ECRONICON OPEN ACCESS

EC DENTAL SCIENCE
Review Article

Pharmacological Interactions of Drugs Used in Odontology. Implications in Patients with Systemic Diseases

Claudio Viveros Amador[1]*, María Dolores Jiménez Farfán[1], Juan Carlos Hernández Guerrero[1], Adán Horacio Viveros Amador[2], Cuauhtli X Serrato Zapata[3] and Héctor Calvillo López[3]

[1]Laboratorio de Inmunología, División de Estudios de Posgrado e Investigación, Facultad de Odontología, Universidad Nacional Autónoma de México, Circuito de la Investigación Científica s/n, Ciudad Universitaria, Ciudad de México, CP, México

[2]Hospital de Alta Especialidad "Manuel Ávila Camacho" Instituto Mexicano del Seguro Social, Centro, Puebla, México

[3]Centro de Rehabilitación y Educación Especial Zapata CREE, Avenida de la Salud s/n, Palo Escrito, Emiliano Zapata, Morelos, CP, México

***Corresponding Author:** Claudio Viveros Amador, Laboratorio de Inmunología, División de Estudios de Posgrado e Investigación, Facultad de Odontología, Universidad Nacional Autónoma de México. Circuito de la Investigación Científica s/n, Ciudad Universitaria, Ciudad de México, CP, México.

Received: June 26, 2020; **Published:** July 23, 2020

Abstract

Due to the increase of systemic diseases worldwide, patients under pharmacotherapeutic regimens for the treatment of their illnesses could require dental care and the administration of additional medications. The main way for a dental professional to make an adequate diagnosis is through an exhaustive review of the clinical antecedents of the patient. A correct diagnosis and a complete clinical history of the patient, including the prescribed drugs, is of great relevance because errors will invariably lead to treatments that can aggravate the disease or resolve poorly the underlying health problem. For this reason, no procedures should be performed if the clinical antecedents of the patient and the exploration are incorrect or incoherent. On the other hand, the need to know the interactions of drugs that can occur in a patient under medical treatment, even for short terms, is to be pointed out, especially in the most susceptible patients, like the elderly or patients with cardiopathies. Management of pain and infection is common in dental treatments and the substances commonly used in the dental practice for their control are non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics and local anesthetics that contain vasoconstrictors, capable of generating pharmacological interactions that can diminish the effect of the medical prescription, increase or exacerbate a biological response. Knowledge of the pharmacokinetic and pharmacodynamics drug interactions diminishes the risk of compromising the medical/dental treatment.

Keywords: *Pharmacological Interactions; NSAIDs; Antibiotics; Local Anesthetics*

Introduction

Dental surgeons play a very relevant role in the prescription of polymedicated patients due to systemic diseases. Cardiovascular diseases are the most common cause of death in the world, and uncontrolled hypertension is a harbinger of such poor outcomes [1]. Seven million deaths worldwide each year are attributed to hypertension. Moreover, WHO estimates that, globally, 422 million adults aged over 18 years were living with diabetes in 2014 [2]. Given the high morbidity and mortality of these two diseases worldwide, it is crucial to

consider that the ill patient with or without medical treatment, can develop undesirably responses when using different types of drugs during and after the dental treatment.

The management of pain and infection is common practice in dental patients [3-5]. Non- nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used drugs [3]. While these drugs have positive benefits in terms of reducing pain and inflammation, they also have potentially serious adverse effects, including gastrointestinal bleeding and kidney failure [6]. In dental care, before, during, and after the intervention, it could be necessary to prescribe different NSAIDs, anesthetics, or antibiotics that could result in combinations with adverse or non-desired effects. The inhibition of the COX enzyme by NSAIDs attenuate the antihypertensive efficacy of the angiotensin-converting-enzyme inhibitors (ACEI) producing an increase in blood pressure (BP) of 5 to 10 mmHg. Patients with controlled BP under different antihypertensive regimens have shown that the COX-2 inhibitors attenuate the antihypertensive effect of the ACEI and beta-blockers [7]. Also, ibuprofen can incidentally induce hypoglycemia in diabetic patients who receive sulphonylurea therapy [8]. This phenomenon has raised the questions whether or not NSAIDs in conventional dosage can be used for the treatment of hyperglycemia in patients who have non-insulin-dependent diabetes mellitus and whether or not NSAIDs added to preexistent hypoglycemic drug therapy taken orally may lead to unanticipated hypoglycemia [9]. Hypertensive patients receiving nonselective β-adrenergic antagonists are vulnerable to hypertension and bradycardia when injected with dental local anesthetic formulations containing epinephrine [10].

The main pharmacological interactions among drugs of common use in the dental practice and those used for the treatment of the most common systemic diseases are exposed in this review, along with the therapeutic strategies targeting this process.

Methods

A literature search was conducted using the electronic databases included from 2005, open access, Medline, Embase and Cochrane Database. The search strategy used the terms 'Blood Pressure' or 'Hypertension' combined sequentially with, 'NSAIDs', type 2 diabetes and inflammation," "NSAIDs in type 2 diabetes," "COX inhibition in type 2 diabetes", "NSAIDs' and antibiotics", "vasoconstrictors and antidepressors", "vasoconstrictors and antihypertensives". The publications discussed in this article review pertinent literature published before 2005. Filters were applied to include both observational and experimental studies on human models. An exclusion criteria was applied for animal or *in vitro* studies. In this review, papers were selected using the following criteria: English-language articles, studies conducted in adults, meta-analyses, randomized active or placebo-controlled trials, prospective studies, observational studies, reporting changes in blood pressure were reviewed.

Mechanism of increased cardiovascular risk with NSAIDs

There are two functional types of enzyme cyclo-oxygenase (COX) that produces prostanoids associated to physiological and pathological responses [11]. COX-1 is present in most tissues and is involved in the gastrointestinal protection, vascular homeostasis, renal hemodynamics and platelet function [12-14]. The mechanism by which NSAIDs promote hypertension is related to the inhibition of COX-1 that also prevents natriuresis and local renal vasodilation, mechanisms that help to regulate the BP. NSAIDs elevate levels of serum aldosterone, which also contributes to sodium retention and, thus, to edema and hypertension [15]. On the other hand, COX-2 induces the production of pro-inflammatory prostanoids responsable of symptoms as pain, heat and swelling. COX-2 regulates other processes as ovulation, ovular implantation, labor induction and reproduction [16]. It has also pathophysiological roles in the central nervous system [17] and participates in malignant transformation [18]. In general terms, the benefits of NSAIDs for their analgesic and anti-inflammatory properties come from COX-2 blockade, whereas most of the side effects come from COX-1 blockade [6]. NSAIDs and COX-2 selective inhibitors may also impair the vasodilatory benefits of prostacyclin [19]. Loss of this mechanism of vasodilation in the face of numerous vasoconstrictors (e.g. angiotensin, catecholamines, endothelin) may potentially lead to increases in systemic vascular resistance and, subsequently, to increases in mean arterial pressure [20].

The association between NSAIDs and hypertension may in part be mediated through potential effect on endothelial function. Endothelial thiols such as glutathione (GSH)-a major intracellular redox buffer that function as cofactor for many antioxidant enzymes-, may

mediate some of the beneficial effects of nitric oxide [21,22]. On the other hand, there are not yet enough clinical data on aspirin in the vascular function and the BP [23]. Currently, the evidence suggests its use for the secondary prevention, for example in patients with atherosclerosis, but the use for primary prevention remains controversial [24].

NSAIDs and beta-adrenergic antagonists

In normotensive and untreated hypertensive patients, NSAIDs are probably having a weak effect on blood pressure [23]. The addition of a NSAID to antihypertensive drugs could reduce the efficacy of antihypertensives, with a poor control of blood pressure. Several classes of antihypertensives are more prone to suffer this interaction: renin-angiotensin-aldosterone inhibitors, diuretics and beta-blockers (Table 1). Elderly patients with hypertension may suffer significant changes in blood pressure control [25]. A proposed mechanism to explain this effect with beta-adrenergic antagonists is that inhibition of PGs by NSAIDs could increase sensitivity to the vasoconstrictor effects of sympathetic nervous system stimulation. Blocking beta receptors increases this sensitivity of the alpha sympathetic nervous system, resulting in abolishment of the blood pressure lowering effect of beta-adrenergic antagonists. Further, some beta-adrenergic antagonists reduce the glomerular filtration rate. In the long-term, this could increase the sensitivity to blood pressure increases by NSAIDs. This effect was observed in 3928 patients prescribed with NSAIDs or acetaminophen and evaluated in a retrospective cohort study that included adult patients who had received their first prescription for NSAID from the general medicine practice of Wishard Health Services in Indianapolis, USA. In this study Hisham., *et al*. observed that the main effect has important implications for those patients with heart failure and hypertension prescribed beta-adrenergic antagonists [20].

NSAID with antihypertensive drugs	Mechanism	Outcome/Result
Beta-adrenergic antagonist	Inhibition of PGs by NSAIDs could increase sensitivity to the vasoconstrictor effects of sympathetic nervous system stimulation [20].	Abolishment of the blood pressure lowering effect of beta-adrenergic antagonist.
Renin-angiotensin-aldosterone system inhibitors	Reduction in prostaglandin synthesis induced by NSAID [32].	Loss of prostaglandins action on vasodilatation to preserve renal blood flow.
Calcium channel antagonist	No interaction reported [25,26].	Patients treated with calcium antagonist can recieve NSAIDs safetly.
Diuretics	Diuretics con lead to hypovolemia and NSAIDS cause inhinition of prostaglacyclin synthesis [33].	Renal afferent arteriolar vasoconstriction. Hipovolemia exerted by diuretics is exacerbated by the vasoconstrictive effect of NSAIDs.

Table 1: *Interaction of NSAIDs with antihypertensive drugs. Classes of antihypertensives prone to suffer this interaction: renin-angiotensin-aldosterone inhibitors, diuretics, and beta-blockers.*

NSAIDs and calcium channel antagonists

Most antihypertensive medications seem to have decreased effects with concomitant NSAID administration, except for calcium channel antagonists and centrally acting sympatholytic drugs [25,26]. Calcium-channel blockers (CCBs) (dihydropyridines [DHPs] and non-dihydropyridines [NDHPs)] have been proposed as a treatment option for patients with hypertension, especially in resistant hypertension and/or when blockers of the renin angiotensin system are not tolerated [6]. There are two major categories of calcium channel antagonists based on their primary physiological effects. They have inhibitory effects on the sinoatrial and atrioventricular nodes resulting in a

slowing of cardiac conduction and contractility. This allows for the treatment of hypertension, reduces oxygen demand, and helps to control the rate in tachydysrhythmias [27]. Ivančica., *et al*. in a prospective clinical trial, in a family practice included 88 treated hypertensives aged over 55 years; 39 controls and 49 also taking NSAIDs for osteoarthritis, they observed that subgroups taking ibuprofen or piroxicam, in the amlodipine subgroups, or in phase II with acetaminophen, the baseline of BP values did not vary substantially [28]. Two reports showed that the combination of celecoxib and amlodipine provided similar BP reduction to an equal dose of amlodipine alone without an increase in adverse effects, at least in the very short term [29,30].

NSAIDs and inhibitors of the renin-angiotensin-aldosterone (RAAS) system

Because of the routine use of NSAIDs, post-operative patients using concomitant diuretics and/or RAAS-inhibitor therapy are prone to an interaction. A known adverse effect of NSAIDs is the occurrence of decreased renal function. This decrease in renal function is directly related to the reduction in prostaglandin synthesis induced by NSAIDs treatment. In subjects without renal impairment, prostaglandins do not play a major role in the regulation of renal function. However, in patients with existing renal disease, prostaglandins act as vasodilators to preserve renal blood flow. These patients are more susceptible to the occurrence of renal adverse effects of NSAIDs. Also, the combined use of NSAIDs with diuretics or RAAS-inhibitors may increase the risk of NSAID-associated decrease in renal function [31]. The renin-angiotensin-aldosterone system plays a pivotal role in the pathogenesis of hypertension. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are first line antihypertensive drug classes that are potent, effective, and mostly safe. Direct renin inhibitors (DRIs) have shown similar BP reduction but more side effects. The efficacy of ACEIs and ARBs (for cardiovascular, cerebrovascular, and renal protection) has been promoted to extend beyond what could be explained by BP reduction alone [32]. In one review, the administration of ibuprofen in 90 hypertensive patients treated with ACEIs induced a blood pressure rise in 16.6% of the subjects; however, in this study, hypertension values are not given, only the percentage of affected patients [3]. Ivančica., *et al*. found that ibuprofen or piroxicam increased blood pressure by 1.1 - 1.6% ($p > 0.290$) only, and there were no significant shifts in the follow-up periods [28].

NSAIDs and diuretics

Use of diuretics can lead to hypovolemia and NSAIDs cause inhibition of prostacyclin synthesis (leading to renal afferent arteriolar vasoconstriction). According to a large population-based study of patients (almost 500,000), patients exposed to diuretics and NSAIDs early in the course of treatment may be more prone to develop acute kidney injury. This result is biologically consistent with the potential effect of a drastic hypovolemia exerted by diuretics, which is further exacerbated by the vasoconstrictive effect of NSAIDs [33]. In a meta-analysis study, patients with treatment of lisinopril/hydrochlorothiazide ibuprofen and piroxicam elevated systolic BP by 7.7 - 9.9% ($p < 0.001$), which, during the acetaminophen period, decreased by 6.9 - 9.4% to 0.3 - 0.9% above baseline ($p < 0.001$). Piroxicam and ibuprofen markedly blunt the effects of antihypertensive drugs whereas acetaminophen is almost inert. Lisinopril/hydrochlorothiazide combination is much more affected by this interaction than amlodipine [34]. A large case-control analysis consisting of 2215 cases of acute kidney injury and 21993 controls without kidney injury, all of whom were taking antihypertensive agents, found that the risk of acute kidney injury was not significantly increased when NSAIDs were combined with diuretics, ACEIs, or ARBs; however, a significant increase was observed in those taking triple therapy consisting of an NSAID, a diuretic, and either an ACEI or an ARB (adjusted rate ratio: 1.31; 95% CI: 1.12 - 1.53) [33]. A prospective clinical trial, included 110 already treated hypertensive patients, aged 56 - 85 years; 50 control patients and 60 patients who were also taking NSAIDs for osteoarthritis treatment. The antihypertensive regimens remained the same during this study, while NSAIDs and paracetamol were crossed-over in three monthly periods. In the lisinopril/hydrochlorothiazide subgroup, both ibuprofen and piroxicam elevated mean arterial pressure by 8.9 - 9.5% ($p < 0.001$) [34]. In a retrospective cohort study, NSAID users had a 2 mmHg increase in systolic blood pressure (95% CI, 0.7 to 3.3), Ibuprofen was associated with a 3 mmHg increase in systolic blood pressure compared to naproxen (95% CI, 0.5 to 4.6), and a 5 mmHg increase compared to celecoxib (95% CI, 0.4 to 10), in this study. Compared to acetaminophen, incident use of NSAIDs, particularly ibuprofen, is associated with a small increase in systolic blood pressure in hypertensive patients [20].

NSAIDs and hypoglycemic drugs

Some NSAIDs incidentally induce hypoglycemia, which is often seen in diabetic patients receiving sulphonylureas. NSAIDs influence various ion channel activities, thus, they may cause hypoglycemia by affecting ATP-sensitive potassium channels functions in insulin secreting beta cells [9]. In addition to an increased risk for gastrointestinal bleeding, salicylates have also been recognized to induce hypoglycemia, especially in concomitant use with sulphonylureas (SUs). Salicylate-induced hypoglycemia is thought to be caused by several mechanisms: increasing insulin secretion in those with type 2 diabetes, increasing insulin sensitivity, displacing SUs from protein-binding sites, and inhibiting renal excretion [35].

In pancreatic beta cells, ATP-sensitive K^+ (KATP) channels function as a molecular sensor of cellular metabolism. KATP are composed of four sulphonylurea receptors and, during glucose metabolism, increased intracellular ATP inhibits channel activity, leading to membrane depolarization and insulin secretion. Inhibition of KATP channels results in depolarization of pancreatic beta cells, and consequently insulin release. Indeed, administration of NSAIDs, such as meclofenamic acid, elevated the $[Ca_{2+}]_i$ and increased insulin secretion in the presence of low, but not high glucose. The risk of NSAID-induced hypoglycemia should be considered when glucose-lowering compounds are administered [9].

Metformin is a biguanide widely used hypoglycemic drug for the treatment of type 2 diabetes (DM2). Metformin exhibits a variety of pharmacological properties, including anti-inflammatory, anti-cancer, and antioxidant properties. It was reported that metformin has been demonstrated to be a therapeutically effective drug candidate for various nervous system disorders, including Parkinson's disease, Huntington's disease and spinal cord injury [36]. A synergistic anti-proliferative effect of diclofenac and metformin has been described as diclofenac lowers the glycolytic activity to induce apoptosis in some neoplasms [37]. In a retrospective study metformin therapy is associated with the decreased severity of lumbar radiculopathy pain. These findings are in line with mechanistic studies from preclinical models demonstrating a powerful antihyperalgesic/antiallodynic effect of metformin on lumbar radiculopathy pain [38] and, in a case report, metformin improved pain symptoms suggesting analgesic efficacy of metformin in humans with a favorable change in their serum biochemical markers, such as fibrinogen [39]. In this regard, other results suggest that in patients who are already receiving metformin therapy, lower doses of ibuprofen/aspirin/tramadol/pregabalin might be sufficient for achieving satisfactory pain relief. Metformin-aspirin combination might be particularly useful because it may achieve multiple therapeutic goals (glucoregulation, pain relief and cardioprotection) [40].

Antibiotics and hypoglycemic drugs

Relevant drug interactions are predominantly related to sulfonylureas, thiazolidinediones, and glinides [41]. Two clinical studies showed that many antimicrobials present a high interaction risk with antidiabetics, especially with sulfonylureas (SUs) [42,43]. Interactions with antimicrobials are clinically most relevant because adverse effects take place most often whenever a drug is added or removed [33], and antimicrobials are usually taken temporarily. Besides their specific pharmacokinetic interactions, there are some antibiotics with glucose lowering effects and, thus, bearing the risk of pharmacodynamic interactions with antidiabetic drugs in general. Studies have shown this interaction with fluoroquinolones [44,45]. Quinolones seem to have an insulinotropic effect by increasing the release of insulin via blockade of ATP-sensitive K^+ channels in a dose-dependent manner [42]. Fluoroquinolones like levofloxacin, ciprofloxacin, or moxifloxacin should be used with caution in patients with diabetes. In a retrospective cohort study of Texas Medicare claims from 2006 to 2009 for patients 66 years or older, clarithromycin (odds ratio [OR], 3.96 [95% CI, 2.42 - 6.49]), levofloxacin (OR, 2.60 [95% CI, 2.18 - 3.10]), sulfamethoxazole-trimethoprim (OR, 2.56 [95% CI, 2.12 - 3.10]), metronidazole (OR, 2.11 [95% CI, 1.28 - 3.47]) and ciprofloxacin (OR, 1.62 [95% CI, 1.33 - 1.97]) were associated with higher rates of hypoglycemia compared with a panel of noninteracting antimicrobials [46]. A large population-based cohort study of patients in Taiwan found that diabetic patients prescribed moxifloxacin had higher rates of hypoglycemia than patients given macrolides [47]. In another study, the cephalosporin, cephalexin, has been shown to reduce renal clearance of metformin and, thus, increasing the area under the plasma concentration-time-curve and Cmax [48]. An increased hypoglycemic

risk with SUs was clinically relevant in about 20% of DM2 patients and 75% of the identified interactions were due to concomitant treatment with trimethoprim, metronidazole, or ketoconazole [47]; increased plasma concentrations of glibenclamides have been observed when clarithromycin is taken concomitantly with SUs [49].

Interactions of vasoconstrictors

Hypertensive patients receiving nonselective β-adrenergic antagonists are vulnerable to hypertension and bradycardia when injected with dental local anesthetic formulations containing the catecholamine, epinephrine [50]. Few recent studies of the interactions between local anesthetics and β-adrenergic antagonists were found. However, the literature available since the 80s reveals, in several clinical trials, a strong association between these medications [51-55]. The mechanism proposed occurs when a β-blocker, such as propranolol, is used and significant systemic absorption of epinephrine occurs, the β-2 vasodilatory effects (and the β1 cardiac stimulatory effects) of epinephrine will be blocked, allowing the α vasoconstrictive effects to function unopposed [56]. Drugs affecting the central nervous system (CNS) norepinephrine presynaptic stores, such as monoaminoxidase inhibitors (MAOIs), or increasing activity of synaptic, selective serotonin reuptake inhibitors (SNRIs), and norepinephrine tricyclic anti-depressors (TCAs) may affect adrenergic neurotransmission in the periphery. Because the activity of epinephrine that reaches the peripheral synaptic cleft is also principally terminated by presynaptic norepinephrine transporter reuptake, drugs that inhibit this process (SNRIs and TCAs) also may prolong and exaggerate epinephrine activity. Levonordefrin (alpha-methyl norepinephrine) has predominantly alpha-2 effects with mild beta-1 effects. Presynaptic reuptake is also responsible for termination of activity at the synapse. Although prolonged activity can also be expected, the effects may be predominantly related to blood pressure [57]. It is also possible that adrenergic receptors become sensitized to the effects of sympathomimetics in patients taking MAOIs. Therefore, it seems prudent that systemic direct-acting intravenous sympathomimetics should be titrated to the desired hemodynamic effect, starting with lower than usual doses to avoid exaggerated tachycardia and/or pressor responses. Likewise, vasoconstrictors in local anesthetic solutions should be used cautiously, monitoring hemodynamics [58].

Discussion

In the dental practice, treatment of acute dental pain in patients with antihypertensive medication is usually not prolonged for more than 4 to 5 days. Some trials found no significant effect on BP when over-the-counter (OTC) doses of ibuprofen or naproxen or prescription-dose ibuprofen were combined with antihypertensives [59]. However, particularly in more susceptible individuals such as the elderly, patients with congestive heart disease and hypertensive patients, interactions are possible even with short periods of treatment. Decreasing systolic blood pressure by just 2 mmHg lowers stroke mortality by 10% and ischemic heart disease mortality by 7% [20]. Important to mention that, the combination of NSAIDs, ACEIs, and diuretics has been shown to increase the risk of acute kidney injury by 31% [11]. Despite that paracetamol has been considered as an option in patients under treatment for hypertension, the relative risks of developing hypertension were similar for both paracetamol and NSAIDs [57]. Compared to paracetamol, incident use of ibuprofen is associated with a small increase in systolic blood pressure in hypertensive patients [20].

Our review does not evaluate selective COX inhibitors (ICOX-2) since these are not first choice drugs for use in dental practice, however, it is important to consider the following if the use is taken as an alternative of these drugs. Different studies in patients with controlled hypertension and different antihypertensive regimens have shown that selective COX-2 inhibitors produce an attenuation of the antihypertensive effect of ACEI and beta blockers, therefore, BP should be evaluated when treatment includes any drug belonging to this family. That is, according to the literature, selective COX inhibitors do not represent an option that is significantly better in terms of decreasing antihypertensive effects compared to conventional NSAIDs [60-63].

As shown in table 2, antidepressives of the MAOIs, SNRIs, TCAs families can interact with anesthetics containing a vasoconstrictor of the sympathomimetic types, producing an increase of BP. Another interaction with antidepressants occurs when lithium toxicity is increased by drugs (NSAIDs) that reduce lithium excretion or increase reabsorption in the kidney [63].

Hypoglycemic drugs interactions with NSAIDs and antibiotics	Mechanism	Outcome/Result
Sulphonylureas with NSAIDs	Administration of NSAIDs elevated the $[Ca^{2+}]_I$ and increased insulin secretion [9].	Risk of NSAID-induced hypoglycemia.
Biguanide (Metformin)	• Diclofenac lowers the glycolytic activity to induce apoptosis in some neoplasms [37]. • Favorable change in serum biochemical markers such fibrinogen [39].	• Sinergistic anti-proliferative effect of diclofenac and metformin. • Improve pain syntoms
SUs with fluoroquinolones (levofloxacin, ciprofloxacin, or moxifloxacin) Cephalisporins (cephalexin)	Increasing the reléase of insulin via a ATP-sensitive channels in a dose-dependent manner [44]. Reduce renal clearance of metformin increasing the area under the plasma concentration–time-curve and Cmax [48].	Hypoglycemia Hypoglycemia
SUs with trimethoprim, metronidazole, or ketoconazole	Prolong the elimination phase half-life and increase the maximum plasma concentration of glimepiride by inhibition of CYP2C9 activity [47].	An increased hypoglycemic risk in DM2 patients.

Table 2: *Interaction of NSAIDs and antibiotics with hypoglycemic drugs. Relevant drug interactions are predominantly related to sulfonylureas, fluoroquinolones and metronidazole.*

Antibiotics and NSAIDs can induce hypoglycemia when used concomitantly with oral hypoglycemic drugs; however, although most of the described interactions are considered noxious, some may lead to beneficial effects as occurs with metformin, which has been related to pro-apoptotic and analgesic effects, and as an adjuvant in some diseases of the nervous system [36-38] (Table 3).

Interactions of catecholamine vasoconstrictors	Mechanism	Outcome/Result
Beta blockers • Monoaminoxidase inhibitors • Selective serotonin reuptake inhibitors. • Tricyclic antidepressors	The β-2 vasodilatory effects (and the β1 cardiac stimulatory effects) of epinephrine will be blocked, allowing the α vasoconstrictive effects to function unopposed [56]. Inhibition of norepinephrine transporter reuptake [57].	Alpha vasoconstrictive effects function unopposed. Prolonged and exaggerated epinephrine activity. Hypertensive crisis

Table 3: *Interaction of vasoconstrictors. The main interactions occur with beta blockers and non-selective antidepressives.*

Conclusion

In dental practice, dentists should be aware of any association among medically prescribed NSAIDs, antibiotics, and anesthetics to mitigate the appearance of pharmacological interactions and the possible consequent adverse reactions. Their use should be based on a clinical evaluation of benefits and risks of pharmacological treatment. It is important to individualize pain and infection management according to each patient. For this purpose, the dentist should obtain information about patient's demographics (sex, age, pregnancy, allergies), history of present and past illness, current symptoms, medications (prescribed, OTC or herbal), medical and family history.

Alternatives of treatment for pain, especially non-pharmacologic approaches, such as physiotherapy, laser therapy, and others should be considered especially in patients with multiple treatments or with high levels of hypertension. Other analgesics, such as acetaminophen, or opiates should be considered in the appropriate medical context as an alternative of treatment.

Sympathomimetic vasoconstrictors should be used carefully in patient with medications of tricyclic antidepressors, MAO inhibitors, and non-selective cardio beta blockers. In all these cases it is important to perform follow up of the prescription to continue, suspend, or modify the chosen treatment.

Funding

The author (s) received no financial support for the research, authorship, and/or publication of this article.

Author Contributions

All authors contributed to the study idea, design and methods and manuscript writing. All authors reviewed, edited and approved the final version of the manuscript.

Bibliography

1. Yach D., *et al*. "The Global Burden of Chronic Diseases". *Journal of the American Medical Association* 291.21 (2004): 2616.
2. WHO Mortality Database. (Geneva: World Health Organization) (2019).
3. Salort C., *et al*. "Interactions between ibuprofen and antihypertensive drugs: incidence and clinical relevance in dental practice". *Medicina Oral, Patología Oral y Cirugía Bucal* 13.11 (2008): E717-E721.
4. Poveda R., *et al*. "Antibiotic use in dental practice. A review". *Medicina Oral Patología Oral y Cirugía Bucal* 12.3 (2007): E186-E192.
5. Felipe B., *et al*. "Knowledge of dental students in relation to local anesthetics and associated complications". *International Journal of Medical and Surgical Sciences* 2 (2015): 461-467.
6. Wilson S., *et al*. "The effect of non-steroidal anti-inflammatory drugs and other commonly used non-narcotic analgesics on blood pressure level in adults". *Journal of Hypertension* 24.8 (2006): 1457-1469.
7. Roldán C., *et al*. "Papel de los inhibidores selectivos de la COX-2 en la hipertensión arterial". *Hipertensión y Riesgo Vascular* 21.1 (2004): 30-37.
8. Li J., *et al*. "Non-steroidal anti-inflammatory drugs increase insulin release from beta cells by inhibiting ATP-sensitive potassium channels". *British Journal of Pharmacology* 151.4 (2007): 483-493.
9. Mork N., *et al*. "Effects of nonsteroidal antiinflammatory drugs in conventional dosage on glucose homeostasis in patients with diabetes". *Western Journal of Medicine* 139.1 (1983): 46-49.
10. Yukako T., *et al*. "A Combination of Dexmedetomidine and Lidocaine Is a Cardiovascularly Safe Dental Local Anesthetic for Hypertensive Rats Treated With a Nonselective β-Adrenergic Antagonist". *Anesthesia Progress* 64.2 (2017): 221-225.
11. Morita I. "Distinct functions of COX-1 and COX-2". *Prostaglandins Other Lipid Mediators* 68.69 (2002): 165-175.
12. Bjarnason I., *et al*. "Mechanisms of Damage to the Gastrointestinal Tract From Nonsteroidal Anti-Inflammatory Drugs". *Gastroenterology* 154.3 (2018): 500-514.

13. Walker C., *et al*. "Cardiovascular safety of non-steroidal anti-inflammatory drugs revisited". *Postgraduated Medicine* 130.1 (2018): 55-71.

14. Liu B., *et al*. "A vasoconstrictor role for cyclooxygenase-1-mediated prostacyclin synthesis in mouse renal arteries". *American Journal of Physiology Renal Physiology* 205.9 (2013): F1315-F1322.

15. Kumar B., *et al*. "Nonsteroidal Anti-inflammatory Drug Use in a Patient With Hypertension: A Teachable Moment". *JAMA Internal Medicine* 175.6 (2015): 892-893.

16. Menon R., *et al*. "Novel concepts on pregnancy clocks and alarms: redundancy and synergy in human parturition". *Human Reproduction Update* 22.5 (2016): 535-560.

17. Yagami T., *et al*. "Pathophysiological Roles of Cyclooxygenases and Prostaglandins in the Central Nervous System". *Molecular Neurobiology* 53.7 (2016): 4754-4771.

18. Agarwal S., *et al*. "Eicosanoids in inflammation and cancer: the role of COX-2". *Expert Review of Clinical Immunology* 5.2 (2009): 145-165.

19. Al-Rashed F., *et al*. "Celecoxib exerts protective effects in the vascular endothelium via COX-2-independent activation of AMPK-CREB-Nrf2 signalling". *Scientific Reports* 8.1 (2018): 6271.

20. Aljadhey H., *et al*. "Comparative effects of non-steroidal anti-inflammatory drugs (NSAIDs) on blood pressure in patients with hypertension". *BMC Cardiovascular Disorders* 12 (2012): 93.

21. Siu AW., *et al*. "Glutathione attenuates nitric oxide-induced retinal lipid and protein changes". *Ophthalmic and Physiological Optics* 35.2 (2015): 135-146.

22. Robaczewska J., *et al*. "Role of glutathione metabolism and glutathione-related antioxidant defense systems in hypertension". *Journal of Physiology and Pharmacology* 67.3 (2016): 331-337.

23. Dzeshka MS., *et al*. "Effects of Aspirin on Endothelial Function and Hypertension". *Current Hypertension Reports* 18.11 (2016): 83.

24. Forman J., *et al*. "Non-narcotic analgesic dose and risk of incident hypertension in US women". *Hypertension* 46 (2005): 500-507.

25. Oliviu V. "Adverse Effects and Drug Interactions of the Non-Steroidal Anti-Inflammatory Drugs. Nonsteroidal Anti-Inflammatory Drugs". *Indech Open Chapter* 3 (2017): 17-31.

26. Snowden S., *et al*. "The effects of nonsteroidal anti-inflammatory drugs on blood pressure in hypertensive patients". *Cardiology in Review* 19.4 (2011): 184-191.

27. Alviar C., *et al*. "Efficacy and Safety of Dual Calcium Channel Blockade for the Treatment of Hypertension: A Meta-Analysis". *American Journal of Hypertension* 2013 26.2 (2013): 287-297.

28. Pavlicevic I., *et al*. "Interaction between antihypertensives and NSAIDs in primary care: A controlled trial". *The Canadian Journal of Clinical Pharmacology* 15.3 (2008) 15. e372-82.

29. Angeli F., *et al*. "Amlodipine and celecoxib for treatment of hypertension and osteoarthritis pain". *Expert Review of Clinical Pharmacology* 11.11 (2018): 1073-1084.

30. Smith S., *et al*. "Fixed-Dose Combination Amlodipine/Celecoxib (Consensi) for Hypertension and Osteoarthritis". *The American Journal of Medicine* 132.2 (2019): 172-174.

31. Nygård P., *et al*. "Effects of short-term addition of NSAID to diuretics and/or RAAS-inhibitors on blood pressure and renal function". *International Journal Clinical Pharmacy* 34.3 (2012): 468-474.

32. Bavishi C., *et al*. "Renin Angiotensin Aldosterone System Inhibitors in Hypertension: Is There Evidence for Benefit Independent of Blood Pressure Reduction?". *Progress in Cardiovascular Diseases* 59.3 (2016): 253-261.

33. Lapi F., *et al*. "Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study". *British Medical Journal* 346 (2013): e8525.

34. Pavlicević I., *et al*. "Prohypertensive effects of non-steroidal anti-inflammatory drugs are mostly due to vasoconstriction". *Collegium Antropologicum* 35.3 (2011): 817-822.

35. Mays H., *et al*. "Drug-Induced Glucose Alterations Part 1: Drug-Induced Hypoglycemia". *Diabetes Spectrum* 24.3 (2011): 171-177.

36. Weng W., *et al*. "Metformin relieves neuropathic pain after spinal nerve ligation via autophagy flux stimulation". *Journal of Cellular and Molecular Medicine* 23.2 (2019): 1313-1324.

37. Renner K., *et al*. "Combined Metabolic Targeting With Metformin and the NSAIDs Diflunisal and Diclofenac Induces Apoptosis in Acute Myeloid Leukemia Cells". *Frontiers in Pharmacology* 9 (2018): 1258.

38. Taylor A., *et al*. "The use of metformin is associated with decreased lumbar radiculopathy pain". *Journal of pain Research* 6 (2013): 755-763.

39. Labuzek K., *et al*. "Controlling newly diagnosed type 2 diabetes mellitus with metformin managed pain symptoms in a patient affected with Dercum's disease". *Pain Medicine* 13.11 (2012): 1526-1527.

40. Pecikoza U., *et al*. "Metformin Synergizes With Conventional and Adjuvant Analgesic Drugs to Reduce Inflammatory Hyperalgesia in Rats". *Anesthesia and Analgesia* 124-4 (2017): 1317-1329.

41. Maeda N., *et al*. "Increase in insulin release from rat pancreatic islets by quinolone antibiotics". *British Journal of Pharmacology* 117 (1996): 372-376.

42. Parekh T., *et al*. "Hypoglycemia after antimicrobial drug prescription for older patients using sulfonylureas". *JAMA Internal Medicine* 174 (2014): 1605-1612.

43. Patsalos P., *et al*. "Clinically important drug interactions in epilepsy: interactions between antiepileptic drugs and other drugs". *Lancet Neurology* 2 (2003): 473-481.

44. Chou H., *et al*. "Risk of severe dysglycemia among diabetic patients receiving levofloxacin, ciprofloxacin, or moxifloxacin in Taiwan". *Clinical Infectious Diseases* 57 (2013): 971-980.

45. Fusco S., *et al*. "Severe hypoglycemia associated with levofloxacin in a healthy older woman". *Journal of American Geriatrics Society* 61 (2013): 1637-1638.

46. Trisha M., *et al*. "Hypoglycemia After Antimicrobial Drug Prescription for Older Patients Using Sulfonylureas". *JAMA Internal Medicine* 174.10 (2014): 1605-1612.

47. Tirkkonen T., *et al*. "Potential CYP2C9-mediated drug-drug interactions in hospitalized type 2 diabetes mellitus patients treated with the sulphonylureas glibenclamide, glimepiride, or glipizide". *Journal of Internal Medicine* 268.4 (2010): 359-366.

48. Stage T., *et al*. "A Comprehensive Review of Drug-Drug Interactions with Metformin". *Clinical Pharmacokinetics* 54.8 (2015): 811-824.

49. Holstein A., *et al*. "Oral antidiabetic drug metabolism: pharmacogenomics and drug interactions". *Expert Opinion On Drug Metabolism and Toxicology* 5.3 (2009): 225-241.

50. Tsutsui Y., *et al*. "A Combination of Dexmedetomidine and Lidocaine Is a Cardiovascularly Safe Dental Local Anesthetic for Hypertensive Rats Treated With a Nonselective β-Adrenergic Antagonist". *Anesthesia Progress* 64.4 (2017): 221-225.

51. Foster C., *et al*. "Propranolol-epinephrine interaction: a potential disaster". *Plastic and Reconstructive Surgery* 72.1 (1983): 74-78.

52. Houben H., *et al*. "Effect of low-dose epinephrine infusion on hemodynamics after selective and nonselective beta-blockade in hypertension". *Clinical Pharmacology and Therapeutics* 31.6 (1982): 685-690.

53. Mackie K., *et al*. "Epinephrine-containing test dose during beta-blockade". *Journal of Clinical Monitoring* 7.3 (1991): 213-216.

54. Hjemdahl P., *et al*. "Influence of beta-adrenoceptor blockade by metoprolol and propranolol on plasma concentrations and effects of noradrenaline and adrenaline during i.v. infusion". *Acta Physiologica Scandinavica. Supplementum* 515 (1983): 45-53.

55. Rehling M., *et al*. "Haemodynamic effects of atenolol, pindolol and propranolol during adrenaline infusion in man". *European Journal of Clinical Pharmacology* 30.6 (1986): 659-663.

56. Hersh E., *et al*. "Beta-adrenergic blocking agents and dental vasoconstrictors". *Dental Clinics of North America* 54.4 (2010): 687-696.

57. Mana Saraghi., *et al*. "Anesthetic Considerations for Patients on Antidepressant Therapy-Part I". *Anesthesia Progress* 64.4 (2017): 253-261.

58. Catalani B., *et al*. "Psychiatric agents and implications for perioperative analgesia". *Best Practice and Research. Clinical Anaesthesiology* 28.2 (2014): 167-181.

59. Moore N., *et al*. "Adverse drug reactions and drug-drug interactions with over-the-counter NSAIDs". *Therapeutics and Clinical Risk Management* 11 (2015): 1061-1075.

60. Zhang M., *et al*. "Inhibition of cyclooxygenase-2 in hematopoietic cells results in salt-sensitive hypertension". *The Journal of Clinical Investigation* 125.11 (2015): 4281.

61. Avendaño M., *et al*. "Role of COX-2-derived PGE2 on vascular stiffness and function in hypertension". *British Journal of Pharmacology* 173.9 (2016): 1541-1555.

62. Varga Z., *et al*. "Cardiovascular Risk of Nonsteroidal Anti-Inflammatory Drugs: An Under-Recognized Public Health Issue". *Cureus* 9.4 (2017): e1144.

63. Huyse F., *et al*. "Psychotropic drugs and the perioperative period: a proposal for a guideline in elective surgery". *Psychosomatics* 47.1 (2006): 8-22.

Volume 19 Issue 8 August 2020