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Interactions between ibuprofen and antihypertensive drugs: Incidence and clinical relevance in dental practice

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Abstract

It has been well documented in the literature that ibuprofen interacts with different groups of antihypertensive drugs (beta-adrenergic blockers, alpha-adrenergic blockers, diuretics and angiotensin-converting enzyme inhibitors), reducing their antihypertensive activity. The mechanism of action of ibuprofen involves inhibition of the enzyme cyclooxygenase, thereby inhibiting the synthesis of inflammatory prostaglandins and vasodilatory prostaglandins that increase renal blood flow and thus favor the excretion of water and sodium. More than five days of treatment with both drugs are normally required for the interaction to manifest. Although the changes in blood pressure resulting from this interaction are typically small, some patients can experience substantial elevations in both systolic and diastolic blood pressure. It has been estimated that the avoidance of minor changes in systolic pressure in patients with osteoarthritis subjected to treatment with nonsteroidal antiinflammatory drugs would avoid over 30,000 deaths due to myocardial infarction, and over 2000 deaths due to coronary disease, in the United States alone.

Key words: Ibuprofen, antihypertensive drugs, analgesics, interaction, dental practice.

Introduction

The management of pain is common practice in dental patients. In many cases patients visit the dental clinic due to persistent pain, while in other situations treatment is required for acute postoperative pain. The substances commonly used in dental practice for the control of pain are nonsteroidal antiinflammatory drugs (NSAIDs), and particularly ibuprofen (1-4).

Ibuprofen is an NSAID offering good control of pain in dental practice, with a favorable benefit/risk ratio. However, its use is not without risks in the form of adverse reactions (gastroduodenal ulcers) and interactions with other drugs (5).

The antiinflammatory properties of ibuprofen are due to inhibition of the activity of the enzyme cyclooxygenase, which plays a key role in the synthesis of prostaglandins (6). These prostaglandins in turn favor inflammatory processes on one hand, and the modulation of vasodilatation, glomerular filtration, tubular secretion of sodium and water, and the renin-angiotensin system on the other (7).

Arterial hypertension (AHT) is very common in Spain, with a prevalence of 25-35% in the adult population (8-10). The condition is more common in the elderly, and many individuals are unaware that they have hypertension. These data illustrate the magnitude of the problem, and indicate that a considerable number of patients requiring dental treatment are using antihypertensive drugs.

A broad range of drugs have been show to be clinically effective in treating AHT (Table 1). Depending on the mechanism of action involved, mention can be made of beta-adrenergic blockers, alpha-adrenergic blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonists (ARAIIs), diuretics, calcium channel blockers, and vasodilators (though the efficacy of the latter is less clear).

Drug interactions occur when the effects of a given drug are modified as a result of the presence of some other drug substance in the body. Such interactions may be pharmacokinetic or pharmacodynamic. The former are related to drug transit through the body, while pharmacodynamic interactions are attributable to the mechanisms of action of the implicated drugs. The consequences of drug interaction may prove deleterious both as a result of antagonism of the affected drug (with a loss of efficacy) and as a consequence of synergism or reinforcement of drug action – thereby generating a risk of toxicity.

The present study reviews and describes the clinically relevant interactions of the analgesic ibuprofen with the different drugs used to treat AHT, since such substances are widely used by patients seen in the dental clinic. To this effect, a Medline search was made based on the key words ibuprofen, antihypertensive drugs and interaction - limiting the search to those studies found in the english literature and conducted in human subjects. Among the articles thus obtained, we selected those best suited to the objectives of our study.

Results

Raddack and Deck conducted a three-week, parallel-group clinical trial involving 41 patients with a mean age of 52 years receiving treatment with at least two antihypertensive drugs, and distributed into three groups (ibuprofen 600 mg every 12 hours, paracetamol or placebo). The results showed the ibuprofen group to experience a significant increase in blood pressure in comparison with the other two groups (11).

The literature reports the case of a patient in which the antihypertensive effect of the beta-blocker pindolol was cancelled by ibuprofen (12). However, in a randomized comparative study, the concomitant administration of propanolol and ibuprofen 400 mg every 6 hours exerted no significant effect upon blood pressure (13).

Koopmans et al. (14) carried out an open-label trial of 8 patients to quantify the increase in blood pressure in subjects treated with the diuretic hydrochlorothiazide 50 mg daily concomitant to four weeks of ibuprofen 400 mg every 8 hours, diclofenac 25 mg three times a day, or sulindac 200 mg every 12 hours. A significant rise in systolic blood pressure was observed in the patients treated with ibuprofen, though the authors concluded that these three NSAIDs can be used without risk in patients treated with hydrochlorothiazide – provided careful blood pressure monitorization is carried out on introducing NSAID treatment.

Gurwitz et al. (15) conducted a randomized, double-blind and placebo-controlled clinical trial of 22 patients over 65 years of age. All the subjects were receiving antihypertensive treatment with the diuretic hydrochlorothiazide, and were subjected to alternating four-week periods of treatment with ibuprofen 600 mg every 8 hours or placebo. The authors concluded that in elderly patients treated with hydrochlorothiazide, ibuprofen induces a significantly greater increase in blood pressure than placebo, and that ibuprofen may negatively affect high blood pressure control in elderly individuals.

The interaction of ibuprofen with the diuretic furosemide has been described in two isolated and independent cases involving ibuprofen doses of 400 mg every 8 hours and 600 mg four times a day, respectively (16,17). In comparison, the interaction of furosemide with the NSAID indomethacin has been well documented in different studies (18,19).

The administration of ibuprofen in 90 hypertensive patients treated with angiotensin-converting enzyme inhibitors induced a blood pressure rise in 16.6% of the subjects (20). Likewise, the case has been reported of an elderly woman in whom the administration of ibuprofen attenuated the antihypertensive effects of captopril (21). However, the administration of ibuprofen 800 mg three times a day in 17 black women receiving fosinopril / hydrochlorothiazide had no effect upon blood pressure (22).

Houston et al. (23) conducted a randomized, double-blind and placebo-controlled clinical trial with a duration of three weeks to evaluate the effects of ibuprofen, naproxen and placebo in patients treated with verapamil – a calcium channel blocker – at a dose of 240-480 mg/day. A total of 162 patients between 18-75 years of age were included in the study. The authors concluded that the addition of ibuprofen or naproxen to antihypertensive treatment with verapamil did not increase blood pressure, and that verapamil offers advantages as antihypertensive treatment in patients requiring NSAIDs during long periods of time. However, that same year Minuz et al. (24) published a study of 12 hypertensive patients treated with amlodipine – another calcium channel blocker – at a dose of 10 mg/day, in which concomitant treatment with ibuprofen 400 mg every 8 hours for three days effectively increased blood pressure.

In a metaanalysis of the effects of NSAIDs upon blood pressure, Johnson et al. (25) found the rise in blood pressure to be greater in the patients receiving antihypertensive treatment. These results were reproduced in the metaanalysis published by Pope et al. (26). In the study of Johnson et al., the NSAIDs inducing the greatest blood pressure increments were found to be piroxicam, indomethacin and ibuprofen, while the metaanalysis of Pope et al. identified naproxen and indomethacin as the drugs inducing the

Tabla 1. Antihypertensive drugs marketed in Spain.

THERAPEUTIC GROUP	DRUG	BRAND NAME
Beta-adrenergic blockers	Atenolol	Blokium, Neatenol, Tenormin, GDP*
	Bisoprolol	Emconcor, Emcoretic, Euradal, GDP*
	Carvedilol	Coropres, GDP*
	Labetalol	Trandate
	Metoprolol	Beloken, Lopresor
	Nadolol	Corgard, Solgol
	Nebivolol	Lobivon, Nebilet, Nebilox, Silostar
	Propanolol	Sumial
	Sotalol	Sotapor, GDP*
Calcium channel blockers	Amlodipine	Amlor, Astudal, Kerniox, Norvas, GDP*
	Diltiazem	Angiodrox, Lacerol, Masdil, Tilker, GDP*
	Felodipine	Fensel, Perfudal, Plendil, GDP*
	Lacidipine	Lacimen, Lacipil, Motens
	Lercanidipine	Lercadip, Lerzam, Zanidip
	Manidipine	Artedil
	Nicardipine	Dagan, Lecibral, Lincil, Vasonase, GDP*
	Nifedipine	Adalat, Dilcor, Pertensal, GDP
	Nimodipine	Admon, Brainal, Calnit, Nimotop, GDP*
	Verapamil	Manidon
Angiotensin-converting enzyme inhibitors	Captopril	Capoten, Cesplon, Dilabar, Garanil, GDP
	Enalapril	Acetensil, Crinoren, Dabonal, GDP*
	Fosinopril	Fositens, Tenso Stop, Tensocardil, GDP
	Lisinopril	Doneka, Iricil, Prinivil, Zestril, GDP*
	Perindopril	Coversil
	Quinapril	Acuprel, Ectren, Lidaltrin, GDP*
	Ramipril	Acovil, Carasel, GDP*
Angiotensin II receptor antagonists	Candesartan	Atacand, Blopress, Parapres
	Eprosartan	Futuran, Navixen, Regulaten, Tevetens
	Irbesartan	Aprovel, Karvea, Karvezide
	Losartan	Cozaar, Fortzaar
	Olmesartan	Ixia, Olmetec, Openwas
	Telmisartan	Micardis, Pritor
	Valsartan	Diovan, Kalpress, Miten, Vals
Alpha-adrenergic blockers	Doxazosin	Carduran, Doximax, Progandol, GDP*
	Prazosin	Minipres
	Urapidil	Elgadil
Diuretics	Amiloride	Ameride, Diuzine
	Bumetanide	Fordiuran
	Chlorthalidone	Higrotona, Aldoleo
	Eplerenone	Elecor, Inspra
	Spironolactone	Aldactone, Spirometon, GDP*
	Furosemide	Seguril, GDP*
	Hydrochlorothiazide	Esidrex, Hidrosaluretil
	Indapamide	Extur, Tertensif, GDP*
	Piretanide	Perbilen
	Teclothiazide	Quimodril
	Torasemide	Dilutol, Tadegan, GDP*
	Triamterene	Salidur
	Xipamide	Diurex

* GDP: generic drug product. GDPs include the name of the drug substance in the brand designation.

greatest pressure increases – no statistically significant association being found between ibuprofen and a rise in blood pressure. However, it should be mentioned that in the study published by Pope et al. the mean age of the patients included in the metaanalysis was 46 years.

Discussion

Interactions between ibuprofen and antihypertensive drugs clinically manifest when ibuprofen is used in chronic treatments. Normally more than 4-5 days of treatment with both drugs are needed for interactions to manifest (7,23,27). In dental practice, ibuprofen is usually prescribed for short periods of time – thus allowing use of the drug for the control of acute dental pain in patients on antihypertensive medication, provided such treatment is not prolonged for more than 4-5 days (7).

However, even with short periods of treatment, interactions are possible - particularly in more susceptible individuals such as the elderly, patients with congestive heart disease, and hypertensive patients with low renin concentrations.

Although the changes in blood pressure produced by such interactions are usually small (5-6 mmHg), some patients may experience substantial both systolic and diastolic blood pressure elevations. It has been estimated that by avoiding even small changes in systolic pressure among patients with osteoarthritis treated with NSAIDs, it would be possible to avoid over 30,000 deaths due to myocardial infarction, and over 2000 deaths due to coronary disease, in the United States alone (27). In other words, the blood pressure increment that may result from such drug interactions increases the risk of acute myocardial infarction and of coronary disease among hypertensive patients by 45-67% (7,23) and 15%, respectively (23).

Not all antihypertensive drugs interact in the same way with ibuprofen. Interaction has been described in sufficient detail in the case of beta-adrenergic blockers, diuretics and angiotensin-converting enzyme inhibitors, though ibuprofen also appear to interact with alpha-adrenergic blockers. However, no such interactions appear to occur with the calcium channel blockers, since their antihypertensive activity is not dependent upon prostaglandin action (7). Still, some cases of interaction have been reported, and caution is advised until further information becomes available. On the other hand, there have been no reported cases of interaction with the angiotensin II receptor antagonists, which have been introduced more recently in therapeutic practice.

The interaction of ibuprofen with the above commented antihypertensive drugs is extendable to other NSAIDs, though it seems that aspirin (acetylsalicylic acid) and sulindac produce no such interactions (28). Likewise, the analgesics paracetamol and codeine do not appear to induce interactions (7), though controversy persists on this point.

It would be good clinical practice to always specify the duration of treatment when prescribing ibuprofen, in order to prevent chronic use of the medication from increasing the risks of both adverse reactions and interactions with other drugs.

Patients subjected to antihypertensive treatment should undergo closer blood pressure monitorization at the start of analgesic treatment with ibuprofen and other nonsteroidal antiinflammatory drugs.

While the use of ibuprofen for the treatment of acute pain offers great advantages in routine clinical practice, due consideration is required of those situations ibuprofen may not be the best choice.

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