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Pharmacological interactions of anti-inflammatory-analgesics in odontology

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Abstract

In this second article we describe the more interesting pharmacological interactions in dental practice based on the prescription of analgesic narcotics, paracetamol and non-selective non-steroid anti-inflammatory drugs (NSAI) (which inhibit cyclooxigenase 1 –COX 1- and cyclooxigenase 2 –COX 2-) and selective NSAIs (COX 2 inhibitors). The importance of preventing the appearance of these pharmacological interactions is because these are medicaments prescribed daily in odontology for moderate pain treatment and inflammation in the oral cavity. Paracetamol can interact with warfarin and therefore care should be taken with chronic alcoholic patients. All NSAIs reduce renal blood flow and consequently are capable of reducing the efficacy of medicaments used for treating arterial hypertension, which act via a renal mechanism. Especial attention should be taken considering the risk of interaction between the antagonists of AT1 receptors of angiostensin II (ARAII) and the NSAIs.

Key words: *Odontology, pharmacological interaction, opiates, paracetamol, alcohol, NSAI, IACE, ARA II, beta-blockers, diuretics, SIRS.*

Introduction

There are various adverse pharmacological interactions implicating narcotic analgesics, paracetamol and NSAI that the oral cavity specialist should be aware of. The objective of this second article is to describe the pharmacological interactions which have major clinical repercussions in dental practice derived from prescribing these medicaments to prevent adverse reactions. Thus the need to carry out a detailed clinical history of the patients´ general health (systemic pathologies), and investigate medication being received which could interact with anti-inflammatory-analgesics.

Interaction of narcotic analgesics

Narcotics are depressors of the central nervous system (CNS) which combine with various subtypes of opiate receptors in the brain, spinal and peripheral medulla. Narcotic analgesics like codeine, dihydrocodeine, oxycodone, tramadol and propoxyphene can be prescribed by odontologists in combination with optimal doses of paracetamol or ibuprofen in order to produce less adverse effects than by administering a single raised dose of the narcotic (1). The opiate and central analgesics have additive sedatory and respiratory depressor effects together with other depressors of the CNS such as sedatory antihistamines, anti-depressors, anti-psychotics, ansiolytics, anticonvulsives, hypnotic sedatives and medicaments for cough (2). Of special interest in pediatric odontology is the potential additive effect of high doses of sedatory narcotics used with local anaesthetics in children because of the associated toxic anaesthetic reactions. The opiate component of the sedative can also induce respiratory acidosis which reduces the combination of local anaesthetics with proteins resulting in an excess of free anaesthetic that CNS cannot distribute. Besides the partial elevation of carbon dioxide pressures produced by opiate premedication increases sensitivity to convulsions induced by the local anaesthetic. (3, 4,) Herbal medicines like kava (for treatment of anxiety), and valerian (used as a sedative and tranquilizer) can also increase sedation by opiates.

The majority of opiate analgesics like codeine, tramadol, meperidine, and central analgesics are metabolized by CYP2D6 suggesting that codeine and tramadol are substrates of CYP2D6 and are therefore promedicaments (5). Antiviral medicaments like ritonavir and cimetidine (H1 antagonist) increase the opiate effect. It has been shown that the administration of antiarrhythmic quinidine eliminates the analgesic activity of codeine and tramadol (6). It is more important for the dentist to be aware of the interaction of the Selective Inhibition of Recaptation of Serotonin (SIRS) which has the theoretic potential of reducing the analgesic activity of codeine and tramadol (1, 5, 6,). Table 1 shows some medical inhibitors of CYP2D6 that can interact with opiate analgesics (7). The inducers of CYP2D6 reduce the efficacy of the opiates (they already accelerate its metabolism). Accordingly, in patients undergoing treatment with a CYP2D6 inducer, the opiate doses may have to be raised. The CYP2D6 inducers include anticonvulsives, carbamazepine, phenobarbital phenitoin, primidona and rifampicin (for treatment of tuberculosis).

Meperidine is a synthetic narcotic used orally for pediatric sedation and occasionally as an analgesic in odontology (8). When administering meperidine to patients receiving other serotoninergic medications including other antidepressors and medicaments for treatment of conduct disorders a serotoninic syndrome could result (9). The serotoninic syndrome is the result of excess production and maintenance of serotonin in the synaptic space. It is characterised by symptoms at the cognitive, autonomic and neuromuscular levels. The more prevalent symptoms can include confusion, disorientation and agitation, symptoms of autonomic nervous system of hypothermia, diaphoresis, sinus tachycardia, hypertension, dilated pupils, tachypnea and nausea. The more profound interactions occur in patients taking SIRS (fluvoxamine, fluoxetine, paroxetine, sertraline, citalopram), depending on the doses. Other agents that block the recaptation of serotonin and norepinephrine can provoke, to a lesser extent, a syndrome of serotonin just like many antidepressors and herbal medicines such as the "San Juan" herb.

Grave and dangerous life threatening incidents have been reported in patients undergoing treatment with MAOI (phenylzine tranylcypromine, isocarboxazides and seligilinine- anti-Parkinson-) and have also been prescribed therapeutic doses of meperidine (synthetic narcotic derivative). Tramadol and propoxyphene, possibly via its own serotoninergic activity, have produced serotoninic syndromes when associated with MAOI. Finally, meperidine, tramadol and propoxyphene should be avoided in

Table 1. Medicament inhibitors of CYP2D6 which can interact with opiate analgesics.

SIRS	ANTIARRHYTHMICS	ANTIDEPRESSORS	ANTIPSYCHOTICS
Fluoxetina	Quinidine	Clomipramine	Haloperidol
Paroxetina	Amiodarone	Desipramine	Tioridazine
Sertralina	Mibefradil		Flufenazine
	Propafenone		

patients who have been under treatment with MAOI for the past 14 days as hyperphenylalaninemia (an increase of phenylalanine in blood during fasting) can arise, and this is dangerous for the life of the patient (2).

Interactions with paracetamol

Paracetamol or acetaminophen is an analgesic used for treating mild to moderate pain and the advantage over NSAI is the absence of collateral effects. It is a potent analgesic similar to acetylsalicylic acid but it is a gastric non-irritant. It is also safe when used in recommended doses over short periods of time which makes it recommendable in odontological practice (1,3). Pharmacological interactions have been reported between paracetamol and sulphinpirazones, phenitoin and zidovudine which are not clinically relevant in odontology if paracetamol is used in therapeutic doses during short periods of time. The interactions with paracetamol of interest to the odontologist are with warfarin and with alcohol (3).

- *Interaction of paracetamol with warfarin*

Various interactions between paracetamol and warfarin have been published. Different studies indicate that paracetamol produces a dose-dependent increase of INR in patients undergoing treatment with warfarin (7-11). This could result in hemorrhages in relation to the intensity of anticoagulation particularly when the INR is greater than 4. Patients taking 9.100 mg of paracetamol a week have 10 times more risk of having an INR greater than 6 (7). The mechanism by which this pharmacological interaction is produced is based on the saturation of P450 cytochrome enzymes, which are responsible for metabolizing warfarin because of the raised concentrations maintained during paracetamol activity. For this reason paracetamol only or in combination with opiates should be prescribed with precaution in patients receiving anticoagulants with warfarin. (7).

- *Interaction of paracetamol with alcohol*

Alcohol, considered a social drink, can have unnoticed pharmacological effects especially in the central nervous system. The ease of obtaining alcohol and paracetamol without prescription should make health specialists aware of possible interactions when prescribing paracetamol to chronic alcoholics. In clinical odontology it is difficult to identify chronic alcoholics. Generally, patients do not recognise their addiction and do not consider their consumption as excessive. Therefore the clinical history should be investigated thoroughly for suspected signs of excessive consumption However, the main reason for consultation is pain which obliges the odontologist to prescribe daily analgesics. As paracetamol lacks gastric effects it is widely prescribed.

In the metabolism of paracetamol the enzyme CYP2E1 (belonging to the group of oxidative enzymes of cytochrome P450) has an essential role. When this enzyme metabolises paracetamol it forms a highly hepatotoxic complex called NAPQI (n-acetyl-p-benzoquinonaimine) which is rapidly detoxified by hepatic glutation (Fig. 1). The CYP2E1 enzyme of the P450 cytochrome also intervenes in the metabolism of ethanol. It has been shown that there is a risk of hepatic altercation when paracetamol is taken shortly before/after alcohol as alcohol induces CYP2E1 raising its concentration. Alcohol is the main substrate for the enzyme and inhibits other substrates like paracetamol. Consequently ethanol metabolism has an influencing role in inhibiting the non-toxic metabolism of paracetamol and the detoxification of NAPQI.

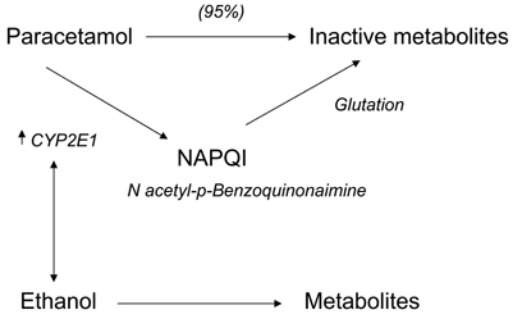

Fig. 1. Metabolism of paracetamol and alcohol.

As a result of this conjugation it has been observed that a sole ingestion of 600 mg/kg of paracetamol in mice produces a notable hepatic lobular necrosis, hemorrhagic congestion and infiltration of erythrocytes but without damaging the hepatic parenchyma. The consumption of 300 mg/kg paracetamol accompanied by ethanol produces lesions in the parenchyma and in the endothelium similar to a sole ingestion of 600 mg/kg paracetamol. As well as the altercations mentioned, the combination of these two substances, and always at the hepatic level, gives rise to stenosis and ischemic changes accompanied by a significant increase of hepatic proteins and transaminases (producing hepatic failure or death by hepatic coma) (12). Even so, the induction of the enzyme CYP2E1 does not appear to adequately explain the magnitude of these adverse effects, assuming they influence other enzymes like CYP3A or mitochondrial glutation (MG). The toxicity of paracetamol shortly before/after alcohol consumption is the result of the induction of the enzyme CYP2E1. However, if consumption is spaced out over a period of time the toxicity is due to the induction of CYP2E1 and a selective depletion of mitochondrial MG.

At the immune system level, the combination of paracetamol and alcohol produces a progressive diminution of circulating leucocytes, and a relative weight reduction of the liver, spleen and thymus in comparison with the

consumption of alcohol alone. There is also a significant reduction of platelet precursors, hemaglutination of sheep erythrocytes and IgG antibodies in response to bovine serum albumen. Accordingly, there is a tendency of phagocyte suppression when both substances are combined. In animal experiments at the renal level, the association of both substances induces an increase in the effect on the proximal tubule cells because of paracetamol. However, the activity of urinary N-acetylglucoronidase, a lysosomal enzyme preferentially located in renal proximal tubules and which catalyses the hydrolysis of glucoronisides and glucoronates and alcohols, is significantly greater. Alcoholic mothers, who consume paracetamol, can via maternal milk, induce a renal effect in the suckling, including a reduction of weight.

The more interesting interaction for the odontologist is that of paracetamol in chronic alcoholic patients (1, 13) as its major drawback is hepatic toxicity resulting from a toxic metabolite produced in the liver by the P-450 cytochrome enzyme system, mainly cytochrome CYP2E1, which is normally detoxified by hepatic glutation (2). Ethanol is also detoxified by CYP2E1, which in turn is an inducer of ethanol, thus chronic ingestion raises the level of this enzyme (Fig. 1). When alcohol consumption is stopped, CYP2E1 is highly increased and exclusively metabolises paracetamol giving rise to large quantities of hepatotoxic metabolites which hepatic glutation is incapable of detoxifying thereby producing irreversible liver damage (14). In non-alcoholic patients the administration of ethanol and paracetamol produces less NAPQI than paracetamol alone. In alcoholic patients and regular consumers, sudden abstinence creates a higher risk of increasing the toxicity of paracetamol (Fig. 1). Therefore it is important for the patient not to suspend alcohol consumption on being prescribing paracetamol (14).

Interaction of NSAIs

NSAIs are medicaments regularly prescribed in dental practice to treat pain and inflammation. NSAIs function by inhibiting prostaglandin-synthetase or cyclooxigenase (COX). COX exists in two isoforms, COX 1 and COX 2. COX 1 (constitutional) has homeostatic functions which includes the maintenance of gastric mucosa (4, 10, 15,). COX 2 (inducible) is implicated in inflammation and fever (Fig. 2). NSAIs can be non-selective inhibitors of COX, that is, they inhibit COX 1 and COX 2 and semi-selective inhibitors of COX 2 (two or three times more selective in blocking COX 2 than COX 1) and highly selective inhibitors of COX 2 (seven times more selective in blocking the activity of COX 2) (Fig. 2). Acetyl salicylic acid is unique among non-selective NSAIs in that it irreversibly acetyls COX 1 in platelets, which justifies its prescription as a cardioprotector. Regarding selective NSAIs of COX 2, some have been withdrawn (like rofecoxib) because of the risk of severe thromboembolic phenomenon. Celecoxib has better tolerance and is less ulcerogenic than conventional NSAIs (however, it has not been demonstrated that there is less risk of digestive hemorrhagia, perforation or pyloric obstruction which also probably require gastro-protection in risk patients). It has an increased potential for cardiovascular mortality via a thrombocytic phenomenon (under study). Etoricoxib and parecoxib should not be dispensed as they also show a cardiovascular risk by analogy with other coxib (16). Following is a description of pharmacological interactions between NSAIs and other pharmacological groups of interest to the odontologist.

- *NSAI anti-aggregates and oral anticoagulants*

The most serious adverse effect of NSAIs is gastrointestinal hemorrhage. The predisposition of gastrointestinal bleeding of NSAI is based on damage produced in the gastric mucosa and in the inhibition of platelet aggregation via its effects on COX 1 (Fig. 2). NSAIs are contraindicated in patients taking other platelet anti-aggregates like dipiridamol, ticlopidine, anagrelide, clopidogrel or oral anticoagulants like warfarin or dicumarol, because of hemorrhagic risk (4). Besides, the hypoprothrombinemic effect is increased by NSAIs. Non selective NSAI should be used with precaution in patients under treatment with acetyl salicylic acid and other salicylates as they also inhibit platelet aggregation and reduce the formation of platelet obstruction (17). It has been observed that acetyl salicylic acid is responsible for producing this interaction when elevated doses are used (> 3 g/day) (1). The NSAI of choice in patients undergoing treatment with oral anticoagulants is diclophenaco (3). Herbal medicines like dong quai (used in treating menopause symptoms) garlic, ginkgo biloba and ginseng have antiplatelet effects and can also give rise to NSAI platelet inhibition (7).

- *NSAI-Metotrexate*

Metotrexate is an anti-neoplasic medicament and immunosuppressive antagonist of folic acid. It inhibits dihydrofolate reductase impeding the reduction of dihydrofolic acid in its active form (tetrahydrofolic), essential for the biosynthesis of purines and pyrimidines which inhibits the synthesis of cellular DNA and RNA. Metotrexate is used for the treatment of rheumatoid arthritis, psoriasis and cancer. It has a low therapeutic index (1, 3). For treating cancer it is administered in high doses with a potential secondary effect of thrombocytopenia, neutropenia, acute renal failure and mucositis. For treating rheumatoid arthritis and other pathologies which require immunosuppression, lower doses are used which produce less secondary effects. NSAIs reduce renal clearance of metotrexate (possibly due to a lowering of perfusion of prostaglandins dependent on renal perfusion), which can produce a toxicity phenomenon (the same as when using high doses in cancer treatment). NSAIs which have been implicated in interactions with metotrexate are ketoprofen, flurbiprofen, naproxen and ibuprofen (1, 2, 18,). The

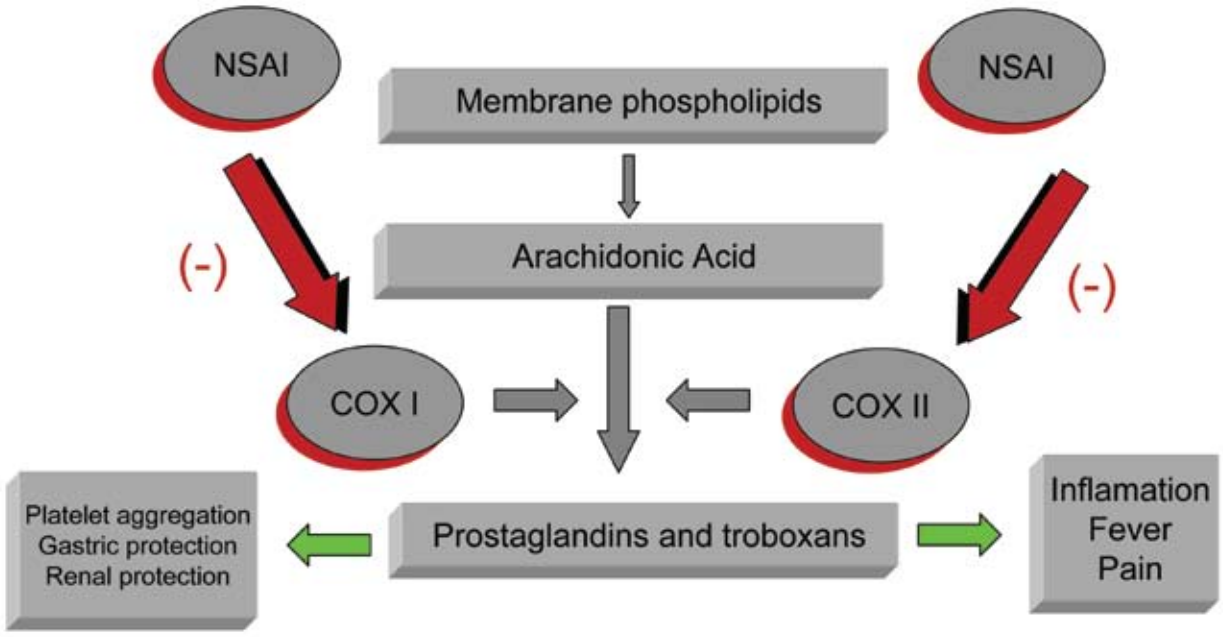

Fig. 2. Mechanism of action of NSAI.

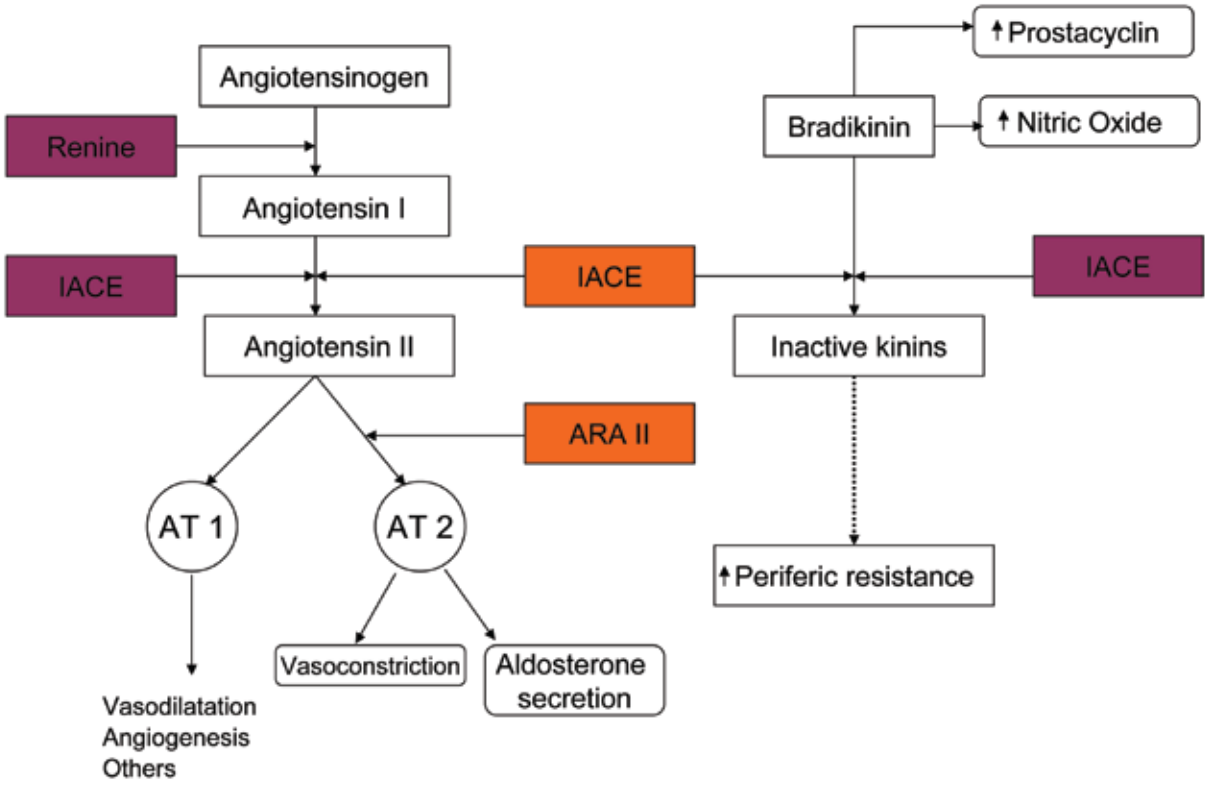

Fig. 3. Mechanism of action of anti-hypersensitive medicaments IACE and ARA II.

severity of these interactions is greater and can lead to renal failure and pancytopenia. The odontologist should be aware that it is not recommended to prescribe NSAIs in these patients, especially in those patients receiving high doses of metotrexate for cancer treatment. Besides, great care should be taken with patients who have other arthritic pathologies and are undergoing treatment with NSAI as it can produce an additive effect with the probability of gastrointestinal and renal damage.

- *NSAI-lithium*

Lithium carbonate (antipsychotic) is the medicament of first choice in patients with bipolar depression and in the maintenance of affective recurrent disorders. Lithium presents a low therapeutic index which frequently produces interactions with other medicaments, including with diet, resulting in intoxication risk. The adverse effects of excessive concentrations of lithium include polyurea, polidipsia, nauseas, vomitos, diarrheas, tremors and sedation which can also lead to convulsions, coma and death. NSAIs increase lithium concentrations in serum predisposing to toxicity as already described. It appears that it produces inhibition of renal prostaglandins which leads to an increase of reabsorption of lithium (lithium is mainly excreted by the kidneys) (2). Indometacine is the NSAI that has a greater effect. Increase of levels of lithium with ketorolac has been observed while sulindac and acetyl salicylic acid does not appear to alter its concentration. Therefore it is advisable to prescribe NSAI over short periods of time to patients taking lithium especially elderly patients (3, 10, 19,). For safety it is recommended to control the plasmic levels of lithium and to adjust the doses (1).

- *NSAI-antihypertensives*

There is sufficient evidence to show pharmacological interactions between NSAIs and four groups of anti-hypersensitive medicaments (1-3, 7, 8, 10,) (Table 2):

1) Inhibitors of Angiotensin Converter Enzyme (IACE).

2) Antagonists of AT1 receptors of Angiotensin (ARAII).

3) Diuretics.

4) Beta-blockers.

These actions depend partly on the mechanisms of renal prostaglandins which have an anti-hypertensive effect (20). Evidence for the interaction of NSAI with these anti-hypertensives comes from numerous cases published and from clinical trials (20). NSAI can increase the mean arterial pressure to 5 mmHg, above all naproxen and ibuprofen (6, 21). The effect of NSAI interaction with anti-hypertensives is observed from the fifth day of combined treatment.

1) IACE: The IACEs (captopril, analapril, fosinopril,lisinopril) (Table 2) produce vasodilatation by blocking the formation of angiotensin 11 and aldosterone, with a parallel increase of bradiquine and vasodilator prostaglandins (Fig. 3). They act on the kidneys, increasing renal plasma flow, reduce intraglomerular pression and maintain glomerular filtration. Together with the tiazides they are the hypertensors that reduce the hypertrophy of the left ventricle the most. The IACE improve the prognosis of diabetes type 1 hypertensive patients, insufficient cardiac congestion (ICC) and pos-

Table 2 Antihypertensive medicaments whose effects are reduced by NSAIs

IACE*	ARA II**	BETA-BLOCKERS	ASA DIURETICS	TIAZIDE DIURETICS
Benazepril	Candesartan	Acebutolol	Furosemide	Hydrochlorotiazide
Captopril	Eprosartan	Atenolol	Bumetanide	Indapamide
Enalapril	Irbesartan	Betaxolol	Etacrinic acid	Metolazone
Fosinopril	Losartan	Bisoprolol	Torasemide	Xipamide
Lisinopril	Telmisartan	Metoprolol	Piretanide	Chlortalidone
Imidapril	Valsartan	Carteolol		
Quinapril	Olmesartan	Nadolol		
Ramipril		Penbutolol		
Trandolapril		Pindolol		
		Propranolol		
		Sotalol		
		Timolol		

* IACE: Inhibitor of Angiostensin Converter Enzyme.
** ARA II: Antagonists of Receptors of Angiotensin II.

tinfarction patients. The prostaglandins are substances which modulate vasodilatation, glomerular filtration, renal tubular secretion of sodium and water and the rennin-angiotensin-aldosterone system. The NSAIs can attenuate the action of the IACE directly by inhibiting the synthesis of renal prostaglandin and indirectly by interfering with the production of prostaglandin induced by the IACEs (1-3, 7, 10).

2) ARA II: the antagonists of AT1 receptors of angiotensin II (ARAII) are a group of medicaments which antagonize the action of angiotensin II through mediation, independently of its route of synthesis (Table 2). In the presence of ARAII, angiotensin II stimulates AT2 receptors, producing diverse activity contraarresting those mediated by AT1 receptors (Fig. 3) (22). In Spain, the following are commercialised: losartán candesertán, eprosartán, irbesartán, olmesartán, telmisartán, valsartán of which potassium losartán serves as a reference for this group (23). They produce vasodilatation, reduction of the liberation of catecholamines at the adrenal and presynaptic levels, of aldosterone and vasopressin, together with a lowering of peripheral resistance. It also produces a discreet increase of the elimination of Na, K, Cl, Mg and uric acid. The ARAII are effective and safe anti-hypertensive medicaments. Actually its basic use is in the treatment of arterial hypertension. Hypertensive patients with diabetes mellitus type 2 and incipient nephropathy, both losartán and irbesartán reduce the risk of terminal renal illness. Its habitual role in therapy is as an alternative to IACE when these are not tolerated (patients with cardiac insufficiency are intolerant to IACE). On the other hand losartán has been shown to reduce the risk of AVC in hypertensive patients with left ventricular hypertrophy. Regarding the possible interactions of this group of hypertensive medicaments with NSAIs, there is evidence that the NSAIs can inhibit the vasodilatatory and natriuretic activity of ARAII (24), but this is not well studied as yet. Therefore it would be prudent to consider the risk produced by a reduction of the hypertensive effect when prescribing NSAI to patients undergoing treatment with ARAII. The hypertensive effect of ARAII is raised when associated with other anti-hypertensive agents and also when combined with tiazides or renal U-tube diuretics to contra arrest the hypopotassemia that these diuretics produce (24).

3) Diuretics: diuretics are much prescribed. They reduce the renal reabsorption of sodium and chlorine. The different segments of neurons on which they act determine its potency and classification. Their more frequent uses are treatment of cardiac, hepatic or renal edema, essential arterial hypertension and hydroelectrolytic disturbances or acid-base equilibrium. The tiazide diuretics act by inhibiting the re-absorption of sodium in the distal tubule and connecter segment while the renal U-loop diuretics (their action is more potent and rapid than the tiazides) inhibit the transport of chlorine in the ascending renal U-loop of Henle (Table 2). The NSAIs interfere with the diuretics by reducing its efficacy in secreting sodium and affects the activity of plasma rennin (1-4, 7, 10, 25,). This interaction is more evident in elderly patients having poor control of arterial hypertension, especially with ibuprofen. This interaction between indomethacin and furosemide has been reported.

4) Beta-blockers: the principal use of beta-blockers is treatment of arterial hypertension, ICC with ventricular systolic dysfunction, angina (stable and unstable), acute myocardial infarction, and arrhythmias. Beta-blockers reduce arterial pressure via diverse mechanisms, including increase of levels of circulating of prostaglandin. It is well established that the beta-blocker-NSAI pharmadynamic interaction is particularly significant when the beta-blocker is administered for hypertension (1-4, 7, 10). Its effect can be inhibited by blocking the synthesis of prostaglandin induced by NSAIs (26). The anti-hypertensive medicaments which do not depend on renal prostaglandins are not implicated in the interaction with NSAIs. Thus the antagonists of calcium channels like nifedipin, verapamil, and diltiazem when administered together with NSAI do not produce an increase in arterial pressure (2, 27). This data is important especially in patients requiring long term treatment with NSAIs (3, 20). Regarding amlodipin, an increase in arterial pressure with ibuprofen has been observed. When prescribing NSAIs it is advisable, that with these antihypertensives (Table 2) the treatment does not exceed five days in order to avoid possible adverse reactions as a result of this pharmacological interaction (shown to be possibly life threatening). In any case, it is possible to produce an interaction, including during short term treatment in elderly patients, in patients with congestive cardiac insufficiency and cases of arterial hypertension with low rennin levels. Taking arterial pressure to control possible effects derived from this interaction makes it obligatory during treatment with NSAI.

- *NSAI-ethanol*

The combined use of alcohol and NSAI significantly increases the risk of bleeding (above all melenas) associated with ulcers and gastro-duodenal lesions. Both damage the gastric mucosa (especially acetyl salicylic acid) (1, 2, 10,). Ethanol stimulates gastric acids and leads to gastrointestinal bleeding induced by aceytl salicylic acid and prolongs the bleeding periods. Alcohol, on stimulating the secretion of gastric acids, also aggravates the toxicity of NSAIs. It is suggested to space out intake of acetyl salicylic acid and alcohol by at least 12 hours. The severity of this interaction is normally probably only moderate (1, 2, 13,).

- *NSAI-sirs*

SIRS are anti-depressors of the "third generation". Today, it is considered the first choice for the treatment of

depression and in a large variety of affective disorders because they are efficient and have few secondary effects. Over the past years an increase in postoperative bleeding after surgical intervention in the buccal cavity of patients taking these anti-depressors has been reported. Besides, a major risk of gastrointestinal hemorrhagia associated with SIRS has also been observed (7, 28). Just as the neurons in the CNS, the platelets have a mechanism for recaptation of serotonin and receptors. Platelets have no nucleus and are incapable of synthesising serotonin so the process of recaptation of serotonin from the blood stream is crucial for storing the platelets. The liberation of this stored serotonin plays an important role in platelet aggregation. SIRS (as in the CNS) block the recaptation of serotonin inside the platelet producing a reduction in the regulation of serotonin on the surface of platelets (7, 28). This makes the SIRS like fluoxetin, paroxetin, sertralin, and citolapran produce a lowering of platelet function and an increased risk of bleeding (29). It has been shown that the combined administration of SIRS with NSAI (especially during prolonged intake) increases the risk of gastrointestinal bleeding (29). Some SIRS like fluvoxamine, paroxetine and sertraline are inhibitors of the CYP2C9 isoenzyme, while some NSAIs like diclofenaco, ibuprofen and naproxen are substrates for the same enzyme of P450 cytochrome (30). Therefore the combination of NSAI with ISRS can produce increased bleeding after oral surgical procedures. In fact until recently this was not taken into account when prescribing NSAIs in dental surgeries to patients undergoing treatment with SIRS (7, 10, 28-30).

- *NSAI-oral hypoglucemics*

Normally there is no adverse or clinically important interaction between hypoglycemic agents and NSAI. However, there are isolated cases of hypoglycaemia in patients taking fenclofenaco with chlorpropamide and metformine, glibenclamide with diflunisal, and ibuprofen with sulfonylurea. Other cases describe a loss of control of the diabetes attributed to indomethacin. It has been observed that piroxicam auments the effects of glibenclamide (2). It is clear that they can produce adverse interaction in hypoglycemics and azapropazone, fenilbutazone, oxifenbutazone and the salicylates (2).

Conclusions

Opiate and central analgesics have additive sedatory and respiratory depressor effects with other depressors of CNS. They also react with SIRS and serotoninergic medication. The interactions, which, in odontological practice, have more repercussions, are between paracetamol and warfarin and alcohol. Prescription of NSAIs in arterial hypertensive patients treated with IACE, beta-blockers, diuretics (of renal U-tube and tiazides) and recently incorporated medicaments like ARAII can increase bleeding after buccal surgery. In fact, until recently this was not taken into account when prescribing NSAI in odontology.

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