, on patients being treated with RAAS inhibitors such as ACE inhibitors and angiotensin receptor blockers found that those taking Ibuprofen in combination with these agents had a 6.5 ± 1.4mm Hg increase in systolic blood pressure and a 3.5±0.9mm Hg increase in diastolic pressure. From the 359 patients evaluated in the study, the greatest proportion of patients in the Ibuprofen group presented with systolic blood pressure increases more than 20mm Hg over the original value; 16.9% of patients in the Ibuprofen group, 5.5% in the Nabumetone group and 4.6% in the Celecoxib group (40,41).

Other Non-Pharmacological Considerations

When presented with a patient with hypertension, controlled or uncontrolled, with fear or anxiety about the dentist or their treatment plan, it leads to a release of endogenous adrenaline which in turn will lead to an increased risk of adverse cardiovascular effects for a hypertensive patient (4). The blood pressure of a patient can also increase within the presence of pain, so the dentist must remember the importance of proper anaesthesia technique and an open line of communication between the dentist and the patient to voice any fear concerns or pains they may have throughout a procedure so that this can be managed (2).

The use of anxiolytics can also be indicated in situations in which patients' anxiety or pain is threatening a clinically significant increase in blood pressure. The most common form of pre-sedation is the use of benzodiazepines such as Diazepam 5-10mg, given to the patient the night before treatment and 1 hour before commencing the treatment. Nitrous oxide can also be considered as a pre-sedatory agent (29).

In the case of performing a long, complex, or largely invasive procedure, the dentist can consider the monitoring of the blood pressure of the patient throughout treatment (1). Other recommendations including ensuring before commencing each day of treatment that the patient has controlled hypertension with values within the safe parameters of <180/110mm Hg and simply scheduling short morning appointments with the patients are also helpful (1,29).

When presented with a patient suffering from hypertension, a dentist must consider the increased risk of haemorrhage that an elevated blood pressure will present. This includes those patients already undergoing pharmacological treatment for hypertension and are

considered to have well controlled hypertension, within the safe parameters to perform surgical treatment.

The dentist must consider an elevated potential risk and take the appropriate local haemostatic measures when performing any invasive restorative or surgical procedures that may present a higher risk of intraoperative bleeding. These local haemostatic measures include the use of anaesthesia with vasoconstrictor, sutures, bone wax, antifibrinolytics such as tranexamic acid, oxidised cellulose, thrombin, fibrin sealants and electric and laser scalpels (2,29).

One must consider that many of the risk factors related to hypertension are shared with other comorbidities, most commonly of which includes ischemic heart disease, and as such one may be presented with a patient undergoing treatment with anticoagulation or antiplatelet therapy adjacent to antihypertensive therapy. Regarding anticoagulation therapy, a dentist must consider a consultation with the physician of the patient and the International Normalized Ratio (INR) of the patient to be measured on the same day as the proposed surgical treatment. If the INR value is below 3.5, it is considered to be within safe parameters to perform the treatment and suspension of the proposed treatment is not indicated, but haemostatic measures must be taken (29). In patients taking antiplatelet medications such as aspirin or clopidogrel, it is not indicated to suspend use of the medication or treatment but precautions must be considered to control the exaggerated haemorrhagic response (2).

Conclusions

To conclude, in modern day dentistry the dentist is faced with a variety of challenges and considerations when treating a hypertensive patient. Understanding the pathogenesis of this condition and risk factors associated, gives the dentist the opportunity to educate themselves and the patients and best advise them on how to proceed safely in regard to their condition. Having a clear comprehension of the variety of drugs used to treat hypertension, the mechanisms in which those drugs act and the associated side effects with these drugs places the dentist in a position to diagnose and treat the patient with the greatest efficacy possible.

Given the frequency of use of many medications and drugs in dentistry, such as local anaesthesia and NSAIDs, the dentist must evaluate each patient individually to recognise any adverse interactions between drugs or side effects and the dentist must have sufficient knowledge to circumnavigate these interactions whilst still providing the most appropriate dental care possible for the patient. When treating each hypertensive patient, the dentist must be able to make an informed judgement on how best to proceed with each patient, whether it be control and education of the risk factors involved with the condition, use of vasoconstrictor when providing local anaesthesia, dangers or complications associated with the prescription of NSAIDs or even possible need of pre-sedation or anxiolytics. Above all, a clear understanding of the considerations and specific precautions required to perform treatments is paramount. Each treatment plan and advice given should be tailored to each patient, depending on the severity of hypertension. Understanding the specific situations of when to consider a consultation with the physician is required, in order to place the safety and wellbeing of the patient first and perform a successful and safe treatment regime.

Responsibility

In regards to social responsibility, hypertension is classified as one of the leading causes of preventable deaths worldwide according to the World Health Organisation in 2001, and studies have exhibited that it is responsible for more cardiovascular disease deaths than any other modifiable risk factor. With more than 1 billion people worldwide suffering from this condition, it is often referred to as “the silent killer”, as symptoms are not exhibited until the severity and risk increases. With this information alone, it is clear dentists and indeed all healthcare professionals bear an environmental and social responsibility to safeguard their patients, given the impact hypertension has on human health. Recognising risk factors of the condition and understanding the risk of possible antihypertensive drug interactions or complications that may arise during the treatment plan is crucial to further improve the care we can provide and avoid preventable life-threatening situations. By considering these special precautions that must be taken with a patient suffering from hypertension and knowing the possible side effects of antihypertensive drugs, the common drug interactions and special non-pharmacological considerations that should be implemented, it can vastly improve all patients quality of life and certainly their safety and quality of care.

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Annexes

HYPERTENSIVE PATIENTS

Management of the Hypertensive Patient in Dental Practice

Brahmleen Kaur, DMD; and Vincent B. Ziccardi, DDS, MD

Abstract: More than 1 billion people worldwide have hypertension. Since the guidelines for classification and treatment of hypertension were updated in 2017 by American College of Cardiology/American Heart Association, it is now estimated that nearly half of the US adult population has hypertension. Hypertension may not show any sign or symptom apart from an elevated blood pressure reading until signs and symptoms of complications occur. Hence, dentists can play a unique role in identifying undiagnosed patients or those with uncontrolled blood pressure levels. This article is intended to provide dental clinicians essential information about hypertension and how the new guidelines affect the classification and treatment of the disease, and it discusses the management of patients with hypertension in the dental office.

LEARNING OBJECTIVES

- Discuss the cardiovascular disease risk associated with high blood pressure
- Identify the guidelines and classification of hypertension, as well as the associated etiology and risk factors
- Demonstrate accurate measurement of blood pressure in an in-office setting and appropriately manage dental patients with hypertension

DISCLOSURE: Dr. Ziccardi is a consultant for Axogen.

Hypertension affects more than 1 billion people worldwide and is a leading cause of morbidity and mortality.[1,2] As per the blood pressure (BP) thresholds by the American College of Cardiology/American Heart Association (AHA) 2017 guidelines, between 2013 and 2016, 46% of the US adult population, or approximately 116.4 million adults, had hypertension, which is defined as blood pressure ≥130/80 mm Hg. The prevalence was seen to increase with age. Prevalence was 26.1% among people aged 20 to 44 years, 59.2% among those aged 45 to 64 years, and 78.2% among those aged ≥65 years. A higher percentage of males had hypertension in the age group up to 64 years, whereas more females were seen to develop hypertension in the population ≥65 years of age.[1] Those who are normotensive at age 55 to 65 and survive to age 80 to 85 have a 90% lifetime risk of developing hypertension during the remaining years of life.[3,4]

Hypertension is a significant risk factor for cerebrovascular disease and stroke.[1] In 2015, an estimated 7.8 million deaths globally could be attributed to systolic blood pressure (SBP) >140 mm Hg.[1] The number of deaths between 1990 and 2015 did not increase in high-income countries but increased in middle- and low-income countries.[1] Hypertension is usually asymptomatic until complications occur.[5] Hence, it is not surprising that 35% of US adults with hypertension are unaware that they have it.[1] Typically, many patients avoid seeking medical or dental care until they are in pain or until serious symptoms arise. Thus, dentists are in a unique position to identify undiagnosed hypertensive patients, refer them to a physician for appropriate medical care, and educate them regarding lifestyle modifications and the risks associated with uncontrolled high blood pressure. Unfortunately, approximately 50% of patients do not comply with taking their medications as directed.[6]

Guidelines and Classification

The risk for cardiovascular disease (CVD) doubles for each rise of 20/10 mm Hg in systolic/diastolic blood pressure.[3,7] From blood pressure levels as low as 115/75 mm Hg upward, the risk of death from both ischemic heart disease and stroke increases, with the increase being progressive and linear.[3] Because of this continuous association between high blood pressure and increased

Clinical, Cosmetic and Investigational Dentistry

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REVIEW

Dental management in patients with hypertension: challenges and solutions

This article was published in the following Dove Press journal:
Clinical, Cosmetic and Investigational Dentistry
17 October 2016
Number of times this article has been viewed

Janet H Southerland[1]
Danielle G Gill[1]
Pandu R Gangula[2–4]
Leslie R Halpern[1]
Cesar Y Cardona[5]
Charles P Mouton[6]

[1]Department of Oral and Maxillofacial Surgery, [2]Department of Oral Biology and Research, [3]Department of Physiology, [4]Center for Women's Health Research, [5]Department of Internal Medicine, [6]Department of Family and Community Medicine, Meharry Medical College, Nashville, TN, USA

Abstract: Hypertension is a chronic illness affecting more than a billion people worldwide. The high prevalence of the disease among the American population is concerning and must be considered when treating dental patients. Its lack of symptoms until more serious problems occur makes the disease deadly. Dental practitioners can often be on the frontlines of prevention of hypertension by evaluating preoperative blood pressure readings, performing risk assessments, and knowing when to consider medical consultation of a hypertensive patient in a dental setting. In addition, routine follow-up appointments and patients seen on an emergent basis, who may otherwise not be seen routinely, allow the oral health provider an opportunity to diagnose and refer for any unknown disease. It is imperative to understand the risk factors that may predispose patients to hypertension and to be able to educate them about their condition. Most importantly, the oral health care provider is in a pivotal position to play an active role in the management of patients presenting with a history of hypertension because many antihypertensive agents interact with pharmacologic agents used in the dental practice. The purpose of this review is to provide strategies for managing and preventing complications when treating the patient with hypertension who presents to the dental office.

Keywords: high blood pressure, dental, guidelines, inflammation, metabolic disease, blood pressure medicines

Introduction

Hypertension is known as the "silent killer" and affects 80 million adults older than 20 years in the US alone[1] and just <1 billion people worldwide.[1–3] By 2025, the number of patients diagnosed with hypertension is expected to be 1.56 billion.[3] Hypertension is responsible for >7 million deaths annually[4] and is one of the leading risk factors for cardiovascular disease mortality.[5] The disease is defined as systolic blood pressure (SBP) of 140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg, or any persons being currently prescribed antihypertensive medicine for the purpose of managing hypertension.[1,2,6] In addition, hypertension is defined as blood pressure readings elevated on at least two occasions with or without provocation.[1]

Hypertension is divided into two main categories: essential/primary hypertension and secondary hypertension.[7,8] Lack of identifiable causative factors for elevated blood pressure is known as essential or primary hypertension, making up ~90%–95% of all hypertensive cases. Secondary hypertension, for which there is an identifiable cause, affects 5%–10% of US adults who are diagnosed with hypertension.[2,7,9] Disorders associated with secondary hypertension include vascular diseases such as coarctation of the aorta and systemic diseases such as Cushing's syndrome; obstructive sleep apnea; adrenal medullary dysfunction;

Correspondence: Janet H Southerland
Department of Oral and Maxillofacial Surgery, Meharry Medical College, 1005 Dr DB Todd Boulevard, Nashville, TN 37208, USA
Tel +1 615 327 6844
Fax +1 615 327 5722
Email jsoutherland@mmc.edu

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Dovepress
http://dx.doi.org/10.2147/CCIDE.S99446

The Assessment and Importance of Hypertension in the Dental Setting

Jonathan Hogan, MD, Jai Radhakrishnan, MD, MS, MRCP, FASN*

KEYWORDS

• Hypertension • Blood pressure • Antihypertensive drugs • Cardiovascular effects

KEY POINTS

- Many patients with hypertension have uncontrolled disease. The dental visit presents a unique opportunity to screen patients for undiagnosed and undertreated hypertension, which may lead to improved monitoring and treatment.
- Although there are no clinical studies, it is generally recommended that nonemergent procedures be avoided in patients with a blood pressure of greater than 180/110 mm Hg.
- Because of the high prevalence of disease and medication use for hypertension, dentists should be aware of the oral side effects of antihypertensive medications as well as the cardiovascular effects of medications commonly used during dental visits.

HYPERTENSION: DEFINITION, IMPORTANCE, AND BENEFITS OF TREATMENT

The most commonly referenced guideline pertaining to blood pressure in adults in the United Sates is the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7),[1] which was published in 2003. JNC 7 defines hypertension as a systolic blood pressure (SBP) greater than 140 mm Hg or a diastolic blood pressure (DBP) greater than 90 mm Hg. These definitions are derived from studies showing increased adverse cardiovascular outcomes in patients with blood pressure above these levels. A meta-analysis demonstrated that for each 20 mm Hg increase of SBP above 115 mm Hg and 10 mm Hg of DBP 75 mm Hg in patients 40 to 70 years of age, the risk of death from cardiovascular events (stroke, myocardial infarction) doubles (**Fig. 1**).[2] JNC 7 also introduced the category of Prehypertension, which is defined as an SBP of 120 to 139 mm Hg and DBP of 80 to 89 mm Hg (**Table 1**). These individuals are at increased risk of developing hypertension.

Division of Nephrology, Department of Medicine, Columbia University College of Physician and Surgeons, 622 West 168th Street, PH 4-124, New York, NY 10032, USA
* Corresponding author.
E-mail address: jr55@columbia.edu

Dent Clin N Am 56 (2012) 731–745
http://dx.doi.org/10.1016/j.cden.2012.07.003 **dental.theclinics.com**
0011-8532/12/$ – see front matter

Hindawi Publishing Corporation
ISRN Hypertension
Volume 2013, Article ID 410740, 8 pages
http://dx.doi.org/10.5402/2013/410740

Review Article

Hypertensive Patients and Their Management in Dentistry

Sanda Mihaela Popescu,[1] Monica Scrieciu,[1] Veronica Mercuț,[1] Mihaela Țuculina,[2] and Ionela Dascălu[2]

[1] *Department of Oral Rehabilitation and Dental Prosthodontics, Faculty of Dental Medicine, University of Medicine and Pharmacy, Petru Rares No. 2–4, 200349 Craiova, Romania*
[2] *Department of Odontotherapy, Endodontics and Orthodontics, Faculty of Dental Medicine, University of Medicine and Pharmacy, 1 Mai No. 68, Craiova, Romania*

Correspondence should be addressed to Sanda Mihaela Popescu; sm_popescu@hotmail.com

Received 1 October 2013; Accepted 22 October 2013

Academic Editors: F. Angeli and K. C. Ortega

Hypertension is a common disease encountered in dental setting. Its wide spreading, terrible consequences, and life-long treatment require an attentive approach by dentists. Hypertension management in dental office includes disease recognition and correct measurement, knowledge of its treatment and oral adverse effects, and risk assessment for dental treatment. Dentist role in screening undiagnosed and undertreated hypertension is very important since this may lead to improved monitoring and treatment.

1. Introduction

Hypertension is defined as values >140 mmHg SBP and/or >90 mmHg DBP, based on the evidence from RCTs that in patients with these BP values treatment-induced BP reductions are beneficial (Table 1) [1]. The same classification is used in young, middle-aged, and elderly subjects, whereas different criteria, based on percentiles, are adopted in children and teenagers for whom data from interventional trials are not available [1].

JNC 7 introduced in 2003 the category of prehypertension, which is defined as SBP of 120 to 139 mmHg and DBP of 80 to 89 mmHg (Table 2) [2]. Patients with prehypertension are at increased risk of developing hypertension, those with blood pressure values 130–139/80–89 mmHg have a two times greater risk of developing hypertension than those with lower values [3].

Hypertension is a highly prevalent cardiovascular disease, which affects over 1 billion people worldwide [2]. Although more than 70% of hypertensive patients are aware of the disease, only 23–49% are treated, and fewer (20%) achieving control [2, 4, 5]. Hypertension prevalence varies by age, race, education, and so forth.

According to ESC-ESH guidelines in 2013, there are limited comparable data available on the prevalence of hypertension and the temporal trends of BP values in different European countries [6]. Overall the prevalence of hypertension appears to be around 30–45% of the general population, with a steep increase with ageing. There also appear to be noticeable differences in the average BP levels across countries, with no systematic trends towards BP changes in the past decade [7–29].

A permanent high blood pressure (BP) affects blood vessels in the kidneys, heart, and brain, increasing the incidence of renal and cardiac coronary heart disease and stroke. Hypertension was called the "silent killer" because it often affects target organs (kidney, heart, brain, eyes) before the appearance of clinical symptoms.

2. Etiology and Classification of Hypertension

Hypertension is classified as primary or essential hypertension (without an organic cause) and secondary hypertension (it has a well-established organic cause).

2.1. Primary or Essential Hypertension (without an Organic Cause). Primary hypertension is the term used for medium

Annals of Internal Medicine

CLINICAL GUIDELINE

Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Synopsis of the 2017 American College of Cardiology/American Heart Association Hypertension Guideline

Robert M. Carey, MD, and Paul K. Whelton, MB, MD, MSc; for the 2017 ACC/AHA Hypertension Guideline Writing Committee*

Description: In November 2017, the American College of Cardiology (ACC) and the American Heart Association (AHA) released a clinical practice guideline for the prevention, detection, evaluation, and treatment of high blood pressure (BP) in adults. This article summarizes the major recommendations.

Methods: In 2014, the ACC and the AHA appointed a multidisciplinary committee to update previous reports of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The committee reviewed literature and commissioned systematic reviews and meta-analyses on out-of-office BP monitoring, the optimal target for BP lowering, the comparative benefits and harms of different classes of antihypertensive agents, and the comparative benefits and harms of initiating therapy with a single antihypertensive agent or a combination of 2 agents.

Recommendations: This article summarizes key recommendations in the following areas: BP classification, BP measurement, screening for secondary hypertension, nonpharmacologic therapy, BP thresholds and cardiac risk estimation to guide drug treatment, treatment goals (general and for patients with diabetes mellitus, chronic kidney disease, and advanced age), choice of initial drug therapy, resistant hypertension, and strategies to improve hypertension control.

Ann Intern Med. 2018;168:351-358. doi:10.7326/M17-3203 **Annals.org**
For author affiliations, see end of text.
This article was published at Annals.org on 23 January 2018.
* For a list of the members of the 2017 ACC/AHA Hypertension Guideline Writing Committee, see the **Appendix** (available at Annals.org).

Hypertension is the leading cause of death and disability-adjusted life-years worldwide (1, 2). In the United States, hypertension accounts for more cardiovascular disease (CVD) deaths than any other modifiable risk factor and is second only to cigarette smoking as a preventable cause of death for any reason (3). The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults provides an evidence-based approach to reduction of CVD risk through lowering of blood pressure (BP) (4).

Guideline Development Process

In 1977, the National Heart, Lung, and Blood Institute (NHLBI) initiated a series of hypertension guidelines, culminating in the 2003 publication of The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (5). In 2013, the NHLBI transferred responsibility for sponsorship of clinical practice guidelines for CVD prevention to the ACC and the AHA (6). In 2014, the ACC and the AHA partnered with 9 other professional associations to develop a new hypertension clinical practice guideline. A 21-member panel of multidisciplinary experts (physicians, nurses, pharmacists, and patient representatives) with no BP-related industry relationships developed the 2017 guideline.

The writing committee conducted a structured review of the literature and commissioned 4 systematic reviews (and meta-analyses when feasible) from an independent evidence review committee to address the following: 1) self-directed and/or ambulatory BP monitoring compared with office-based BP measurement to prevent adverse outcomes and achieve better BP control, 2) the optimal target for BP lowering during antihypertensive therapy, 3) whether various antihypertensive drug classes differ in their comparative benefits and/or harms as first-line treatment, and 4) whether initiating treatment with 1 antihypertensive drug (monotherapy) is more or less beneficial than starting with 2 drugs (7).

The writing committee used the methods of the ACC/AHA Task Force on Clinical Practice Guidelines (8) to make 106 recommendations, each characterized by class (strength) of recommendation (an estimate of the magnitude and certainty of benefit in proportion to risk) and level (quality) of evidence (rating the type, quantity, and consistency of data from clinical trials and other sources). Five "official" reviewers from the ACC and the AHA, 9 "organizational" reviewers representing the partner professional organizations, and 38 "content" reviewers with expertise in hypertension reviewed the recommendations before approval by the governing bodies of the ACC, the AHA, the American Society for Preventive Cardiology, the Preventive Cardiovascular Nurses Association, the American Academy of Physician Assistants, the Association of Black Cardiologists, the American Pharmacists Association, the American College of Preventive Medicine, the American Society of Hypertension, the American Geriatrics Society, and

See also:

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Clinical Anatomy 32:678–681 (2019)

REVIEW

A Review of the Clinical Anatomy of Hypertension

LAUREN WAHL[1] AND R. SHANE TUBBS[1,2*]

[1]*Seattle Science Foundation, Seattle, Washington*
[2]*Department of Anatomical Sciences, St. George's University, St. George's, Grenada, West Indies*

Hypertension is defined as the persistent elevation of blood pressure above normal limits. It can be classified according to whether the contributing factors are genetics and environmental (primary hypertension) or underlying medical conditions and medications (secondary hypertension). The goal of this review is to increase recognition of the various anatomical etiologies of hypertension. Clin. Anat. 32:678–681, 2019.

Key words: high blood pressure; primary hypertension; secondary hypertension

INTRODUCTION

Hypertension is the persistent elevation of the systolic blood pressure at 140 mm Hg, or higher, and diastolic blood pressure at 90 mm Hg, or higher, in adults 18 years of age or older and is one of the most common conditions seen in primary care (James et al. 2014). There are two different types of hypertension, primary and secondary, each with its own propensity to cause different amounts of injury. Primary hypertension, also referred to as essential hypertension, is most common, affecting 90–95% of hypertensive patients (Sawicka et al. 2011). It arises etiologically from both genetic and environmental factors (Sawicka et al. 2011). Secondary hypertension arises from factors such as medication or an underlying medical condition, most commonly pathologies of the renal system such as chronic kidney disease (Bell et al. 2015). Secondary hypertension affects between 5 and 10% of hypertensive patients (Sawicka et al. 2011). Hypertension has been colloquially dubbed the "silent killer" as there are not always significant symptoms; however, its long-term effects, such as myocardial infarction, aneurysms, stroke, renal failure, and death, can be detrimental if it is not detected and treated (James et al. 2014). It often presents with headaches, fatigue, and dizziness, and there can be other nonspecific symptoms (Sawicka et al. 2011). Distinguishing the different types of hypertension, each with its myriad of etiologies, can help health care providers make correct diagnoses and ultimately provide the most effective treatment plan and care for patients. Herein, we discuss hypertension in general and also anatomical pathoetiologies.

ETIOLOGY

Hypertension is a multifactorial disease that includes genetic, environmental, pathological, anatomical, and pharmacological factors, and is a difficult disease to diagnose properly without an extensive patient background and exam (Bell et al. 2015). Approximately one in three American adults have hypertension, most of them without knowing it, and statistical projections predict that 29% of the world's population will have the condition by the year 2025 (Kearney et al. 2005; CDC 2016).

Primary hypertension stems most commonly from combinations of environmental factors and mutations of certain genes involved in regulating blood pressure, and although it is incurable it can be controlled by appropriate clinical intervention (Coy 2005; Bell et al. 2015). The environmental factors include a sedentary lifestyle, obesity, increased smoking and alcohol intake, and psychological stress (Sawicka et al. 2011). Other medical conditions, or medications with side effects that exacerbate blood pressure mechanisms, cause secondary hypertension (Bell et al. 2015). While primary hypertension cannot be cured, only managed, secondary hypertension can be controlled and remediated by discontinuing the use of the causative medication

*Correspondence to: R. Shane Tubbs, Seattle Science Foundation, 550 17th Ave, James Tower, Suite 600, Seattle, WA 98122. E-mail: shanet@seattlesciencefoundation.org

Received 14 February 2019; Accepted 11 March 2019

Published online 3 April 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/ca.23369

THE JOURNAL OF FAMILY PRACTICE

The Diagnosis of Essential and Secondary Hypertension in Adults

Steven A. Dosh, MD, MS

August 1, 2001

Print

J Fam Pract. 2001 August;50(08):707-712.

Steven A. Dosh, MD, MS
Escanaba, Michigan
From the OSF Medical Group. Reprint requests should be addressed to Steven A. Dosh, MD, MS, OSF Medical Group, 3409 Ludington, Escanaba, MI 49837. Email: doshstev@msu.edu.

Hypertension is arbitrarily defined as a diastolic blood pressure (DBP) of 90 mm Hg or higher, a systolic blood pressure (SBP) equal to or higher than 140 mm Hg, or both, on 3 separate occasions. It affects 24% of the population of the United States and is common among black (28%), white (24%), and Hispanic (14%) Americans. The prevalence of hypertension increases with age and is more than 70% among people 65 years and older. Among principal diagnoses given by family physicians for outpatient visits, only acute respiratory tract infection (7%) is more common than hypertension (6%). The annual direct medical cost of caring for hypertension exceeds $10 billion.

This article will discuss the pathophysiology and diagnosis of hypertension from an evidence-based perspective. An upcoming Applied Evidence article will cover treatment of hypertension and prognosis.

Pathophysiology

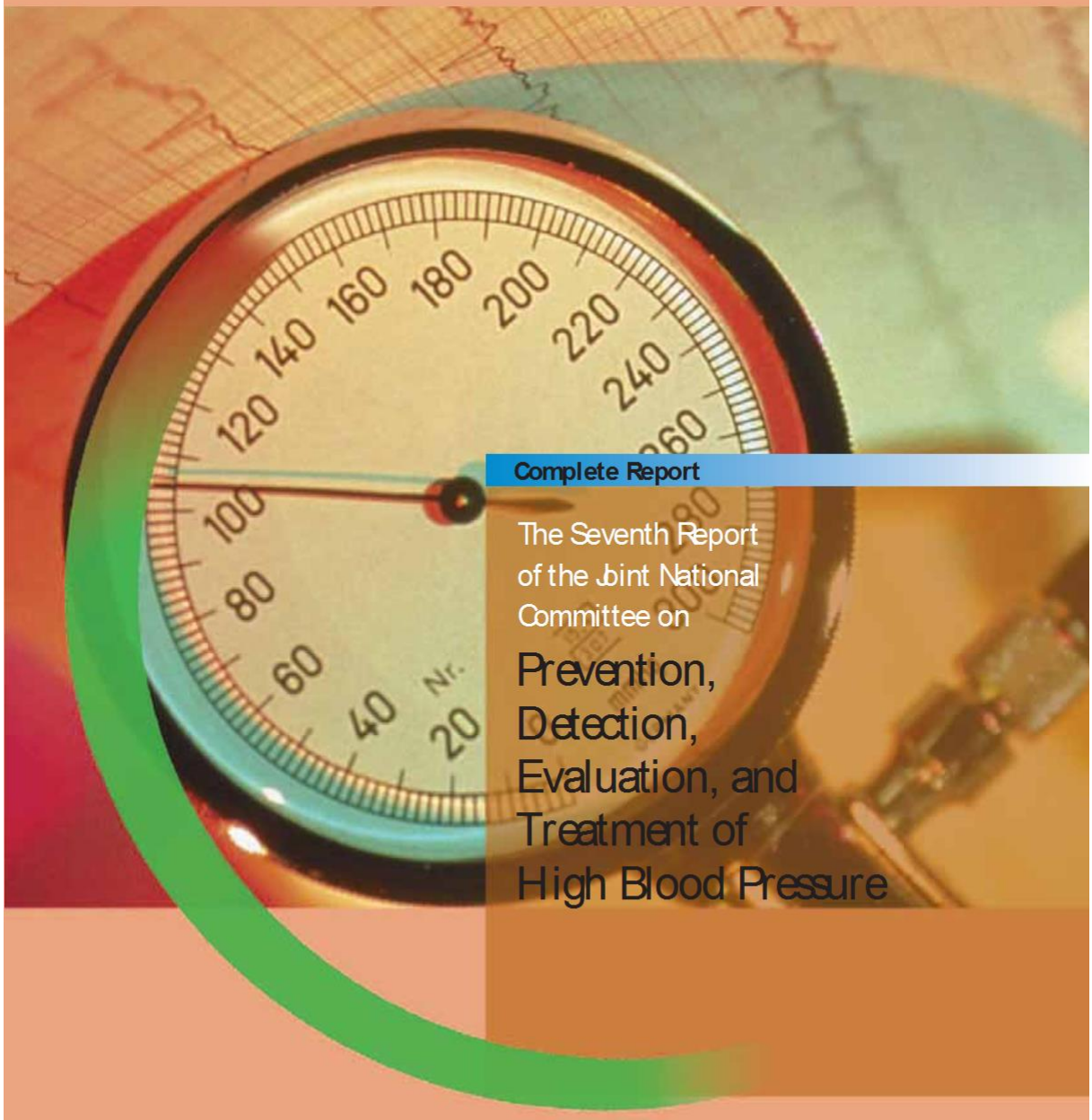
Idiopathic, or essential, hypertension accounts for more than 95% of cases and appears to be caused by a complex interaction between genetic predisposition and environmental factors. The predisposition to essential hypertension is polygenic in origin and may find full expression when combined with environmental factors, such as obesity, low physical activity levels, high stress levels, high alcohol consumption, high dietary sodium, and low dietary potassium, calcium, and magnesium. The complex interaction of genetics and environment may affect sodium, catecholamines, the renin-angiotensin system, insulin, and cell membrane function, causing elevation of the blood pressure.

The more common identifiable causes of hypertension include chronic renal disease (2%-5%), renovascular disease—including renal artery atherosclerosis and fibromuscular dysplasia—(0.2%-0.7%), Cushing syndrome (0.1%-0.6%), pheochromocytoma (0.04%-0.1%), and primary hyperaldosteronism (0.01%-0.3%). Although obesity, excessive alcohol consumption, oral contraceptive therapy, and sleep apnea may cause hypertension, they are not typically included as identifiable causes of hypertension. The prevalence of the latter conditions as identifiable causes of hypertension remains to be defined.

Diagnosis

The presence of hypertension must be confirmed by blood pressure measurements obtained with proper technique. The blood pressure of all patients 18 years and older should be measured at each health care visit because of the high prevalence of hypertension. Patients should be encouraged to abstain from nicotine and caffeine for at least 30 minutes before the measurement of the blood pressure. Measurement should be made with a mercury sphygmomanometer or a recently calibrated aneroid device. The bladder of the blood pressure cuff should encircle 80% of the arm. The pressure should be taken after at least 5 minutes of rest

National High Blood Pressure Education Program



Complete Report

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Heart, Lung, and Blood Institute

Curr Hypertens Rep (2016) 18: 70
DOI 10.1007/s11906-016-0677-y

Salt Sensitivity: Challenging and Controversial Phenotype of Primary Hypertension

Rossella Iatrino[1,2] · **Paolo Manunta**[1,2] · **Laura Zagato**[2]

Published online: 10 September 2016

Abstract Increases in life expectancy and cardiovascular adverse events in patients with hypertension highlight the need for new risk-reduction strategies to reduce the burden of degenerative diseases. Among the environmental factors, high salt consumption is currently considered the most important risk factor of hypertension. However, while high salt intake significantly raises blood pressure in some individuals, others do not show variation or even decrease their blood pressure. This heterogeneity is respectively classified as salt sensitivity and salt resistance. In this review, we propose salt sensitivity as a useful phenotype to unravel the mechanistic complexity of primary hypertension. The individual variability in blood pressure modification in response to salt intake changes derives from the combination of genetic and environmental determinants. This combination of random and non random determinants leads to the development of a personal index of sensitivity to salt. However, those genes involved in susceptibility to salt are still not completely identified, and the triggering mechanisms underlying the following development of hypertension still remain uncovered. One reason might be represented by the absence of a specific protocol, universally followed, for a standard definition of salt sensitivity. Another reason may be linked to the absence of common criteria for patient recruitment during clinical studies. Thus, the generation of a reliable approach for a proper recognition of this personal index of sensitivity to salt, and through it the identification of novel therapeutic targets for primary hypertension, should be one of the aspirations for the scientific community.

Keywords Hypertension · Salt sensitivity · Endogenous ouabain · Renin-angiotensin-aldosterone system · Salt intake · Genetics · Candidate gene · GWAS · Personalized therapy

This article is part of the Topical Collection on *Prevention of Hypertension: Public Health Challenges*

✉ Rossella Iatrino
iatrino.rossella@hsr.it

[1] Vita-Salute San Raffaele University, Milan, Italy

[2] Genomics of Renal Diseases and Hypertension Unit, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy

Introduction

Essential hypertension is one of the major public health challenges due to its high prevalence (in one third of the world's population) and the increased risk of adverse events, such as stroke, heart and kidney failure [1]. Essential hypertension is a complex disease, characterized by a large variety of determinants, such as genetic factors, race/ethnicity, age, body mass, and diet, as well as associated comorbidities (diabetes, chronic kidney diseases, etc.).

This interplay between environmental and genetic factors, both crucial determinants of hypertension, interacts and affects intermediary phenotypes which favor the increase in total vascular resistance and in cardiac output, consequently inducing hypertension [2]. Among all the intermediary phenotypes, the evaluation of salt sensitivity has been proposed to unravel the mechanistic complexity of primary hypertension [3–7].

Several studies have shown that primary hypertension is globally responsible for almost 50 % of the mortality rate [8]. However, these statistics mentioned above do not distinguish salt-sensitive from salt-resistant hypertension or they do not even include normotensive patients who are salt-sensitive [9••].

Salt sensitivity has been estimated in 51 % of hypertensive patients and in 26 % of normotensive subjects, posing a major public health problem in USA and in Westernized societies [7].

CONTINUING EDUCATION

Hypertension: The Silent Killer: Updated JNC-8 Guideline Recommendations

Authors:
Kayce Bell, Pharm.D. Candidate 2015
Harrison School of Pharmacy, Auburn University;

June Twiggs, Pharm.D. Candidate 2015
Harrison School of Pharmacy, Auburn University;

Bernie R. Olin, Pharm.D.,
Associate Clinical Professor of Pharmacy Practice,
Drug Information and Learning Resource Center,
Harrison School of Pharmacy, Auburn University

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Alabama Pharmacy Association | 334.271.4222 | www.aparx.org | apa@aparx.org

European Heart Journal (1998) **19**, 372–377

Clinical Perspectives

Diagnosis and investigation of essential and secondary hypertension

Introduction

Hypertension is a common and important modifiable risk factor for cardiovascular disease. It has been convincingly demonstrated that reducing blood pressure, even modestly, in hypertensive patients, reduces the subsequent rate of stroke and coronary heart disease. A long-term reduction of 5–6 mmHg in diastolic blood pressure is associated with approximately 35–40% less stroke and 20–25% less coronary heart disease related deaths[1]. Because of the commonness of hypertension, the supposed simplicity of blood pressure measurement, and the widespread availability of effective and well-tolerated antihyptensive agents the management of hypertension has been predominantly the task of primary care doctors. Despite this, cases exist which are more complicated, either because of hypertensive complications, co-incident but unrelated diseases, or because of difficulties in diagnosis or management, such as 'white coat' hypertension, resistant hypertension or suspected secondary hypertension. Detecting secondary hypertension, and so identifying potentially curable causes without excessive investigation of low risk patients or undue use of expensive and potentially harmful tests, is a problem often faced by cardiac specialists to whom such patients may frequently be referred.

Hypertension — definition, diagnosis and treatment

There is no natural dividing line between normotension and hypertension. Essential hypertension is a numerical description not a distinct disease. In a meta-analysis of nine prospective observational studies a continuous direct positive relationship between diastolic blood pressure and both stroke and coronary heart disease was observed[2]. Therefore any definition of essential hypertension based on blood pressure readings is inevitably arbitrary. In theory hypertension could be defined as a level of blood pressure above that at which intervention has been shown to reduce risk[3]. This, of course, means that different populations (e.g. young vs old, men vs women) should have different diagnostic thresholds. However, there are also the problems of proving mortality reduction in a randomized controlled trial for each new threshold level of blood pressure. Another factor is that in most large prospective trials blood pressure has been measured in special trial settings, with trained nursing personnel using more rigorously maintained sphygmomanometers than is typical in routine practice. It is uncertain whether other forms of blood pressure measurement, such as routine blood pressure estimation by doctors or newer more sophisticated measurement by ambulatory blood pressure monitoring would lead to the same diagnostic and treatment thresholds. It is usually recommended that clinicians base clinical decisions on multiple measurements made over multiple visits with the patient in the sitting position after several minutes rest. A cuff of appropriate size for the patient's arm should be used with Korotkoff phase V (when the sound disappears) taken to be diastolic blood pressure[4]. At least three measurements should be taken, with a minimum of 3 min between each, and the values averaged. Blood pressure levels often settle on further assessments as patients become used to the clinic environment. Unless the hypertension is severe or there is associated target organ damage e.g. left ventricular hypertrophy, measurements should be repeated over a 3–6 month period. This is the ideal as it closely follows the methods of the randomized control trials, upon which our evidence-to-treat is based. In practice, however, this is far from what actually happens. Frequent errors are made with sloppy technique, poorly maintained apparatus and far too few readings prior to a diagnosis being made and treatment commenced[5,6]. As a result people may be unnecessarily treated.

Submitted 13 May 1997, and accepted 9 June 1997.

Correspondence: Dr J. Mayet, Department of Cardiology, Royal Brompton Hospital, London SW3 6NP, U.K.

0195-668X/98/030372+10 $18.00/0 hj970595

Pediatr Nephrol
DOI 10.1007/s00467-016-3334-4

EDUCATIONAL REVIEW

Diuretics in the treatment of hypertension

Douglas L. Blowey[1]

Received: 8 May 2015 / Revised: 11 January 2016 / Accepted: 12 January 2016
IPNA 2016

Abstract Diuretics have long been used for the treatment of hypertension. Thiazide diuretics are the most commonly prescribed diuretics for hypertension, but other classes of diuretics may be useful in alternative circumstances. Although diuretics are no longer considered the preferred agent for treatment of hypertension in adults and children, they remain acceptable first-line options. Diuretics effectively decrease blood pressure in hypertensive patients, and in adults with hypertension reduce the risk of adverse cardiovascular outcomes. Because of varied pharmacokinetic and pharmacodynamic differences, chlorthalidone may be the preferred thiazide diuretic in the treatment of primary hypertension. Other types of diuretics (e.g., loop, potassium sparing) may be useful for the treatment of hypertension related to chronic kidney disease (CKD) and other varied conditions. Common side effects of thiazides are mostly dose-related and involve electrolyte and metabolic abnormalities.

Keywords Hypertension · Children · Thiazide diuretic · Hydrochlorothiazide · Chlorthalidone · Diuretics

While supervising the nephrology fellow's clinic you are presented with an obese 15-year-old Caucasian boy with repeated elevated office blood pressure readings that have persisted despite a 6-month trial of lifestyle modifications. Both parents developed hypertension in their mid-20s and several members of the family developed cardiovascular disease between 40 and 50 years of age. Aside from obesity, his physical examination is unremarkable as are his serum electrolytes, creatinine, urinalysis, and thyroid studies. Hemoglobin A1c is mildly elevated and the fasting lipid profile demonstrates a mild increase in total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The echocardiogram shows mild concentric left ventricular hypertrophy (LVH) with normal function.

In view of the blood pressure elevations that have persisted despite lifestyle modifications, a strong family history of hypertension and cardiovascular disease, and target organ involvement (e.g., LVH), the fellow recommends starting pharmacologic treatment and suggests initiating therapy with a diuretic. A discussion among the fellows in clinic results in the formation of several clinical questions related to diuretic use and hypertension.

Are diuretics recommended as preferred first-line antihypertensive agents in current hypertension guidelines?

In the current adult guidelines for the management of hypertension [1–6], the thiazide class of diuretics is recommended as one of several potential preferred drugs for initial antihypertensive drug therapy (Table 1). This is a change from previous guidelines that recommended the use of thiazide diuretics as the preferential initial therapy, a recommendation that was based on outcome trials available at that time (e.g., ALLHAT) [7, 8], cost, and other considerations. Using the most up-to-date literature on treatment, overall mortality, and cardiovascular, cerebrovascular, and renal outcomes, the member consensus opinion of the majority of the Eighth Joint National Committee (JNC 8) [1] concluded that a thiazide diuretic, angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor antagonist (ARB), or long-acting

* Douglas L. Blowey
dblowey@cmh.edu

[1] Pediatrics and Pharmacology, Division of Pediatric Nephrology, Children's Mercy Hospital, University of Missouri, 2401 Gillham Road, Kansas City, MO 64108, USA

Published online: 16 March 2016

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THE DENTAL
CLINICS
OF NORTH AMERICA

Dent Clin N Am 50 (2006) 547–562

Dental Management of Patients with Hypertension

J. Bruce Bavitz, DMD, FACD

Department of Surgical Specialties, University of Nebraska Medical Center, College of Dentistry, 40th and Holdrege, Lincoln, NE 68583-0757, USA

Surprisingly, there is little if any data to indicate that treating a patient with hypertension alone increases the risk for adverse outcomes or complications. Most dentists, however, realize that hypertension often leads to cardiovascular disease, renal disease, and strokes, which are conditions that increase the risk for complications, both during and after dental care. Oral and systemic side effects may also arise from the medicines used to treat hypertensive patients. This article reviews the current thought on the pathogenesis, diagnosis, and treatment of hypertension, and provides guidance on how best to treat patients with this common medical problem.

Physiology

Blood pressure (BP) is determined by how much blood the heart pumps (ie, cardiac output) and by the resistance to blood flow in the vascular system. Cardiac output in turn is determined by how often the pump contracts (ie, heart rate) and by the amount of blood ejected during each beat (ie, stroke volume). High blood pressure, therefore, results from either narrow inflexible arteries, an elevated heart rate, increased blood volume, more forceful contractions, or any combination of the above. BP is never constant; it peaks right after the ventricles contract (systole) and reaches its low point as the ventricles fill (diastole). Mean arterial pressure (MAP) is calculated by multiplying the diastolic BP by two, adding the systolic BP, and dividing by three. Diastolic BP is multiplied by two as, on average, the heart spends roughly twice the amount of time in diastole as in systole.

The long-term regulation of BP is controlled predominantly by the kidneys through their variable release of the enzyme renin. Renin goes on to

E-mail address: jbavitz@unmc.edu

doi:10.1016/j.cden.2006.06.003 dental.theclinics.com

Review Article

β-Blockers: A Review of Their Pharmacological and Physiological Diversity in Hypertension

Annals of Pharmacotherapy
1–11

DOI: 10.1177/1060028013519591
aop.sagepub.com
SAGE

Toni L. Ripley, PharmD, BCPS, FCCP, AQ-Cardiology[1] and Joseph J. Saseen, PharmD, BCPS, FASHP, FCCP[2]

Abstract

Objective: To review the pharmacology, pharmacokinetics, and pharmacodynamic properties of commonly used β-blockers (atenolol, carvedilol, metoprolol succinate, metoprolol tartrate, and nebivolol). **Data Sources:** A MEDLINE literature search (1966-May 2013) was performed using the following key terms: *hypertension, β-blockers, atenolol, carvedilol, metoprolol tartrate, metoprolol succinate, nebivolol, pharmacology, pharmacodynamics, pharmacokinetics, blood pressure, metabolic, lipid, central aortic pressure, diabetes*, and *insulin resistance*. References from publications reviewed were included. **Study Selection and Data Extraction:** English-language articles identified were reviewed. Animal studies and studies in patients for a primary diagnosis of coronary artery disease were excluded. **Data Synthesis:** β-Blockers are no longer recommended first-line therapy for primary hypertension, based on data showing that β-blockers are inferior to other antihypertensives and no better than placebo, in spite of provision of blood pressure reduction. Because atenolol is the β-blocker used in 75% of these studies, uncertainty about widespread application to all β-blockers exists. Different pharmacological and physiological properties, both within β-blockers and compared with other antihypertensives, may explain divergent effects. Evidence shows that β-blockers have a truncated effect on central aortic pressure, an independent predictor of cardiovascular events, compared with other antihypertensive classes; differences within the class may exist, but the evidence is inconclusive. Metabolic effects differ within the β-blocker class, with evidence that carvedilol causes less metabolic dysregulation. **Conclusion:** Emerging evidence reveals physiological differences within the β-blocker class and in comparison to other antihypertensives. These differences provide insight into the diverse clinical effects β-blockers provide in cardiovascular disease.

Keywords

β-blockers, hypertension, pharmacology, central aortic pressure, metabolic, pharmacodynamics

The use of β-blocker therapy as a first-line treatment for hypertension has been the subject of considerable controversy for the past decade.[1] Historically, β-blocker therapy had been recommended as one of the initial treatment options for primary hypertension, dating back to 1977 in the first report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC 1).[2] They were consistently the second most frequently prescribed antihypertensive agent until 1990, when calcium channel blockers (CCBs) and angiotensin converting enzyme (ACE) inhibitors became more frequently used.[3] In the 2003 JNC 7 report, β-blockers were regarded as 1 of 5 viable first-line therapy treatments in the management of hypertension.[4] However, more current recommendations from the American Heart Association and the National Institute for Health and Clinical Excellence no longer recommend β-blockers as a first-line therapy option in primary hypertension.[5,6] In the 2013 Canadian Hypertension Education Program recommendations, β-blockers are not recommended as first-line therapy for uncomplicated hypertension, specifically in patients 60 years of age or older.[7] These contemporary recommendations advise that β-blocker therapy is best used as add-on therapy with an ACE inhibitor or angiotensin receptor blocker (ARB), CCB, and/or diuretic.

The recommendation to relegate β-blockers to add-on therapy is a consequence of clinical trial and meta-analysis data that demonstrated that β-blockers were inferior to other

[1]University of Oklahoma College of Pharmacy, Oklahoma City, OK, USA
[2]University of Colorado, Anschutz Medical Campus, Aurora, CO, USA

Corresponding Author:
Toni L. Ripley, Department of Pharmacy, Clinical and Administrative Sciences, University of Oklahoma College of Pharmacy, 1110 North Stonewall, Oklahoma City, OK 73117, USA.
Email: Toni-ripley@ouhsc.edu

REVIEW ARTICLE

Am J Cardiovasc Drugs 2007; 7 Suppl. 1: 17-23
1175-3277/07/0001-0017/$44.95/0

Calcium Channel Blockers: Differences Between Subclasses

William H. Frishman

Department of Medicine, New York Medical College, Valhalla, New York, USA

Abstract

Calcium channel blockers (CCBs) share a common mechanism of action. However, the manner in which they exert their pharmacological effects is different between subclasses. Dihydropyridine (DHP) CCBs tend to be more potent vasodilators than non-dihydropyridine (non-DHP) agents, whereas the latter have more marked negative inotropic effects. Both subclasses have a similar capacity to lower BP; however, non-DHPs appear to offer potential advantages in the management of patients with chronic kidney disease and diabetic nephropathy. Representatives of both classes are now available in fixed-dose combinations containing an ACE inhibitor, the benefits of which include effective 24-hour BP control, a reduced incidence of adverse effects, and improved adherence.

Calcium channel blockers (CCBs) are a chemically diverse group of drugs, although they share a common underlying mechanism of action.[1] All CCBs act on blood vessels, where they cause vasodilation, and/or on the myocardium, where they variably decrease cardiac contractility.[2] However, the structural differences between CCBs result in contrasting tissue specificities and necessitate categorization into two main subclasses – dihydropyridine (DHP) agents, such as amlodipine, nifedipine, nicardipine and felodipine, and non-dihydropyridine (non-DHP) agents such as verapamil (a phenylalkylamine) and diltiazem (a benzothiazepine derivative).[1]

The pharmacological actions of first- and second-generation CCBs are primarily a result of their ability to block calcium influx through the L-type calcium channels in excitable membranes.[2-4] Whereas DHPs are more vasoselective than non-DHPs,[2] non-DHPs have a more negative chronotropic and inotropic effect than DHPs.[5] In this regard, both verapamil and diltiazem have been referred to as 'heart rate-lowering' agents because of their tendency to reduce pulse rate.[5]

Although the pharmacological differences between CCB subclasses are well recognized, the degree to which these are reflected in differing clinical outcomes is less well established. This paper briefly reviews the pharmacologic differences between DHPs and non-DHPs and explores the clinical implications of these differences.

1. Use in Hypertension

In published guidelines on the management of hypertension, CCBs are suggested as candidates for first-line therapy either alone or in combination with other antihypertensive agents. The Seventh Report of the Joint National Committee (JNC-7) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends CCBs as first-line agents when there is a compelling indication – i.e. high risk of coronary disease and/or diabetes. For all other patients thiazide diuretics are recommended as first-line pharmacologic therapy, either alone or in combination with one of the other classes of agents.[6]

The European Society of Hypertension (ESH)–European Society of Cardiology (ESC) guidelines for the management of arterial hypertension are less prescriptive than JNC-7, suggesting that any of the main antihypertensive classes are appropriate for initiating and maintaining therapy.[7] These guidelines emphasize the importance of individualizing therapy, suggesting that non-DHP agents are appropriate for patients with angina pectoris, carotid atherosclerosis, and supraventricular tachycardia.[7] They also recommend DHP CCBs for elderly and pregnant patients and those with isolated systolic hypertension, angina pectoris, peripheral vascular disease, and carotid atherosclerosis.[7]

DHP and non-DHP CCBs similarly reduce BP.[8-11] In 50–75% of patients with mild-to-moderate hypertension, monotherapy with a CCB produces a significant response (i.e. ≥10mm Hg in diastolic BP or normalization).[12] Response rates to CCBs are particularly robust in Black patients, a large subgroup with a high incidence of hypertension.[13,14] Brewster and colleagues[15] undertook a review of the efficacy of different classes of antihypertensives in Black patients enrolled across 30 trials. They found that CCBs, diuretics, central sympatholytics, peripheral

The Journal of Physiological Sciences
https://doi.org/10.1007/s12576-019-00679-4

REVIEW

Renin–angiotensin system research: from molecules to the whole body

Eriko Takimoto-Ohnishi[1,2] · **Kazuo Murakami**[1]

Received: 8 December 2018 / Accepted: 17 April 2019

Abstract
Hypertension is one of the most important risk factors and a leading cause of death from cardiovascular and cerebrovascular diseases. Based on numerous previous studies, hypertension is thought to be caused by the complex mutual interactions of genetic factors and environmental factors, such as excessive salt intake and stress. However, its detailed mechanisms are not yet clearly understood. The renin–angiotensin system (RAS) is a key hormonal system in the pathogenesis of hypertension. New knowledge is still accruing on this cascade, even after more than 120 years since the discovery of renin. To clarify the molecular mechanisms of RAS in vivo, we created transgenic mice with chronic hypertension. These mice carry the human genes encoding renin, a hypertensive enzyme, and its substrate angiotensinogen. Hypotensive mice homozygous for a targeted disruption of the angiotensinogen gene were also created. This review presents our 47-year history of RAS research.

Keywords Hypertension · Renin · Angiotensinogen · Renin–angiotensin system · Transgenic mice · Knockout mice

Introduction

Hypertension is the most prevalent clinical symptom, affecting 1.13 billion people worldwide [1]. The number of people with uncontrolled hypertension has risen over the years because of population growth and ageing. Complications of hypertension are thought to cause 9.4 million deaths each year, and without further action the World Health Organization (WHO) has predicted this number will increase [2, 3]. The renin–angiotensin system (RAS) is a regulatory cascade that plays major physiological roles in blood pressure regulation and electrolyte homeostasis (Fig. 1). Renin (EC 3.4.23.15), an aspartyl protease, catalyzes the specific cleavage of angiotensinogen to decapeptide angiotensin I (AI), the first and rate-limiting step in the RAS. The biologically inactive AI is then converted by angiotensin-converting enzyme (ACE) to the bioactive octapeptide, angiotensin II (AII). AII acting via its receptors induces a variety of physiological effects such as vasoconstriction, increasing cardiac output and promoting aldosterone synthesis. Dysregulation of the RAS plays a pivotal role in the pathogenesis of hypertension. Clinical evidence for the impact of RAS blocking agents suggested that renin-dependent mechanisms may be involved in more than 70% of patients with essential hypertension [4]. Most recently, a machine learning of big data on the treatment of hypertension has identified that ACE inhibitors and angiotensin receptor blockers were the most common treatment, used by 73% of the patients, as single drugs as well as in combinations with other antihypertensive medications [5]. Although it is beyond doubt that RAS blockers effectively lower blood pressure, the beneficial effects of that cannot be simply explained on the basis of changes in the circulating RAS. Recent evidence demonstrated that these blockers have other pleiotropic properties independent of their hypotensive effects, such as enhancement of cognition [6].

The complexity of the RAS has increased considerably in the past two decades [7]. This system was originally believed to be exclusively a circulating system, but because components of the RAS have been demonstrated in a variety of tissues, local RAS has been proposed as a paracrine function

✉ Eriko Takimoto-Ohnishi
onishi-e@ncchd.go.jp

✉ Kazuo Murakami
murakami-k@msg.biglobe.ne.jp

[1] Bio-Laboratory, Foundation for Advancement of International Science, 3-24-16 Kasuga, Tsukuba, Ibaraki 305-0821, Japan

[2] Department of Maternal–Fetal Biology, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan

Published online: 26 April 2019

Accepted Manuscript

Title: Antihypertensive drugs

Author: Stéphane Laurent

PII: S1043-6618(17)30846-0
DOI: http://dx.doi.org/doi:10.1016/j.phrs.2017.07.026
Reference: YPHRS 3657

To appear in: *Pharmacological Research*

Received date: 10-7-2017
Revised date: 26-7-2017
Accepted date: 28-7-2017

Please cite this article as: {http://dx.doi.org/

Effect of Diuretics on Salivary Flow, Composition and Oral Health Status: A Clinico- biochemical Study

Article *in* Annals of Medical and Health Sciences Research · July 2014

DOI: 10.4103/2141-9248.139311 · Source: PubMed

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Lichenoid Eruption Associated with Hydrochlorothiazide and Possible Cross Reactivity to Furosemide

Éruption lichénoïde associée à l'hydrochlorothiazide avec possible réaction croisée avec le furosémide

Karim Aouam[1], *Hichem Bel Hadj Ali*[2], *Monia Youssef*[2], *Amel Chaabane*[1], *Mohamed Habib Hamdi*[3], *Naceur A. Boughattas*[1] *and Jamel Eddine Zili*[2]

1 Service de Pharmacologie, Faculté de Médecine, Monastir, Tunisia

2 Service de Dermatologie, Hôpital Fattouma Bourguiba, Monastir, Tunisia

3 Service de Médecine et de Chirurgie Buccales, Clinique Universitaire de Médecine Dentaire, Monastir, Tunisia

Text received 4 May 2009; accepted 27 July 2009

Case notified 8 august 2007, Regional Tunisian Centre of Pharmacovigilance

Keywords: lichenoid eruption; hydrochlorothiazide, furosemide, adverse effect

Mots clés : éruption lichénoïde ; hydrochlorothiazide ; furosémide ; effet indésirable

1. Introduction

Lichen planus is an inflammatory mucocutaneous condition with characteristic violaceous flat-topped papules and plaques. Pruritus is often severe. Involvement of oral or genital mucosa in some cases may be debilitating.[1] The aetiology of lichen is unknown, but stress, autoimmunity, underlying mesodermal diseases, and infection (especially by hepatitis B and cytomegalovirus) have all been suggested.[2] Many drugs can provoke eruptions that are clinically and histologically similar to lichen planus. However, in drug-induced lichenoid eruption, there can be more eczematization and scaling, greater tendency toward residual hyperpigmentation, Wickham's striae are usually absent, it appears as a symmetric eruption on the trunk or extremities, a photodistributed pattern is found in high percentage, and involvement of oral mucosa is less common.[2] The first substance accused of eliciting lichenoid eruption is arsenic. Some drugs (*e.g.* gold salts, non steroidal anti-inflammatory drugs…) may also cause a lichenoid eruption.[2] The potential of the thiazide diuretics group to elicit adverse cutaneous reactions has been recognized since it became prescribed on a large scale. There have been subsequent reports of vasculitis,[3] photosensitive eruption,[4] etc.

Thiazide diuretics belong to sulphonamide which can be subdivided into three principal pharmacological groups: antibiotics, diuretics and hypoglycaemics. Knowles *et al.*[5] classified sulfonamides into two different groups: antibiotic sulphonamide and non antibiotic sulphonamide (diuretic and hypoglycaemic sulfonamide and other drugs such as celecoxib, sumatriptan and nimesulide).

Diuretic-induced lichenoid eruption is very rare and cross reactivity within this pharmacological class has, to our knowledge never been reported. We describe a case of a probable association between hydrochlorothiazide (HCTZ) and a lichenoid eruption which recurred after furosemide administration.

2. Case Report

A 56-year-old man presented with an acute onset of a pruritic rash which started on his trunk and spread to his whole body. His past medical history included hypertension and Sharp syndrome for which he was taking irbesartan-HCTZ and methotrexate. Methotrexate and irbesartan-HCTZ were started respectively about 2 years and 8 months before the skin eruption. On physical examination, the patient had violaceus and scaly plaques on the trunk, back and limbs (figure 1). There were bilateral shallow erosions of the labial mucosa surrounded by a network of lacy white striae (figure 2). The blood count and the biochemical profile were normal. The hepatitis B virus serology was negative. A biopsy of the involved skin showed hypergranulosis, liquefaction in the basal layer and lymphocyte infiltration of the dermal-epidermal junction, highly consistent with a lichenoid drug reaction. Desonide (0.1%) and cetirizine provided no relief. The responsibility of HCTZ was than suspected and irbesartan-HCTZ was replaced by irbesartan. The skin eruption and pruritis had resolved within two weeks. Approximately 6 weeks later, patch test to irbesartan-HCTZ (5% petrolateum using Finn Chambers) was performed on his back. It was totally negative at days 2 and 3. Because his blood pressure was still high, furosemide 40 mg daily was administered and pruritic erythematous plaques and red

Article published by EDP Sciences

ARCHIVES OF ORAL BIOLOGY 55 (2010) 164–169

available at www.sciencedirect.com

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journal homepage: http://www.elsevier.com/locate/aob

Short communication

Relationships of beta-blockers and anxiolytics intake and salivary secretion, masticatory performance and taste perception

Leandro Faria de Matos [a,b], *Stela Márcia Pereira* [b], *Estela Kaminagakura* [b], *Leandro Silva Marques* [a], *Cássio Vicente Pereira* [b], *Andries van der Bilt* [c], *Luciano José Pereira* [a,b,d,*]

[a] *Clinical Dentistry Department, Vale do Rio Verde University – UNINCOR, Três Corações, MG, Brazil*
[b] *Dentistry Department, Lavras University Center – UNILAVRAS, Lavras, MG, Brazil*
[c] *Oral Physiology Department, University Medical Center Utrecht, The Netherlands*
[d] *Physiology and Pharmacology Department, Federal University of Lavras – UFLA, Lavras, MG, Brazil*

ARTICLE INFO

Article history:
Accepted 21 November 2009

Keywords:
Mastication
Anxiolytic
Antihypertensive
Taste

ABSTRACT

Objective: Assess the influence of salivary flow on physiological parameters of the stomatognathic system in patients who take beta-blockers or anxiolytic medications.
Design: Sixty patients were divided into three groups based on the following criteria: Group 1, control ($n = 20$; no use of medication); Group 2, use of antihypertensive beta-blockers ($n = 20$); and Group 3, use of benzodiazepine anxiolytics ($n = 20$). Salivary flow was assessed by determining stimulated and non-stimulated flow/minute. The quantification of the sense of taste was determined on a visual analogue scale (VAS) using solutions of 0.9% NaCl (salty), 50% sucrose (sweet), 20% unsweetened coffee (bitter) and 4.2% vinegar (sour). The DMFT index (number of decayed/missing/filled teeth) was determined by a calibrated examination, following the criteria of the World Health Organization (WHO). Masticatory performance was assessed with an Optosil comminution test and Rosim–Ramler equation.
Results: The results did not reveal a significant correlation between salivary flow and masticatory performance ($p > 0.05$). We observed significant decreased non-stimulated salivary flow for Group 2 ($p = 0.05$) when compared to controls. However, taste perception was not influenced by salivary secretion amongst groups. Furthermore, we observed a significant negative correlation between non-stimulated salivary flow and DMFT in Group 1 ($p = 0.02$; $r = -0.52$).
Conclusions: Patients under beta-blockers therapy presented reduced non-stimulated salivary flow when compared to controls, without influencing the sense of taste or masticatory performance. The use of anxiolytics did not affect salivary flow and taste perception in the studied sample.

* *Corresponding author at*: Universidade Federal de Lavras – UFLA – DMV – Setor de Fisiologia e Farmacologia Caixa Postal 3037, Campus Universitário, Lavras, MG, CEP 37200-000, Brazil.
E-mail addresses: lucianojosepereira@yahoo.com.br, lucianojosepereira@dmv.ufla.br (L.J. Pereira).
0003–9969/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.archoralbio.2009.11.011

KEY WORDS
Gingival enlargement, Calcium Channel Blockers, Phenytoin, Ciclosporin, Treatment

LEARNING OBJECTIVES
- To review the aetiology and prevalence of drug-influenced gingival enlargement
- To understand management of gingival enlargement based on meticulous plaque control and surgical reduction of residual enlarged tissues
- To understand when drug substitution may be appropriate and how to approach this

AUTHORS
Noha Zoheir BDS, MFDS, M Clin Dent (Periodontology)
Clinical Teacher in Periodontology, Unit of Periodontology, Centre for Host Microbial Interactions, Faculty of Dental, Oral & Craniofacial Sciences, Kings College London

Francis J. Hughes BDS, FDS RCS, PhD
Professor of Periodontology, Unit of Periodontology, Centre for Host Microbial Interactions, Faculty of Dental, Oral & Craniofacial Sciences, Kings College London

NOHA ZOHEIR, FRANCIS J. HUGHES
Prim Dent J. 2019;8(4):34-39

THE MANAGEMENT OF DRUG-INFLUENCED GINGIVAL ENLARGEMENT

ABSTRACT
INTRODUCTION:
Drug-influenced gingival enlargement (DIGE) is a reaction to specific medications, namely phenytoin, ciclosporin and calcium channel blockers. DIGE is encountered increasingly in clinical practice due to the widespread use of calcium channel blocker drugs particularly. Approaches to its management are discussed in this review.

METHODS: Narrative review of the literature and discussion of clinical implications.

FINDINGS: Management of DIGE involves nonsurgical treatment and may require surgical reduction of the overgrown gingival tissues. Management is complicated by the difficulties in achieving adequate plaque control, given the unfavourable contour of the enlarged gingival tissues, and the high frequency of recurrence of DIGE after surgical management. Replacing the drug involved can be very beneficial in selected cases, but the management of the underlying medical condition limits its application. The decision to replace a drug is not the responsibility of the dental practitioner, but the patient's physician may make it after consultation.

CONCLUSIONS: Management of DIGE can be challenging and may require close co-operation between the dental practitioner and a hygienist, a periodontist and the patient's physician. Long term supportive maintenance programmes need to be in place for optimal outcomes.

Introduction

Gingival enlargement is a relatively common problem encountered in dental practice. Untreated enlarged gingival tissues can affect aesthetics, mastication, speech and ability to perform plaque control, resulting in periodontal problems and potentially dental caries. Gingival enlargement can occur due to inflammation, neoplasms, systemic conditions, and the use of drugs that influence the clinical presentation of the gingiva and affect the progression of periodontal diseases. These can ultimately affect the patient's well-being and need long term support from the dental team.

The literature in this field contains many case reports and case series, but relatively few large-scale studies on prevalence rates and well-controlled trials of treatment outcomes. This inevitably means that the available information is incomplete, and often contradictory, but we have here aspired to distill the evidence for clarity. More detailed discussion of the aetiology and pathogenesis of DIGE is also available in a number of recent reviews[1-3].

Drug-influenced gingival enlargement

Drug-Influenced gingival enlargement (DIGE) manifests as an abnormal growth of the gingiva due to the administration of specific drugs, namely phenytoin, ciclosporin and calcium channel blockers (CCBs). Gingival changes can appear within 3 months of drug administration[4].

Although discussion of the pathogenesis and clinical features of DIGE in various drugs has often treated them as a single entity, there is good evidence that the drugs may have significantly different effects on the tissues. Clinically, phenytoin-associated gingival enlargement is typically fibrous in presentation, whereas with ciclosporin, the gingival enlargement

Current Hypertension Reports (2018) 20:55
https://doi.org/10.1007/s11906-018-0859-x

GUIDELINES/CLINICAL TRIALS/META-ANALYSIS (JB KOSTIS, SECTION EDITOR)

ACE Inhibitor-Induced Angioedema: a Review

William J. Kostis[1] &Mrinali Shetty[2] &Yuvraj Singh Chowdhury[2] &John B. Kostis[1]

Abstract
Purpose of Review This study aims to examine current knowledge on the occurrence, pathophysiology, and treatment of angioedema among patients who receive angiotensin-converting enzyme inhibitors.
Recent Findings Angiotensin-converting enzyme inhibitors (ACE-I), a medication class used by an estimated 40 million people worldwide, are associated with angioedema that occurs with incidence ranging from 0.1 to 0.7%. The widespread use of ACE-I resulted in one third of all emergency department visits for angioedema. Angioedema occurs more frequently in African Americans, smokers, women, older individuals, and those with a history of drug rash, seasonal allergies, and use of immunosuppressive therapy. The pathophysiology of ACE-I-induced angioedema involves inhibition of bradykinin and substance P degradation by ACE (kininase II) leading to vasodilator and plasma extravasation. Treatment modalities include antihistamines, steroids, and epinephrine, as well as endotracheal intubation in cases of airway compromise. Patients with a history of ACE-I-induced angioedema should not be re-challenged with this class of agents, as there is a relatively high risk of recurrence.
Conclusion ACE-I are frequently used therapeutic agents that are associated with angioedema. Their use should be avoided in high-risk individuals and early diagnosis, tracheal intubation in cases of airway compromise, and absolute avoidance of re-challenge are important.

Keywords Angiotensin II - Angioedema - Angiotensin-converting enzyme inhibitors - Hypertension - Bradykinin

Introduction

> "In one instance, possibly in two, death resulted from a sudden oedema glottides [1]."
> - William Osler

Angioedema is a well-documented and occasionally lethal side effect of angiotensin-converting enzyme inhibitors (ACE-I). Angioedema is a pale, non-pruritic, well-demarcated, non-pitting edema involving the skin and subcutaneous tissue or submucosa. When involving the airway, the feeling of impending asphyxia may be terrifying for the sufferer [2, 3]. A retrospective analysis identified angioedema as the most common non-asthmatic acute allergic reaction leading to hospitalizations in New York State from 1990 to 2003 [4]. In the four decades since the development of captopril in 1975 (FDA approval 1981), ACE-I have become the some of the most prescribed medications in the USA, with lisinopril being the second most prescribed agent in 2016 [5]. Concurrent with the growing use of ACE-I, the rate of hospitalization for angioedema in the USA has increased from 3.3 to 4.0 per 100,000 within 15 years [6].

The History of Angiotensin-Converting Enzyme Inhibitors

Workers in Brazil who were bitten by the Brazilian pit viper Bothrops jararaca die within minutes from severe hypotension. Mauricio Rocha e Silva and his student, Sergio Ferreira, at the University of São Paulo, studied the effects of the snake venom and identified peptides thought to potentiate the action of bradykinin [7]. Ferreira brought the bradykinin potentiating

This article is part of the Topical Collection on Guidelines/Clinical Trials/Meta-Analysis

* William J. Kostis
wkostis@nwjms.rutgers.edu

1 Rutgers Robert Wood Johnson Medical School, Cardiovascular Institute, 125 Paterson Street, CAB-4100, New Brunswick, NJ 08901, USA

2 Saint Peter's University Hospital, New Brunswick, NJ, USA

Published online: 08 June 2018

Journal Pre-proof

Angioedema as a systemic disease

Jana Kazandjieva, MD. George Christoff

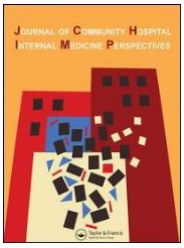
PII: S0738-081X(19)30146-4

DOI: https://doi.org/10.1016/j.clindermatol.2019.07.035

Reference: CID 7376

To appear in: *Clinics in Dermatology*

Please cite this article as: J. Kazandjieva and M. George Christoff, Angioedema as a systemic disease, *Clinics in Dermatology*(2019), https://doi.org/10.1016/j.clindermatol.2019.07.035



Journal of Community Hospital Internal Medicine Perspectives

ISSN: (Print) 2000-9666 (Online) Journal homepage: http://www.tandfonline.com/loi/zjch20

Drug-induced visceral angioedema

Prashanth M. Thalanayar, Ibrahim Ghobrial, Fritz Lubin, Reena Karnik & Robin Bhasin

To cite this article: Prashanth M. Thalanayar, Ibrahim Ghobrial, Fritz Lubin, Reena Karnik & Robin Bhasin (2014) Drug-induced visceral angioedema, Journal of Community Hospital Internal Medicine Perspectives, 4:4, 25260, DOI: 10.3402/jchimp.v4.25260

To link to this article: https://doi.org/10.3402/jchimp.v4.25260

Published online: 29 Sep 2014.

Title: Cardiovascular drugs-induced oral toxicities: a murky area to be revisited and illuminated

Author: Pitchai Balakumar Muthu Kavitha Suresh Nanditha

PII: S1043-6618(15)00211-X
DOI: http://dx.doi.org/doi:10.1016/j.phrs.2015.09.007
Reference: YPHRS 2929

To appear in: *Pharmacological Research*

Received date: 20-7-2015
Revised date: 22-8-2015
Accepted date: 8-9-2015

Please cite this article as: Balakumar Pitchai, Kavitha Muthu, Nanditha Suresh.Cardiovascular drugs-induced oral toxicities: a murky area to be revisited and illuminated.*Pharmacological Research* http://dx.doi.org/10.1016/j.phrs.2015.09.007

European Journal of Pharmacology 679 (2012) 127–131

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Pulmonary, Gastrointestinal and Urogenital Pharmacology

Effects of α_1-adrenoceptor antagonists on phenylephrine-induced salivary secretion and intraurethral pressure elevation in anesthetized rats

Hiroko Yanai-Inamura, Akiyoshi Ohtake *, Yukiko Noguchi, Toshiki Hatanaka, Masanori Suzuki, Koji Ueshima, Shuichi Sato, Masao Sasamata

Applied Pharmacology Research Laboratories, Drug Discovery Research, Astellas Pharma Inc., 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan

ARTICLE INFO

Article history:
Received 29 July 2011
Received in revised form 16 January 2012
Accepted 23 January 2012
Available online 1 February 2012

Keywords:
α_1-Adrenoceptor antagonist
Intraurethral pressure
Salivary secretion

ABSTRACT

α_1-Adrenoceptor antagonists are widely used for the treatment of voiding dysfunction associated with benign prostatic hyperplasia. Activation of α_1-adrenoceptors is reported to induce salivary secretion in rats and humans. However, the effects of α_1-adrenoceptor antagonists on salivary secretion remain unknown. Here, we investigated the effects of the α_1-adrenoceptor antagonists prazosin, silodosin, tamsulosin and urapidil on phenylephrine-induced salivary secretion and compared the results with the effects on phenylephrine-induced intraurethral pressure (IUP) elevation in anesthetized rats. All antagonists inhibited phenylephrine-induced salivary secretion and IUP elevation in a dose-dependent fashion. Comparison of DR_{10} values (the dose required to shift the dose–response curve 10-fold to the right) in both tissues showed that the inhibitory effect of silodosin was significantly more potent in the salivary gland than in the urethra (18-fold), but tamsulosin (2.3-fold), prazosin (1.7-fold) and urapidil (1.1-fold) did not show comparable tissue selectivity. These results suggest that α_1-adrenoceptor antagonists inhibit not only urethral contraction but also salivary secretion, and that high tissue selectivity for the salivary gland over the urethra as shown by silodosin may contribute to the incidence of dry mouth.

1. Introduction

Benign prostatic hyperplasia is a common disorder in middle-aged and elderly men which produces bladder outlet obstruction. In these patients, lower urinary tract symptoms characterized by poor stream, hesitancy in initiation of micturition, urinary frequency, nocturia and urgency were observed. α_1-Adrenoceptor antagonists are currently the front-line treatment for voiding dysfunction associated with benign prostatic hyperplasia, with major adverse effects such as dizziness, orthostatic hypotension and light-headedness. However, a recent clinical study has focused attention on an additional adverse event: dry mouth (Kawabe et al., 2006). This study reported a high incidence of dry mouth with silodosin (in 10.3% of patients) compared with tamsulosin (3.6%) and placebo (4.5%). Furthermore, Yamada et al. (2001) and Okura et al. (2002) reported that silodosin selectively bound to α_1-adrenoceptors in the rat prostate and submandibular glands which predominantly contain the α_{1A}-adrenoceptor subtype. These results suggest that α_1-adrenoceptor antagonists may induce dry mouth and that the incidence of dry mouth varies among α_1-adrenoceptor antagonists.

The salivary glands are innervated by both the sympathetic and parasympathetic nerves of the autonomic nervous system. It has been reported that salivary secretion is primarily mediated by the activation of distinct receptors such as muscarinic receptors, α- and β-adrenoceptors and peptidergic receptors (Baum, 1993). In fact, it has been demonstrated that carbachol (a muscarinic receptor agonist), phenylephrine (an α_1-adrenoceptor agonist) and isoproterenol (a β-adrenoceptor agonist) all induce salivary secretion in rats (Popović et al., 2005). The α-adrenoceptors have been found to regulate the secretion of fluid and electrolytes and may have an effect on the secretion of proteins in saliva (Klein, 2002). The presence of α_{1A}- and α_{1B}-adrenoceptor mRNA and proteins has been confirmed in rat submandibular glands and in the SMG-C10 acinar cell line (Bockman et al., 2004; Faure et al., 1994; Nishiura et al., 2001; Rokosh et al., 1994). Moreover, Huang et al. (2006) indicated that α_{1A}- and α_{1B}-adrenoceptor proteins in human submandibular glands are functional and contribute to the regulation of salivary production and secretion.

Although activation of α_1-adrenoceptors is clearly implicated in salivary secretion in rats and humans, the effects of α_1-adrenoceptor antagonists on salivary secretion remains unknown. Here, we investigate the effects of α_1-adrenoceptor antagonists on phenylephrine-induced salivary secretion, and compared these results with their effects on phenylephrine-induced intraurethral pressure (IUP) elevation in anesthetized rats.

* Corresponding author. Tel.: +81 29 863 6635; fax: +81 29 852 2955.
E-mail address: akiyoshi.ohtake@astellas.com (A. Ohtake).

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doi:10.1016/j.ejphar.2012.01.019

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Dent Res J (Isfahan). 2012 Mar-Apr; 9(2): 127–132.
doi: 10.4103/1735-3327.95224: 10.4103/1735-3327.95224
PMCID: PMC3353686
PMID: 22623926

An emphasis on the wide usage and important role of local anesthesia in dentistry: A strategic review

Preetinder Singh[1]

[1]Department of Periodontology and Oral Implantology, Swami Devi Dyal Hospital and Dental College, Barwala, Distt. Panchkula (Haryana), India

Address for correspondence: Dr. Preetinder Singh, H.no. 28, Sangam Enclave, Sector 48-A, Chandigarh - 160 047, Haryana, India. E-mail: preetinder.perio@yahoo.com

Received 2011 Apr; Accepted 2011 Sep.

Abstract

Local anesthesia forms the major part of pain-control techniques in dentistry. The prevention and elimination of pain during dental treatment has benefited patients, their doctors and dental hygienists, enabling the dental profession to make tremendous therapeutic advances that would otherwise have been impossible. Introduced in the late 1940s, the amide local anesthetics represent the most used drugs in dentistry. Local anesthetics also represent the safest and most effective drugs in all of medicine for the prevention and management of pain. They are also accompanied by various adverse effects which should be well known and be able to be controlled by the clinician. The article reviews the types of agents used as local anesthetics and their effects on the human body.

Keywords: Anesthesia, anesthetics, dental, local/adverse effects, pharmacology, vasoconstrictor agent

INTRODUCTION

Local anesthetics are the most commonly used drugs in dentistry. Pain and dentistry are often synonymous in the minds of patients, especially those with poor dentition due to multiple extractions, periodontal disease requiring surgery or symptomatic teeth requiring endodontic therapy. Dental practitioners, before the procedure, identify a good anesthetic as one that allows them to focus solely on operative procedures without distractions from pain-induced patient movements. Research has shown that the fear of pain associated with dentistry is closely associated with intraoral administration of local anesthetics, which is the most common method for blocking pain during dental procedures. This is considered aversive due to the pain associated with the injection and the perceived threat of needle puncture prior to the injection.[1] Another survey finding was that those individuals who reported themselves as highly fearful of dentistry were worried about receiving oral injections and demonstrated an association between high dental anxieties and missed or delayed appointments.[2] This article provides a brief overview of local anesthetics to reinforce clinician's knowledge of these agents.

Local Anesthesia: Agents, Techniques, and Complications

Orrett E. Ogle, DDS[a,*], Ghazal Mahjoubi, DMD[b,c]

KEYWORDS

• Local anesthesia • Topical anesthetics
• Cain allergy • Techniques for dental anesthesia

Local anesthesia is a reversible blockade of nerve conduction in a circumscribed area that produces loss of sensation. The chemical agents used to produce local anesthesia stabilize neuronal membranes by inhibiting the ionic fluxes required for the propagation of neural impulses. Today's anesthetics are safe, effective, and can be administered with negligible soft-tissue irritation and minimal concerns for allergic reactions. Indeed, no aspect of office oral surgery is as important as good pain control. Excellent local anesthesia permits the dental surgeon to perform the necessary surgical procedure in a careful, unhurried fashion that will be less stressful for both the operator and the patient. The achievement of good local anesthesia requires knowledge of the agents being used, the neuroanatomy involved, and adherence to good techniques.

This article reviews the widely used local anesthetic agents and common techniques for obtaining local anesthesia, and also discusses some frequently seen complications.

AGENTS

Topical Anesthetics

Topical anesthetics are substances that can cause surface anesthesia of skin or mucosa. In dentistry these agents are used to temporarily anesthetize the tiny nerve

The authors have nothing to disclose.

[a] Oral and Maxillofacial Surgery, Department of Dentistry, Woodhull Medical and Mental Health Center, 760 Broadway, Brooklyn, NY 11206, USA
[b] Department of Dentistry, Woodhull Medical and Mental Health Center, 760 Broadway, Room 2C:320, Brooklyn, NY 11206, USA
[c] Department of Oral and Maxillofacial Surgery, Woodhull Medical and Mental Health Center, 760 Broadway, Room 2C:320, Brooklyn, NY 11206, USA
* Corresponding author.
E-mail address: orrett.ogle@woodhullhc.nychhc.org

Dent Clin N Am 56 (2012) 133–148
doi:10.1016/j.cden.2011.08.003 **dental.theclinics.com**
0011-8532/12/$ – see front matter

J Young Pharm, 2017; 9(4): 453-456
A multifaceted peer reviewed journal in the field of Pharmacy
www.jyoungpharm.org | www.phcog.net

Review Article

Dental Management of the Cardiovascular Compromised Patient: A Clinical Approach

Saurabh Singh[1*], Khushboo Gupta[1], Kavita Nitish Garg[2], Neeraj Kumar Fuloria[3], Shivkanya Fuloria[3], Teerthesh Jain[4]
[1]Faculty of Dentistry, AIMST University, Bedong 08100, Kedah Darul Aman, MALAYSIA.
[2]Department of Oral Pathology, Career Dental College, Lucknow, Uttar Pradesh, INDIA.
[3]Unit of Pharmaceutical Chemistry, Faculty of Pharmacy AIMST University, Bedong, Kedah Darul Aman, MALAYSIA.
[4]Department of Prosthodontics, Imam Abdul Rahman Bin Faisal University, Dammam, SAUDI ARABIA.

ABSTRACT
Cardiovascular disease trends, complications, and associated therapeutics, impact the dental health and treatment. Such patients require special consideration with regard to when and which dental treatment is appropriate and what precautions are required. A clinical approach is provided for the dental management of patients with Arterial hypertension, Heart failure, and Ischemic Heart disease, Cardiac Arrhythmias, Infective Endocarditis, Stroke and Cardiac Pacemaker. A Medline-PubMed search was conducted of the literature over the last 20 years using the keywords: "cardiovascular diseases", "dental management", "arterial hypertension", "heart failure", "ischemic heart disease", "cardiac arrhythmias", "infective endocarditis", "stroke" and "cardiac pacemaker". A total of 46 articles were reviewed, of which 32 were literature reviews, 3 were expert committee guides and updates and 11 original research papers. The appropriate management of dental patients with cardiovascular disease is contingent on appropriate assessment and evaluation. This article aims to allay many of these uncertainties by describing the commoner cardiac conditions, the risk they pose during dental practice and how they may affect dental treatment. It outlines prophylactic and remediable measures that may be taken to enable safe delivery of dental care.

Key words: Cardiovascular disease, Dental management, Arterial hypertension, Heart failure, Ischemic heart disease, Cardiac arrhythmias, Infective endocarditis, Stroke and cardiac pacemaker.

Key message: This review aims to allay many of these fears and focuses on common Cardiovascular compromised conditions and risk they pose during dental practice that necessitate extra awareness and caution to prevent potential complications causing otherwise unnecessary morbidity and mortality.

Correspondence

Dr. Saurabh Singh MDS, Lecturer, Faculty of Dentistry, AIMST University, Bedong 08100, MALAYSIA.

Phone: +60103721009

Email: drsaurabhomfs@gmail.com

DOI: 10.5530/jyp.2017.9.89

INTRODUCTION

Cardiovascular disease is the leading global cause of death, accounting for more than 17.3 million deaths per year.[1] Nearly half of all African-American adults have some form of cardiovascular disease. Compared with western countries, most Asian countries have higher age related mortality from cardiovascular disease.[2] Along with the associated morbidity, such disorders are important because many patients are associated with treatment. So, patient with cardiovascular disease constitute risk cases in dental practice. The dental management of these medically compromised patients can be problematic in terms of oral complications, dental therapy, and emergency care. The present study consists of a literature review dental management of patients suffering from various cardiovascular diseases.

MATERIALS AND METHODS

A Medline-PubMed search was conducted of the literature over the last 37 years using the keywords: "cardiovascular diseases", "dental management", "arterial hypertension", "heart failure", "ischemic heart disease", "cardiac arrhythmias", "infective endocarditis", "stroke" and "cardiac pacemaker". A total of 46 articles were reviewed, of which 32 were literature reviews, 3 were expert committee guides and updates and 11 original research papers.

Cardiovascular diseases and their dental management

1. ***Hypertension:*** Hypertension is high blood pressure. Hypertension is defined as values >140 mmHg systolic pressure and/or >90 mmHg diastolic pressure.[3,4]

Dental management:

1. A well-controlled hypertensive patients does not pose a risk in clinical practice.
2. The patient is to be instructed to take his or her medication as usual on the day of dental treatment. Prior to such treatment, the patient blood pressure should be recorded.[5,6]
3. It is preferable for the visits to be brief and in the morning. The prescription of anxiolytic agents may prove necessary in particularly anxious patients (5-10 mg of diazepam the night before and 1-2 hours before the appointment) before dental treatment, or alternatively sedation with nitrous oxide may be considered.
4. In the case of emergency dental visits, treatment should be conservative, with the use of analgesics and antibiotics. NSAIDs should not be prescribed for longer than this five-day period.[7,8]
5. Patients with cardiovascular disease are at a greater risk of massive endogenous adrenalin release secondary to deficient local anesthesia than of reaction to the small amount of vasoconstrictor used in local anesthetics.[9,10,11,12] Nevertheless, vasoconstrictor use should be limited, taking care not to exceed 0.04 mg of adrenaline.[1]

Drug interactions in general dental practice – considerations for the dental practitioner

B. E. S. Dawoud,*[1] A. Roberts[2] and J. M. Yates[3]

VERIFIABLE CPD PAPER

IN BRIEF

- Provides an update on the most common drugs prescribed in primary care by the GMP and the considerations the GDP should take before prescribing.
- Highlights practical steps the clinician may take to help reduce potentially harmful drug interactions.
- A useful reminder for the consideration of alternatives to conventional drug therapy.

PRACTICE

The aim of this article is to explore the diverse and complex nature of pharmacological drug-drug interactions in the general dental practice setting. Using published NHS statistics, this article will highlight medications for common medical conditions that could interact with frequently prescribed drugs by the general dental practitioner.

INTRODUCTION

A drug interaction may be defined as a situation when a substance, which in this case is another prescribed drug, affects the activity of a drug already taken by a patient. The potential outcome of a drug interaction can vary and could be synergistic (causing an amplification of the intended therapeutic effect of the drug), antagonistic (depressing the therapeutic effect of the drug) or additive (two drugs combining to potentiate either or both actions). All of these outcomes may have potentially damaging or fatal consequences.

Contemporary medical care has advanced significantly in recent years, increasing patients' life expectancy. This is partly due to an increase in therapeutic drug prescribing to help with the management of many common conditions. Published NHS statistics highlighted that during 2012-2013 there were 961 million prescriptions dispensed in the UK, compared with 886 million in 2009.[1,2] This increase was primarily due to an increase in the life expectancy of the UK population and the resulting polypharmacy, whereby many patients rely on a combination of drugs to maintain various essential bodily functions and minimise the effects of acquired medical conditions. Further estimates indicate that 75% of patients over the age of 55 are taking medications on a repeat prescription basis.[2] Given this gradual increase in dispensed medications, it is almost certain that the general dental practitioner (GDP) will encounter patients taking medications that could potentially interact with those delivered or prescribed in dental practice. As a consequence thought should be given by the GDP before prescribing, to determine whether the potential exists for harmful drug interactions that may have an adverse effect on the patient.

It is the intention of this article to highlight common medical conditions and the drugs frequently associated with them. Furthermore, specific reference will be made to medications that can be prescribed by GDPs, and which could have potentially adverse or damaging consequences.

DRUG INTERACTION TYPES

Drug interactions may be categorised broadly into pharmacodynamic or pharmacokinetic interactions:[3]

Pharmacodynamic interactions

Pharmacodynamic interactions are those that modify the pharmacological effect of a drug without altering its concentration in the tissue fluid.[3] This means that the effect of one drug is changed by the presence of another drug at the same molecular site, leading to a summation, or opposition, of the effects of the drugs. These interactions may be summarised into antagonistic, additive or enhanced effects.

Antagonistic effects

This is an interaction between two drugs that have opposing pharmacological effects, leading to a reduced effectiveness of one or both of the drugs administered. A typical example would be for drugs that tend to increase blood pressure, such as non-steroidal anti-inflammatory drugs (NSAIDs); these may inhibit the antihypertensive effect of drugs such as angiotensin-converting enzyme (ACE) inhibitors or diuretics.

Additive and enhanced synergistic effects

When two or more drugs are given with the same pharmacodynamic profiles, the additive effects of the two together may result in an excessive response of the target tissue and thus toxicity. An 'additive synergy' is when the final effect is equal to the sum of the effects of both drugs. When the final effect is greater than additive, it is known as 'enhanced synergy' or potentiation. An example of a synergistic effect would be the simultaneous provision of a benzodiazepine and opioid medication. Both drugs are pharmacodynamically similar and if given together can lead to an increase in the sedative effect on the central nervous system, which may cause respiratory depression.

It is worth mentioning that not all additive effects are harmful. Some drugs are given in combination with others to encourage this additive effect. One such interaction is the anti-microbial co-amoxiclav. Penicillinase-producing bacteria are resistant to penicillin and therefore the combination of clavulanic acid (an inhibitor of penicillinase) with amoxicillin achieves the desired effect.

Pharmacokinetic interactions

Pharmacokinetic interactions are those that alter the concentration of a drug that reaches its site of action. Therefore, one drug alters the concentration of another drug in the system (either an increase or decrease). This modification could occur at any phase of absorption, distribution, metabolism or excretion of the drug.

[1]Dental Foundation Trainee, 228-230 Ash Dental Practice, Manchester, Eccles, M30 0PF; [2]Consultant in Restorative Dentistry, [3]Professor of Oral and Maxillofacial Surgery, University Dental Hospital of Manchester, Higher Cambridge Street, Manchester, M15 6FH
*Correspondence to: Basim Dawoud
Email: basim.d@gmail.com

Refereed Paper
Accepted 26 September 2013
DOI: 10.1038/sj.bdj.2013.1237
[1]British Dental Journal 2014; 216: 15-23

DRUG INTERACTIONS

Three Serious Drug Interactions that Every Dentist Should Know About

Elliot V. Hersh, DMD, MS, PhD; and Paul A. Moore, DMD, PhD, MPH

Abstract: Patients with complex medical and drug histories are becoming more commonplace in dental practice. This article reviews three serious adverse drug interactions that are well supported by the literature and can impact dental practice. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the renal excretion of lithium and lead to lithium toxicity. Metronidazole and fluconazole inhibit the metabolism of warfarin by blocking cytochrome P-450 2C9 (CYP-2C9), the major metabolic pathway of warfarin, with the end result being dramatic increases in patients' international normalized ratios (INRs) and potentially fatal bleeding. Propranolol and other nonselective beta-adrenergic blocking agents can inhibit the vasodilatory effect of epinephrine in dental local anesthetic solutions, leading to hypertensive reactions and a concomitant reflex bradycardia. It is important for clinicians to recognize and avoid these serious drug interactions. By doing so, they will provide the safest and best treatment for their patients.

LEARNING OBJECTIVES

- identify three serious drug interactions that impact dental practice
- discuss adverse events related to drug interactions in certain patients, as described in cases and clinical studies
- identify alternative medications that can be employed to avoid these serious drug interactions

Unquestionably, the aging dental patient population is consuming more and more drugs, including a variety of psychotropic medications and cardiovascular drugs.[1] The most common drugs that dentists prescribe or administer include nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen (Table 1), antibiotics and antifungals such as metronidazole (eg, Flagyl®) and fluconazole (eg, Diflucan®), and local anesthetics containing the vasoconstrictor epinephrine (Table 2). What many clinicians do not realize is that these commonly employed drugs in practice can be involved in serious adverse drug interactions with medications patients are taking for a variety of medical conditions. This article will review three of the serious interactions that can potentially occur within the practice of dentistry.

NSAIDs And Lithium

As illustrated in Table 1, there are a variety of NSAIDs from which dentists can choose to manage odontogenic and postoperative pain. These analgesics represent the first line drugs that should be employed in this situation because of their unique mechanism of action, an inhibition of prostaglandin synthesis at the site of surgical trauma, which renders these drugs highly effective in the treatment of postoperative dental pain.[2,3] There are numerous evidence-based, double-blind, placebo-controlled published studies that demonstrate the overall effectiveness of these drugs after the surgical removal of impacted third molars.[4-11] However, in certain patients, NSAIDs should be avoided or used cautiously because of the possibility of precipitating a serious adverse drug interaction. A comprehensive review of this subject can be found in previous publications.[12,13] One such drug is lithium.[14]

Lithium is a major remedy in the treatment of bipolar depressive disorder.[15] It has a low therapeutic index, which means the difference between effective doses and toxic doses is relatively small. Therefore, plasma levels of lithium must be carefully monitored to ensure therapeutic effectiveness while avoiding toxicity.[15] The NSAIDs inhibit the renal excretion of lithium and can cause plasma lithium to accumulate to toxic levels, potentially leading to renal, gastrointestinal, and central nervous toxicity.[14-18] Both ibuprofen 1800 mg/day and naproxen 750 mg/day for 6 days have been demonstrated to increase previously stable lithium plasma levels, and the magnitude of this effect varied widely among individuals.[16,17] Ibuprofen produced a mean increase of 34% (range 12% to 66%),

An Echocardiographic Study of Interactions Between Pindolol and Epinephrine Contained in a Local Anesthetic Solution

Mitsutaka Sugimura, DDS,* Yasuaki Hirota, DDS, PhD,† Tohru Shibutani, DDS, PhD,† Hitoshi Niwa, DDS, PhD,† Tomonori Hori, DDS, †Yongsun Kim, DDS,† and Hideo Matsuura, DDS, PhD†

*Department of Dental Anesthesiology, Iwate Medical University, School of Dentistry, Iwate, Japan, and †Department of Dental Anesthesiology, Osaka University, Faculty of Dentistry, Osaka, Japan

An increasing number of dental patients are taking β-adrenergic blockers for the treatment of hypertension or angina pectoris. If epinephrine-containing local anesthetics are administered to such patients, interactions between epinephrine and the β-blocking agent may induce cardiovascular complications. We assessed in volunteers the effects of intraoral injection with 2% lidocaine containing 1:80,000 epinephrine (L-E) on cardiac function after pretreatment with the β-blocking agent pindolol. M-Mode echocardiography was used for the assessment. The injection of L-E after administration of pindolol did not alter cardiac preload, whereas it reduced the stroke volume, due to an increase in afterload and a decrease in myocardial contractility. Reductions in stroke volume and heart rate led to a decrease in cardiac output. Because total peripheral vascular resistance increased markedly, blood pressure was elevated despite the reduced cardiac output. These results suggest that cardiac function of dental patients on β-blocker therapy can be adversely affected by epinephrine-containing local anesthetics. Therefore, when such an anesthetic solution has to be used in patients on β-blocker therapy, careful systemic monitoring is needed.

Of the various drugs available for the treatment of cardiovascular disease, β-adrenergic blockers are among the most commonly used for controlling hypertension and angina pectoris.[1] The number of dental patients receiving chronic β-blocker therapy has been increasing in recent years. If epinephrine-containing local anesthetics are administered to these patients, drug interaction with β blockers may cause severe cardiovascular complications.[2–5] Surprisingly, little of the cardiovascular pathophysiology caused by these drug interactions has been studied. We therefore examined, using M-mode echocardiography, the cardiac effects of intraoral injection of epinephrine-containing 2% lidocaine after pindolol treatment in healthy young adults.

METHODS

The subjects were seven healthy adult male volunteers without a history of cardiac disease or hypertension. Their ages ranged from 25 to 33 yr (mean, 27.7 yr), and their weights from 58 to 71 kg (mean, 65.0 kg). Pindolol (Carvisken) was used as the β blocker. The local anesthetic used was 2% lidocaine containing 1:80,000 epinephrine (L-E). Each subject was given a 5-mg pindolol tablet and two cartridges of L-E (3.6 mL total volume, containing 45 μg of epinephrine and 72 mg of lidocaine).

Before β-blocker treatment, the subject rested in the supine position, and cardiac function was then assessed by measuring systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR). M-Mode echocardiography was also performed at this time. For M-mode echo measurements, a transducer was placed at the left margin of the sternum in the fourth intercostal space. Beams were generated in the direction that allowed simultaneous echo collection from the ventricular septum and the left ventricular posterior wall using two-dimensional guidance. Left ventricular end-diastolic diameter (EDD) was measured when the R wave on an electrocardiogram reached a peak. Left ventricular end-systolic diameter (ESD) was measured when

Received August 17, 1993; accepted for publication January 11, 1994.

Address correspondence to Dr. Mitsutaka Sugimura, Department of Dental Anesthesiology, Iwate Medical University, School of Dentistry, 1-3-27, Chuo-dori, Morioka, Iwate 020, Japan.

Anesth Prog 42:29–35 1995

ISSN 0003-3006/95/$9.50
SSDI 0003-3006(95)00023-W

Anesthetic Management of the Hypertensive Patient: Part I

Russell Yancey, DDS

PGY-2 Resident, New York University–Langone Hospital Dental Anesthesiology Service, Brooklyn, New York

Hypertension is an important health challenge that affects millions of people across the world and is a major risk factor for cardiovascular disease. It is critical that anesthesia providers have a working knowledge of the systemic implications of hypertension. This review article will discuss the medical definitions of hypertension, the physiology of maintaining blood pressure, outpatient treatment of hypertension, anesthetic implications, and the common medications used by anesthesia providers in the treatment of hypertension. Part I will provide an overview of hypertension and blood pressure regulation. In addition, drugs affecting predominantly renal control of hypertension, such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and renin-inhibiting agents, will be discussed. In part II, the remaining major antihypertensive medications will be reviewed as well as anesthetic implications of managing patients with hypertension.

Key Words: Hypertension; Antihypertensives; Anesthetic; Review.

Blood pressure typically fluctuates throughout the day, but hypertension, or high blood pressure, can cause undue stress on the patient's heart, vasculature, and other organs, leading to a variety of health problems. Those health problems include heart disease and stroke, which are the leading causes of death in the United States.[1] Almost half of Americans are identified as having high blood pressure according to the recent classification changes of high blood pressure in 2017 by the American Heart Association and the American College of Cardiology. Only an estimated 54% of those people have their condition under control.[2] Hundreds of thousands of deaths each year are primarily due to high blood pressure,[1] and this disease ends up costing patients in the United States $48.6 billion each year.[3]

Because of the growing public health concern that is associated with hypertension, it is important that dental providers are knowledgeable about the implications, management, and treatment options available for the hypertensive patient. This article will provide a contemporary review of the definition, physiology, pharmacologic management, and other concerns surrounding the anesthetic management of the hypertensive patient.

Received April 27, 2018; accepted for publication April 30, 2018.

Address correspondence to Dr Russell Yancey, 408 77th Street, Apt C4, Brooklyn, NY 11209; russellsmuscles@gmail.com.

Anesth Prog 65:131–138 2018 | DOI 10.2344/anpr-65-02-12

CLASSIFICATION AND GUIDELINES

There are 2 types of hypertension: essential hypertension and secondary hypertension. Essential hypertension accounts for approximately 95% of the cases and represents a form of hypertension without a clear cause.[4] However, many health care providers recognize that a number of factors may contribute to increased blood pressure, including but not limited to obesity, insulin resistance, high alcohol intake, high salt intake, aging, sedentary lifestyle, stress, low potassium intake, and low calcium intake.[5] Secondary hypertension has a clear etiology with many causes that may include renal disease, hyperthyroidism, obstructive sleep apnea, hyperaldosteronism, and many others.[4]

There are 4 levels of blood pressure, as outlined by the American Heart Association/American College of Cardiology in the updated 2017 guidelines (see Table 1). The choice and the naming of the categories were based on a pragmatic interpretation of blood pressure–related cardiovascular disease risk and benefit of blood pressure reduction in clinical trials. Prior to diagnosing a person with hypertension, it is important to use an average based on greater than 2 readings obtained on more than 2 occasions to estimate the individual's blood pressure level.[5] The new guidelines also recommend allowing patients to rest at least 5 minutes prior to taking the blood pressure readings and taking the blood pressure measurement while the patient is seated, feet on the floor, and the arm at the level of the heart with an appropriately sized cuff that encircles at least 80% of the arm.[5,6]

Slow Down to Brake: Effects of Tapering Epinephrine on Potassium

Sivaprasad Veerbhadran, MCh, CVTS,
Asher Ennis Nayagam, DNB, CVS,
Sandeep Ramraj, MD, and
Jaganathan Raghavan, MCh, CVTS

Department of Cardiovascular and Thoracic Surgery, Railway Headquarters Hospital, Perambur, Chennai; and Department of Anesthesia, Railway Headquarters Hospital, Perambur, Chennai, India

Hyperkalemia is not an uncommon complication of cardiac surgical procedures. Intractable hyperkalemia is a difficult situation that can even lead to death. We report on a postoperative case in a patient in whom a sudden decrease of epinephrine led to intractable hyperkalemia and cardiac arrest. We wish to draw the reader's attention to the issue that sudden discontinuation of epinephrine can lead to dangerous hyperkalemia.

(Ann Thorac Surg 2016;102:e37–8)

Hyperkalemia is often seen as a complication of cardiac surgical procedures. Intractable hyperkalemia is defined as hyperkalemia not responding to routine medical management (glucose insulin infusion, salbutamol nebulization diuresis, potassium binding agents, calcium gluconate). Intractable hyperkalemia is a difficult condition that can even lead to death. We wish the reader to understand that sudden stopping of epinephrine can lead to dangerous hyperkalemia.

A 3-year-old child who was diagnosed with double-outlet right ventricle (DORV), ventricular septal defect, and pulmonary stenosis was admitted to the hospital with a recurrent respiratory infection. Echocardiography showed DORV with a large subaortic ventricular septal defect with overriding of the aorta and the left pulmonary artery (PA) originating from the ascending aorta as its first branch. The patient was evaluated and was taken for intracardiac repair with left PA translocation. On cardiopulmonary bypass, the left PA transected from the aorta and was translocated to the main PA above the level of the pulmonary valve. The right ventricular outlet tract was dilated with a Hegar dilator. In view of the raised pulmonary vascular resistance from the left branch PAs, a bidirectional Glenn (BDG) procedure was performed. The patient was shifted to the intensive care unit (ICU) and was given 0.1 μg of epinephrine, a sildenafil infusion, and milrinone. After 12 hours, the patient was extubated. After extubation, the patient had stable hemodynamics, with a serum potassium level of 4.5 mmol. Because his blood pressures were very high, the epinephrine dose was reduced to 0.025 μg. Over the next 3 hours, the child's potassium level started rising, reaching 7.1 mmol, and it was did not respond to standard treatment (glucose insulin infusion, salbutamol nebulization, diuresis, potassium binding agents, calcium gluconate). As a result, peritoneal dialysis was started. After 2 hours, the patient had bradycardia and cardiac arrest. The patient was then resuscitated (cardiopulmonary resuscitation given for 5 minutes, followed by mechanical ventilation) and was stabilized with the same supports. Echocardiography demonstrated good BDG flow and ventricular function. Because a blood transfusion had been given, hemolysis was thought to be a cause of the hyperkalemia, but the patient's reticulocyte count was less than 0.9%. A complete workup for hemolytic anemia was performed, and the results were normal.

Once sudden tapering of epinephrine was recognized as a possible cause, the epinephrine was increased to 0.1 μg. Potassium levels dropped to normal gradually. After 2 days of continuing the same treatment, the child's cardiac output improved. Peritoneal dialysis was discontinued once urine output improved. The patient was subsequently extubated.

Comment

Hyperkalemia is often encountered in cardiac surgical ICUs and is defined as a potassium level greater than 5.5 mmol/L [1]. The physiology and potassium handling mechanisms have been extensively studied and reported [2, 3]. Most cases of hyperkalemia are secondary to renal dysfunction either at the glomerular level or at the distal convoluted tubules. Other causes are redistribution of potassium ion across the cellular membrane, a diet rich in potassium, and the use of potassium-affecting medications [4].

As for epinephrine and its effect on potassium, it is well known that epinephrine causes hypokalemia [5, 6]. This results from epinephrine-induced stimulation of β_2 receptors present in skeletal muscle that causes an intracellular shift of potassium. The reverse happens when epinephrine is tapered; in that situation, an extracellular shift leads to hyperkalemia.

Our patient had progressive worsening of hyperkalemia over a 6-hour period despite aggressive medical management. Review of ICU treatment records suggested to us that epinephrine was instantly reduced at the time high blood pressures occurred, which went unnoticed. This could be the most likely cause. Because this possibility was missed, a detailed evaluation for causes of secondary hemolytic anemia was done; the findings ultimately turned out to be normal. Because the patient's leukocytes and platelets were normal, pseudohyperkalemia was unlikely. Once the true cause was suspected, epinephrine was restored to the previous dose .The patient's complete recovery in this case is the result of a combination of early suspicion of the probable cause, prompt ICU intervention,

Accepted for publication Nov 9, 2015.

Address correspondence to Dr Veerbhadran, Department of Cardiovascular and Thoracic Surgery, Railway Headquarters Hospital, Perambur, Chennai, Tamil Nadu, India; email: sp116@rediffmail.com.

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2015.11.026

Expert Opinion on Pharmacotherapy

ISSN: 1465-6566 (Print) 1744-7666 (Online) Journal homepage: https://www.tandfonline.com/loi/ieop20

The pharmacological management of dental pain

Joseph V. Pergolizzi, Peter Magnusson, Jo Ann LeQuang, Christopher Gharibo & Giustino Varrassi

To cite this article: Joseph V. Pergolizzi, Peter Magnusson, Jo Ann LeQuang, Christopher Gharibo & Giustino Varrassi (2020): The pharmacological management of dental pain, Expert Opinion on Pharmacotherapy, DOI: 10.1080/14656566.2020.1718651

To link to this article: https://doi.org/10.1080/14656566.2020.1718651

Published online: 06 Feb 2020.

Australian Prescriber
VOLUME 40 : NUMBER 3 : JUNE 2017

ARTICLE

Peptic ulcer disease and non-steroidal anti-inflammatory drugs

SUMMARY

Non-steroidal anti-inflammatory drugs including low-dose aspirin are some of the most commonly used medicines. They are associated with gastrointestinal mucosal injury.

Before prescribing, it is important to assess the patient's gastrointestinal risk factors such as age and history of peptic ulcers. Patients at high risk may require co-prescription to reduce the risk of peptic ulcers.

A daily dose of a proton pump inhibitor is the most effective method of reducing the risk of ulcers induced by non-steroidal anti-inflammatory drugs.

Musa Drini
Associate lecturer
Medical School
Australian National University

Staff specialist
Canberra Hospital

Gastroenterologist
gastrotrACT

Canberra

Keywords
misoprostol, non-steroidal anti-inflammatory drugs (NSAIDs), peptic ulcers, proton pump inhibitors

Aust Prescr 2017;40:91–3
http://dx.doi.org/10.18773/austprescr.2017.037

CPD FOR PHARMACISTS

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Introduction

A peptic ulcer is a defect in the upper gastrointestinal mucosa that extends through the muscularis mucosa into deeper layers of the gut wall. There are two major risk factors for peptic ulcer disease – *Helicobacter pylori* and non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs including low-dose aspirin are some of the most commonly used drugs. They have good efficacy and a long history of clinical use, but can cause peptic ulcers which may have fatal complications.[1] Given widespread use of NSAIDs and aspirin, the associated gastrointestinal toxicities have substantial implications for the healthcare system.[2]

Mechanism of action

The therapeutic effects of NSAIDs are mediated by their inhibition of prostanoid biosynthesis.[3] Prostanoid derivatives arise from the conversion of arachidonic acid by cyclo-oxygenase (COX) isoenzymes following cell injury.

There are two distinct isoforms of COX. COX-1 is present in the majority of cells including endothelial cells, gastrointestinal epithelium and platelets, and functions continuously. In contrast COX-2 is present in only a few tissues and is induced by inflammation. NSAIDs exert their therapeutic anti-inflammatory and analgesic effects by inhibiting COX-2. The gastric and renal toxicities of the drugs are related to inhibition of the COX-1 isoform.[4,5] There is a spectrum of COX-1 and COX-2 inhibition across the class of NSAIDs.

Ulcers and NSAIDs

Peptic ulcer disease is a well-recognised complication of NSAID use. Inhibition of COX-1 in the gastrointestinal tract leads to a reduction of prostaglandin secretion and its cytoprotective effects in gastric mucosa. This therefore increases the susceptibility to mucosal injury.[6] Inhibition of COX-2 may also play a role in mucosal injury.

Risk factors

Gastrointestinal toxicity with NSAIDs, including low-dose aspirin, is highest in patients with risk factors. These include increased age (>65 years), past history of peptic ulcer disease, heart disease, and co-prescription of antiplatelets, corticosteroids and anticoagulants. In addition, using higher doses of NSAIDs leads to an increased risk of upper gastrointestinal complications.[7] Prolonged NSAID use and *H. pylori* infection are also associated with an increased risk of gastrointestinal toxicity.

In patients who are chronic users of NSAIDs and who have no risk factors, only 0.4% have serious adverse events. However, the risk is as high as 9% in patients with multiple risk factors.[8] Before prescribing for a patient with risk factors always consider if there are alternatives to NSAIDs.

Which NSAID to use?

All NSAIDs cause some degree of gastrointestinal toxicity. Large pooled data from placebo-controlled trials show that all evaluated NSAIDs including COX-2 inhibitors, diclofenac, ibuprofen and naproxen were associated with an increased risk of gastrointestinal injury.[9] However, this risk varies between the drugs. The relative risk of upper gastrointestinal complications for aceclofenac, celecoxib and ibuprofen is low (<2). Diclofenac, meloxicam and ketoprofen are intermediate (2–4) while naproxen, indomethacin and diflunisal have a higher relative risk (4–5). The highest pooled relative risk is associated with piroxicam (7.4) and ketorolac (11.5).[7]

Nonsteroidal anti-inflammatory drugs and antihypertensives: how do they relate?

Zovinar Der Khatchadourian, DDS,[a,*] Isabel Moreno-Hay, DDS, PhD,[b,*] and Reny de Leeuw, DDS, PhD, MPH[c]
McGill University, Montreal, Quebec, Canada; University of Kentucky, Lexington, KY, USA

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely available as over-the-counter medications, despite their numerous side effects and drug interactions. The aim of this article is to increase awareness of the hypertensive potential of NSAIDs and their interference with antihypertensives. Patients with hypertension appear to be more susceptible than normotensive individuals to the blood pressure–increasing effect of NSAIDs. Most studies have found that short-term use of NSAIDs does not pose a major risk for hypertension or increase in cardiovascular disease in healthy individuals. The calcium channel blockers and β-blockers seem to be least affected by the concomitant use of NSAIDs. A dentist must weigh the benefits and disadvantages of using NSAIDs in patients taking antihypertensive drugs. For those who may be at greater risk, such as patients with hypertension and the elderly, careful selection of the class of NSAID and close monitoring are appropriate measures, especially if long-term use is anticipated. (Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117: 697-703)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely available as over-the-counter medications in drugstores and supermarkets not only in the United States but also worldwide. In 2010, an estimated US $1.1 billion were spent on nonnarcotic analgesic drugs in the United States.[1]

NSAIDs are very commonly used medications despite their numerous side effects and drug interactions. For instance, the acute administration of NSAIDs has been associated with serious adverse outcomes, such as allergic reactions, renal failure, coagulation problems, and worsening of asthma. Furthermore, the long-term administration of NSAIDs can cause serious gastrointestinal (GI) adverse effects (e.g., bleeding, ulcers), renal failure, and congestive heart failure.[2-4] Minor side effects, such as nausea, dizziness, or gastric irritation, have also been reported.[4-6] Several studies have found that the risk for complications increases in susceptible patients, for example those who present with a history of ulcers, cardiovascular disease, diabetes, or renal complications.[7,8] The risk of deleterious effects with NSAID use is increased in the elderly population,[4,5,9] yet Seager and Hawkey[9] found in their study that over half of 24 million NSAID prescriptions written in a year in the United Kingdom were prescribed to the elderly population. Owing to the deleterious effects of NSAIDs, Seager and Hawkey[9] debated whether NSAIDs should be prescribed to manage conditions that are not life-threatening. Often overlooked is the fact that long-term use of NSAIDs can cause hypertension.[10]

NSAIDs also have numerous drug interactions. For instance, most NSAIDs affect platelet function, leading to increased risk of bleeding, when administered with other drugs that impair hemostasis, such as warfarin and selective serotonin reuptake inhibitors. NSAIDs also displace many other drugs, including warfarin and anticonvulsants, from albumin, thus leading to increased risk of bleeding and potentially toxic levels of the displaced drugs. Other oftenoverlooked interactions of NSAIDs follow from their reduction of the renal sodium excretion and inhibition of prostaglandin (PG) synthesis. These actions attenuate the effects of several classes of antihypertensive medications.[11,12]

The aim of this article is to increase awareness of the blood pressure (BP)–increasing potential of NSAIDs and their interference with antihypertensives. First we provide an overview of the prevalence of hypertension and the effect it may have on cardiovascular disease (CVD). We then discuss the mechanisms of action of NSAIDs, with emphasis on their potential to increase BP. Finally, we discuss the most common antihypertensive medications and describe how NSAIDs may interfere with their actions.

Statement of Clinical Relevance

Dentists should be aware that NSAIDS can increase blood pressure, especially in patients with hypertension. In addition, NSAIDs can interfere with the blood pressure–lowering mechanisms of antihypertensives.

*These authors have equally contributed to the article.
[a]Faculty Lecturer, Montreal General Hospital, Faculty of Dentistry, McGill University.
[b]Resident, Orofacial Pain Center, College of Dentistry, University of Kentucky.
[c]Professor and Chief, Division of Orofacial Pain, University of Kentucky.
Received for publication Jul 30, 2013; returned for revision Feb 4, 2014; accepted for publication Feb 21, 2014.

2212-4403/$ - see front matter
http://dx.doi.org/10.1016/j.oooo.2014.02.028

The Effects of Nonsteroidal Anti-Inflammatory Drugs on Blood Pressure in Hypertensive Patients

Stanley Snowden, PharmD, and Robert Nelson, PharmD Candidate†*

Abstract: Nonsteroidal anti-inflammatory drugs (NSAIDs) are ubiquitous medications used by a wide range of people from otherwise healthy normotensive patients to hypertensive patients with many significant comorbidities. Through a variety of mechanisms related to prostaglandin inhibition, including sodium retention and vasoconstriction, these agents may increase blood pressure. This leads to potentially detrimental effects. A review of the current literature regarding this topic yielded 2 meta-analyses and 10 randomized controlled trials. There is evidence of small blood pressure increases in normotensive patients taking NSAIDs approximating +1.1 mm Hg. Patients with treated hypertension show variable increases with NSAID treatment, ranging up to +14.3 mm Hg for systolic pressure and +2.3 mm Hg for diastolic blood pressure. Most antihypertensive medications seem to have decreased effects with concomitant NSAID administration, with the exception of calcium channel blockers. Given the current literature, it appears that NSAIDs increase blood pressure in patients with controlled-hypertension, but the quantity of this increase is variable. If possible, patients who have hypertension should avoid taking NSAIDs.

Key Words: hypertension, nonsteroidal anti-inflammatory drugs, cyclooxygenase-inhibitors

(*Cardiology in Review* 2011;19: 184–191)

One of the most common disease states that clinicians encounter is hypertension. The prevalence of hypertension in American adults has been estimated at 32%.[1] Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications. In the United States alone, 23% of adults over 18 years of age use ibuprofen and 3.5% use naproxen.[2] NSAIDs are commonly used for minor injuries, headaches, fever, rheumatoid arthritis (RA), and osteoarthritis (OA), among other indications. It is therefore quite probable that many patients will at some point, and perhaps chronically, take NSAIDs, even if they have hypertension.

Nonsteroidal anti-inflammatory drugs function by inhibiting the cyclooxygenase (COX) enzymes that produce prostaglandins (PGs).[3] Cyclooxygenase enzymes are divided between the COX-1 and COX-2 isoforms. COX-1 enzymes are considered to be constitutive in most tissues, whereas COX-2 enzymes are upregulated with inflammation and cellular injury,[4] although they are also constitutive in the brain and kidney.[5]

NSAIDs as a drug class are divided between the nonselective and COX-2 selective categories. Nonselective NSAIDs bind both forms of the enzymes, with examples such as ibuprofen, naproxen, indomethacin, and piroxicam. Relative COX-1 and 2 selectivity for nonselective NSAIDs are presented in Table 1. COX-2 selective NSAIDs include celecoxib, and the previously marketed rofecoxib and valdecoxib. Lumiracoxib, etoricoxib, and parecoxib are COX-2 inhibitors that are not marketed in the United States. Lumiracoxib is available in South America and central Europe.[6] Etoricoxib is marketed in South America, Europe, the Middle East, and Southeast Asia. Parecoxib is found in Europe, Southeast Asia, Australia, and New Zealand.

A common adverse effect of NSAIDs is gastrointestinal (GI) mucosal breakdown. This is caused by decreased production of PGs by COX-1 enzymes in the GI mucosa.[7] Avoiding GI ulceration was the driving force behind the creation of COX-2 selective NSAIDs. The COX-2 selective NSAIDs have indeed been shown to have decreased GI effects,[8,9] but some have been implicated in increasing the risk of myocardial infarction.[9] This led to the discontinuation of marketing for all COX-2 inhibitors in the United States except for celecoxib. Celecoxib was spared from discontinuation because of conflicting data on the risk of cardiovascular (CV) adverse events related to its use. Two trials[10,11] comparing celecoxib and placebo for prevention of colorectal adenomas found an increased risk for CV-related death with celecoxib use, whereas another trial[12] comparing celecoxib with ibuprofen or diclofenac in OA and preliminary results from a trial[13] comparing celecoxib, naproxen, and placebo in prevention of Alzheimer disease showed no increased risk for celecoxib.

It is thought that NSAIDs may affect blood pressure (BP) because of their inhibition of PG production via the COX enzymes. Prostaglandins E_2 and I_2 have been shown to be potent smooth muscle vasodilators.[14] The production of PGI_2 has been shown to be decreased in COX-2-inhibited subjects.[15] It is possible that the decrease in PGI_2 allows for greater vasoconstrictive effects from endothelin.[16] Likewise, PGI_2 and PGE_2 seem to attenuate the release of norepinephrine.[17] Natriuresis mediated by PGE_2 in the thick ascending loop of Henle and collecting duct is decreased by NSAID treatment.[18] Sodium retention caused by NSAIDs is known to occur in up to 25% of patients and may contribute to BP increases.[19] Another possible explanation for BP increases is that by blocking the COX enzymes, arachidonic acid is shunted to cytochrome P450 enzymatic pathways. Some of the metabolites generated through these pathways, including various epoxyeicosatrienoic and hydroxyeicosatetraenoic acids, have been identified as having vasoconstrictive properties.[20]

There has been significant controversy regarding the safety of using NSAIDs in hypertensive patients. This review article seeks to discern what effect NSAIDs have on blood pressure, specifically in hypertensive patients.

METHODS

A literature search was conducted using PubMed with the following search terms: "hypertension," "blood pressure," "nonsteroidal anti-inflammatory drugs," and "cyclooxygenase 2 inhibitors." These terms were cross referenced with each other with the following limits: humans, clinical trial, meta-analysis, randomized controlled trial, clinical trial, phase III, clinical trial, phase IV, comparative study, controlled clinical trial, journal article, English, and all adults from January 1, 1991 to March 8, 2011. The publi-

From the *Pharmacy Administration, University of New Mexico Hospital, Albuquerque, NM; and †College of Pharmacy, University of New Mexico, Albuquerque, NM.

Correspondence: Stanley Snowden, PharmD, Pharmacy Administration, University of New Mexico, 2211 Lomas Blvd NE, Albuquerque, NM 87106. E-mail: ssnowden@salud.unm.edu.

ISSN: 1061-5377/11/1904-0184

DOI: 10.1097/CRD.0b013e31821ddcf4

FPIN's Clinical Inquiries

Cardiovascular Effects of NSAIDs

KAITYANN SHERVE, PharmD; CHRISTOPHER J. GERARD, MD; and JON O. NEHER, MD
Valley Family Medicine Residency, Renton, Washington
LEILANI ST. ANNA, MLIS, AHIP, *University of Washington Health Sciences Library, Seattle, Washington*

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Clinical Question

Do nonsteroidal anti-inflammatory drugs (NSAIDs) cause a clinically significant increase in blood pressure?

Evidence-Based Answer

Aspirin does not elevate blood pressure. Among nonselective NSAIDs, ibuprofen increases the risk of hypertension and stroke. Diclofenac does not increase the risk of hypertension, but does increase the risk of stroke. Naproxen (Naprosyn) does not increase the risk of hypertension or stroke. Celecoxib (Celebrex) does not increase the risk of hypertension or stroke.

Evidence Summary

ASPIRIN AND NONSELECTIVE NSAIDS

Two meta-analyses (N = 158 studies) evaluated aspirin trials that included data on blood pressure.[1,2] Aspirin dosages were greater than 1.5 g per day. There was no statistically significant effect on blood pressure. In a trial of 18,700 patients with hypertension, participants were randomized to receive aspirin (75 mg daily) or placebo for a mean of 3.8 years.[3] There was no effect on blood pressure. There were significant reductions in rates of myocardial infarction among participants who were also receiving angiotensin-converting enzyme inhibitors (risk ratio [RR] = 0.39; 95% confidence interval [CI], 0.21 to 0.71).

A systematic review identified 32 randomized controlled trials (RCTs) that included 3,626 patients who were treated for at least four weeks with nonselective NSAIDs.[4] Patients were monitored for changes in blood pressure and rates of hypertension during treatment. Most studies enrolled patients with osteoarthritis or rheumatoid arthritis, although some included patients with other conditions. Patients who received ibuprofen had a greater incidence of new hypertension compared with those in the control group (2.9% vs. 1%; RR = 2.9; 95% CI, 1.4 to 5.7; number needed to harm = 53).

CYCLOOXYGENASE-2 INHIBITORS

A meta-analysis of 19 RCTs that included 45,000 patients with arthritis evaluated blood pressure after more than four weeks of treatment with cyclooxygenase-2 inhibitors, nonselective NSAIDs, or placebo[5] *(Table 1[1,5-7])*. Another meta-analysis that included 49 RCTs with 130,000 patients—most of whom had arthritis—evaluated the effects of these agents on the diagnosis of hypertension after more than four weeks of treatment.[6] Celecoxib was not associated with an increased rate of hypertension. The study did not report absolute risk changes or provide numbers needed to treat or harm.

CARDIOVASCULAR OUTCOMES

A meta-analysis compared the cardiovascular safety of naproxen, ibuprofen, diclofenac, and celecoxib.[7] It included 31 RCTs (N = 120,000 patients) that had more than 100 patient-years of follow-up per treatment arm, and that reported on the cardiovascular end points of myocardial infarction, stroke, cardiovascular death, and death from any cause *(Table 1[1,5-7])*. None of the drugs significantly increased the risk of myocardial infarction. Compared with placebo, diclofenac increased the risk of stroke, the total cardiovascular death rate (rate ratio = 4.0; 95% CI, 1.5 to 13), and all-cause mortality (rate ratio = 2.3; 95% CI, 1.0 to 4.9). Ibuprofen, naproxen, and celecoxib had no significant effect on the total cardiovascular death rate or all-cause mortality.

Therapeutics and Clinical Risk Management

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REVIEW

Adverse drug reactions and drug–drug interactions with over-the-counter NSAIDs

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management
15 July 2015
Number of times this article has been viewed

Nicholas Moore[1]
Charles Pollack[2]
Paul Butkerait[2]

[1]Department of Pharmacology, Université de Bordeaux, Bordeaux, France; [2]Pfizer Consumer Healthcare, Madison, NJ, USA

Abstract: Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen have a long history of safe and effective use as both prescription and over-the-counter (OTC) analgesics/antipyretics. The mechanism of action of all NSAIDs is through reversible inhibition of cyclooxygenase enzymes. Adverse drug reactions (ADRs) including gastrointestinal bleeding as well as cardiovascular and renal effects have been reported with NSAID use. In many cases, ADRs may occur because of drug–drug interactions (DDIs) between the NSAID and a concomitant medication. For example, DDIs have been reported when NSAIDs are coadministered with aspirin, alcohol, some antihypertensives, antidepressants, and other commonly used medications. Because of the pharmacologic nature of these interactions, there is a continuum of risk in that the potential for an ADR is dependent on total drug exposure. Therefore, consideration of dose and duration of NSAID use, as well as the type or class of comedication administered, is important when assessing potential risk for ADRs. Safety findings from clinical studies evaluating prescription-strength NSAIDs may not be directly applicable to OTC dosing. Health care providers can be instrumental in educating patients that using OTC NSAIDs at the lowest effective dose for the shortest required duration is vital to balancing efficacy and safety. This review discusses some of the most clinically relevant DDIs reported with NSAIDs based on major sites of ADRs and classes of medication, with a focus on OTC ibuprofen, for which the most data are available.

Keywords: adverse effects, nonsteroidal anti-inflammatory drugs, gastrointestinal, cardiovascular, renal

Introduction

Cyclooxygenase (COX) inhibitors, commonly called nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, diclofenac, and naproxen, have anti-inflammatory and analgesic/antipyretic properties across a wide range of dosing regimens. Prescription-strength NSAIDs are effective for relief of chronic musculoskeletal pain and inflammation in conditions such as rheumatoid arthritis (RA) or osteoarthritis (OA).[1,2] Lower, over-the-counter (OTC) doses of NSAIDs are effective for short-term (eg, ≤10 days) relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, common cold, muscular aches, and arthritis.[3] NSAIDs taken at OTC doses can also be effective at relieving painful episodes in patients with chronic diseases such as OA.[4] Ibuprofen is an NSAID with a long history of safe and effective use at both prescription (maximum 2,400–3,200 mg/d) and OTC (<1,200 mg/d) doses.[3,5] Single-dose studies using OTC doses have confirmed that ibuprofen (400 mg) provides superior analgesic efficacy to acetaminophen (1,000 mg).[6,7]

All NSAIDs inhibit COX, an enzyme that converts arachidonic acid to prostaglandins, thereby mediating pain, inflammation, and fever. In the process,

Correspondence: Nicholas Moore
Department of Pharmacology, U657, Université de Bordeaux, 146 rue Leo Saignat, F-33076, Bordeaux, France
Tel +33 5 5757 1560
Fax +33 5 5757 4671
Email nicholas.moore@pharmaco.u-bordeaux2.fr

http://dx.doi.org/10.2147/TCRM.S79135

AJH 2003; 16:135–139

Effects of Nabumetone, Celecoxib, and Ibuprofen on Blood Pressure Control in Hypertensive Patients on Angiotensin Converting Enzyme Inhibitors

Robert Palmer, Robert Weiss, Randall M. Zusman,
Ann Haig, Susan Flavin, and Brian MacDonald

Nonsteroidal anti-inflammatory drugs interfere with certain antihypertensive therapies. In a double-blind study, 385 hypertensive patients stabilized on an angiotensin converting enzyme inhibitor were treated with nabumetone, celecoxib, ibuprofen, or placebo for 4 weeks. Ibuprofen caused significantly greater increases in systolic ($P < .001$) and diastolic ($P < .01$) blood pressures (BPs) compared to placebo, but not nabumetone or celecoxib. The proportion of patients with systolic BP increases of clinical concern at end point was significantly higher ($P < .001$) for the ibuprofen group (16.7%; 15 of 90), but not for the nabumetone group (5.5%; 5 of 91) or the celecoxib group (4.6%; 4 of 87) compared to the placebo group (1.1%; 1 of 91). Am J Hypertens 2003;16:135–139

Key Words: Hypertension, nabumetone, angiotensin converting enzyme inhibitor, celecoxib.

Hypertension and arthritis are common comorbid conditions, especially in the elderly. Among the elderly, 12% to 15% take nonsteroidal anti-inflammatory drugs (NSAID) and antihypertensive medication concurrently.[1] The NSAID have been shown to attenuate the blood pressure (BP)-lowering effects of diuretics, β-blockers, α-blockers, and angiotensin converting enzyme (ACE) inhibitors,[2,3] leading to a loss of BP control in a substantial proportion of patients. Using a meta-analysis of randomized clinical trials, the effect of NSAID on BP in patients taking antihypertensive agents was evaluated.[4,5] These studies found that NSAID increased mean BP by approximately 5 mm Hg in patients taking antihypertensive therapy.[4,5] Such elevations in BP may be clinically important, as studies have shown that during several years an increase of 5 to 6 mm Hg in diastolic BP may be associated with a 67% increase in risk of stroke and a 15% increase in coronary heart disease events.[1,6] Therefore, large numbers of patients may be placed at risk of cardiovascular events because of the NSAID interaction with antihypertensive drugs.

The exact mechanism for the NSAID effect on BP is unclear, but most likely involves inhibition of renal prostaglandin synthesis. Prostaglandins play an important role in the control of renal function by way of a variety of regulatory mechanisms, including enhanced sodium and potassium excretion and control of renal blood flow.[2] Renal function is especially dependent on prostaglandin synthesis under conditions of volume depletion or reduced renal perfusion, such as congestive heart failure, where prostaglandins maintain renal blood flow.[2]

Not all NSAID have the same effect on renal function.[2,4,5] The adverse cardiorenal effects of ibuprofen have been well documented when combined with ACE inhibitors.[3,7] Although cyclooxygenase-2 (COX-2) selective inhibitors have less gastrointestinal toxicity than traditional NSAID, they retain the adverse cardiorenal side effects of conventional NSAID.[8] The COX-2 selective NSAID have been associated with increases in BP,[8,9] diminished renal function,[8,10] and elevated risk of myocardial infarction.[11] Nabumetone, a pro-drug that is converted in the liver to the active metabolite 6-methoxy 2-naphthylacetic (6-

Received June 11, 2002. First decision July 27, 2002. Accepted September 12, 2002.

From the SmithKline Beecham Pharmaceuticals (RP, AH, SF, BM), a wholly owned subsidiary of GlaxoSmithKline Pharmaceuticals, Collegeville, Pennsylvania; Androscoggin Cardiology Associates (RW), Auburn, Maine; and Harvard Medical School (RMZ), Boston, Massachusetts.

This research was supported by SmithKline Beecham Pharmaceuticals a wholly owned subsidiary of GlaxoSmithKline Pharmaceuticals, Collegeville, PA.

The results of this research were presented at the Sixteenth Annual Meeting of the American Society of Hypertension, May 15–19, 2001, San Francisco, California.

Address correspondence and reprint requests to Ann Haig, BSN, GlaxoSmithKline Pharmaceuticals, Oncology and Musculoskeletal diseases, 1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989; e-mail: ann.e.haig@gsk.com

0895-7061/03/$30.00
PII S0895-7061(02)03203-X