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Pharmacological interactions of vasoconstrictors

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Abstract

This article is the first of a series on pharmacological interactions involving medicaments commonly prescribed and/or used in odontology: vasoconstrictors in local anaesthetics and anti-inflammatory and anti-microbial analgesics. The necessity for the odontologist to be aware of adverse reactions as a result of the pharmacological interactions is due to the increase in medicament consumption by the general population. There is a demographic change with greater life expectancy and patients have increased chronic health problems and therefore have increased medicament intake. The presence of adrenaline (epinephrine) and other vasoconstrictors in local odontological anaesthetics is beneficial in relation to the duration and depth of anaesthesia and reduces bleeding and systemic toxicity of the local anaesthetic. However, it might produce pharmacological interactions between the injected vasoconstrictors and the local anaesthetic and adrenergic medicament administered exogenically which the odontologist should be aware of, especially because of the risk of consequent adverse reactions. Therefore the importance of conducting a detailed clinical history of the general state of health and include all medicaments, legal as well as illegal, taken by the patient.

Key words: *Epinephrine, odontology, tricyclic antidepressors, beta-blockers, general anaesthetics, cocaine.*

Characteristics of pharmacological interactions

* *Concept of pharmacological interaction*

A pharmacological interaction is the modification of the pharmadynamics and/or the pharmakinetics of the medicament as a result of the treatment together with other medicaments, dietary factors (nourishment, diet, medicinal plants), social habits (smoking, alcohol consumption) or underlying pathologies. In pharmacological interactions there will always be a medicament objective (MO), which will modify its effects and a medicament accelerator (MA) which modifies the effects of the latter. The characteristics of the potential MO are potential intense effects, undesirable serious dose dependency, narrow therapeutic index, stressed dose-response curve (small changes in the dose produce great changes in the plasma concentration) and that the basic illness closely depends on the medicament in question.

* *Mechanisms of the pharmacological interactions*

The pharmacological interactions can be produced through one or various mechanisms at the pharmakinetic and/or pharmadynamic levels (1).

1) Pharmakinetic. When a medicament alters the absorption, distribution, metabolism or renal excretion of another medicament.

-Absorption: Inhibition of the absorption of the medicament objective by physical or chemical means. This Pharmacological Interaction (PI) is avoidable administering the medicaments at three or four hour intervals.
-Distribution: by competing for adhering to plasma proteins.
-Metabolism: the enzymatic systems involved in the biotransformation of the majority of the medicaments are found principally in the smooth endoplasmic reticulum of the liver, which contains an important group of oxidative enzymes called oxidases of mixed or mono-oxigenase function. Here the cytochrome family highlights the P450 cytochrome system (2). The following is the nomenclature of these enzymes: CYP followed by the number that represents the family of isoenzymes. This is followed by letter that represents the subfamily and then another number representing the individual gene (e.g. CYP3A4). There are more than 30 isoenzymes of the P450 cytochrome of which the more important are CYP1A2, CYP2C9, CYP2D6, CYP2E1 and CYP3A4. The isoform CYP3A4 is the most abundant of the cytochrome family in the liver and human intestine. In pharmacological interactions at the metabolism and biotransformation level (the most important) an enzymatic induction or inhibition can be produced.
During enzymatic induction the MA induces the metabolism of the MO, reducing its plasma concentration and therefore its efficiency. For induction to occur it is necessary that the medicaments share the same enzymes and that the MA is capable of inducing enzyme synthesis, a procedure which takes between one and two weeks. During enzymatic inhibition the MA inhibits the metabolism of the MO, increasing its plasma concentration and the risk of toxicity. In this case the effects are immediate (3).
-Renal excretion of other medicaments: the interactions at this level are less important.
2) Pharmacodynamic. The combination of two medicaments which have a similar pharmacological action generally produce additive or synergic effects for both desired or undesired results. Medicaments with contrary pharmacological effects are antagonistic. The adverse effects as a result of this interaction can be prevented by monitoring and adjusting the doses.
** Clinical repercussions of pharmacological interactions*
The pharmacological interactions are responsible for 4.4% of hospitalizations attributed to medicaments and represent 4.6% of all adverse reactions by medicaments in hospitalized patients. The spectrum of medicament-medicament interactions is so wide that it can range from those that are not clinically important to those that represent a risk of severe adverse reaction in the patient. It is essential to identify and select those interactions according to clinical and therapeutic repercussions (Table 1) (4). In a young patient a pharmacological interaction can pass unnoticed, however, in an adult it can show up as a severe adverse reaction and can sometimes also be wrongly interpreted as a worsening of the illness, poor adherence of treatment or even inefficacy of some of the medicaments. The factors which make an interaction between medicaments clinically relevant are index or therapeutic margin, affinity of the enzyme for the medicament, dose, age, sex, pathology and of course ingestion of other medicaments.
** Medicaments of risk in pharmacological interactions*
Medicaments which can probably produce pharmacological interactions have common characteristics. There are four pharmacological groups which should be taken into account when carrying out a clinical history suspected of producing possible interactions:
1) Medicaments which act in the gastrointestinal tract or which alter intestinal mobility.
2) Medicaments with a high affinity for plasma proteins which can displace other medicaments. In this group the odontologist should always be alert to include non-steroid anti-inflammatories (NSAI) which are prescribed daily in dental practice.
3) Medicaments which modify liver metabolism. These are divided into two groups, inductors and inhibitors. The inductor medicaments stimulate the metabolism of other medicaments. The inhibitors inhibit metabolism.
4) Medicaments which alter renal function and clear up other medicaments (e.g. penicillin, cefalosporin) (3).
** Therapeutic index*
The therapeutic index of a medicament is defined as the quotient between the minimum efficiency concentration and the minimum toxicity concentration. If a medicament is affected by an interaction it will have more clinical repercussions if the medicament presents a narrow therapeutic margin. The odontologist should be aware that the lower the therapeutic index of the medicament the higher the risk of producing a pharmacological interaction. Consequently this should be taken into account when making up a clinical history: it is important to be aware that the following medicaments present a narrow therapeutic margin: hypoglucemics, oral anticoagulants, antiepileptics, antiarrhythmics, cardiotonic glucosides, oral anticonceptives, aminoglucosides, antineoplastics, medicaments of the central nervous system (CNS like lithium salts, antidepressors and neuroleptics (5). Once the general mechanisms of the pharmacological interactions have been clarified the pharmacological interactions of the vasoconstrictors (epinephrine) will be described in this first article which would be of interest for the odontologist because of the clinical repercussions which could be derived. Also the norm of action to prevent the appearance of adverse reactions derived from these interactions making odontological practice more secure when administering local anaesthetics with vasoconstrictors.

Epinephrine and adrenergic system

The adrenergic vasoconstrictors are commonly used therapeutic agents in odontology. The most used vasoconstrictor is adrenaline, also called epinephrine (from Greek epi, up, and nefron, kidney) which is injected in combination with local

Table 1. Classification of pharmacological interactions according to clinical relevance.

Category of Pharmacological Interaction	Clinical Importance
Tipo A	Without importance
Tipo B	Effect unestablished
Tipo C	Possible therapeutic effect change or adverse effects. Avoided by adjusting doses.
Tipo D	Severe adverse effects. No therapeutic effects. Doses adjusted with difficulty. Avoid contact with e.g. Warfarine

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* FASS (Pharmaceutical Specialities in Sweden). Stockholm: INFO Lakemedelsinformation AB (Drug information), 1997.URL: http://www.fass.se (Swedish).

Table 2. Classification of antidepressives in function of pharmalogical action.

TRICYCLICS	HETEROCYCLICS	SIRS*	MAOI**	Non selective MAOI
Amytriptiline		Bupropion Citaloprane		
Clomipramine	Maprotiline	Duloxetine Escytaloprane		Phenylzine
Dotiepine Doxipine	Miaserine	Flouxetine	Moclobemide	Nialamide
Imipramine	Mirtazapine	Fluvoxamine Paroxetine		Tranylcipromine
Nortriptiline	Trazodone	Sertraline		
Trimipramine		Venlafaxine		

* SIRS: selective inhibitors of recaptation of serotonin
**MAOI: monoaminooxidase inhibitor

anaesthetics to eliminate pain (6). Epinephrine differs from noradrenalin, or norepinephrine, in that it has a more rapid and shorter effect. Epinephrine is a catecholamine monoamine (belonging to the group of catecholamines which have a catechol group and a radical amine) sympathicomimetically derived from phenylalanine and tyrosine amino acids. In general, the catecholamines act on the sympathetic nervous system provoking different effects mainly through the action on adrenergic receptors.

The adrenergic system is composed of alpha and beta, and various subtypes (beta1 and 2 and alpha 1 and 2). The beta 1 receptors increase cardiac frequency and beta 2 receptors increase vasodilatation of the vascular bases at the pulmonary level. The action of the beta adrenergic system is principally systemic and those of the alpha adrenergic are peripheral with some systemic action. The stimulation of the alpha receptors increases vasoconstriction at the local peripheral circulation with a limited systemic activity. The stimulation of beta 1 tends to raise arterial pressure while beta 2 tends to reduce it. The alpha stimulation system increases arterial pressure non dramatically (7). Epinephrine is the most potent alpha receptor. It is 2 to 10 times more active than noradrenaline and more than 100 times more potent than isoproterenol (8). Interest in the use of vasoconstrictor in odontology is due to the fact that the majority of local anaesthetics produce a dilatation of blood vessels (9). Therefore the addition of a vasoconstrictor, like epinephrine, reduces local blood flow (in oral mucous, submucous and periodontium it produces a selective alpha stimulation) resulting in vasoconstriction, delayed rate of absorption of local anaesthetic and prolongs its local effect, always taking into account that epinephrine should be used at a low concentration (10).

It is important to know the concentration of the vasoconstrictor which a phial of local anaesthetic contains. Generally the capacity of a phial of local anaesthetic is 1.8 ml. A concentration of 1:100,000 epinephrine usually means 0.01 mg of epinephrine in 1 ml of anaesthetic solution, therefore a phial of local anaesthetic at this concentration of vasoconstrictor contains 0.018 mg of epinephrine (18 micrograms).

Interaction of vasoconstrictors with tricyclic antidepressors

Tricyclic antidepressors such as imipramine, amitriptyline and doxepin were the first medicaments used for the treatment of depression and other behavioural pathologies (11) (Table 2). They are the better known (and more effective) antidepressors and the standard by which to compare other antidepressor groups. The disadvantage is that it has many secondary effects, above all in elderly people. The most serious being disturbance of auricle-ventricle conduc-

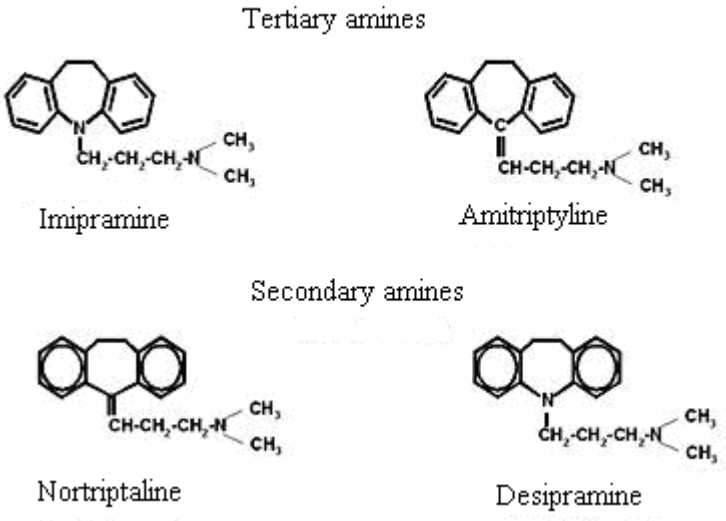

Fig. 1. Tricyclic antidepressors chemical structure.

tion. Nowadays it is suggested for depressive disturbances in the elderly with melancholy when other antidepressors are inefficient. They are a pharmacological group which receive their name from their chemical structures which include a chain of three rings (Figure 1). The mechanism of tricyclic antidepressors is based on their capacity to inhibit the recaptation of neurotransmittors by neuronal receptors (adrenaline, noradrenaline) and serotonine, thus increasing its concentration. The result is the potentiation of the activity of these neurotransmittors. This also blocks the muscarine receptors and the alpha 1 adrenergics which directly depresses the myocardium (Figure 2).

The principal mechanism by which noradrenaline is eliminated from the adrenoreceptor is by inactivating it so that the concentration of the noradrenaline outside the neuron can increase. Consequently if more noradrenaline is diffused in the organism (or any other direct action alpha or beta agonist) a massive stimulation of the cardiovascular adrenergic receptors is produced implicating an increase in arterial pressure due to an excess of sympaticometical amines in the synaptic spaces producing a respective response. This is the reason why the action of the tricyclic antidepressors can further modify the cardiovascular response to the vasoconstrictors used in odontology (12). There is discrepancy among authors regarding the pharmacological interaction of tricyclic-epinephrine antidepressors and the adverse reactions resulting from this interaction. Some deny the existence f this interaction arguing that epinephrine presents a vasodilatatory effect on acting on the beta 2 adrenergenic receptors counter arresting its vasoconstrictory action (6). Others suggest using low doses of epinephrine in local anaesthetics in odontological operations in out-patients can normally produce small changes in arterial pressure. As the cardiovascular state of the patients

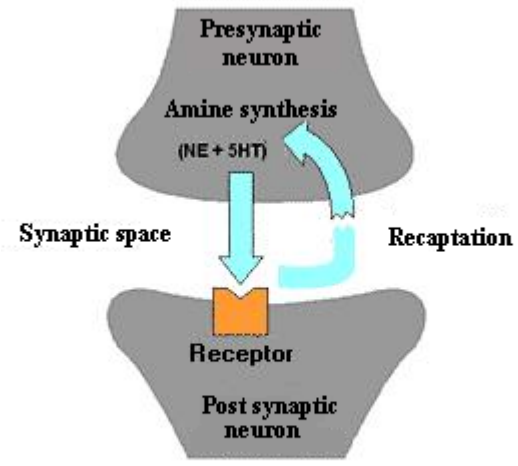

Fig. 2. Mechanism of the action of tricyclic antidepressors.

is not monitored the cardiac rhythmic changes can pass unnoticed or wrongly diagnosed as an anxiety or hypersensitive response. Experimental studies are carried out over a short period of time during which the patient is receiving tricyclic antidepressors. Some authors and laboratories argue that the administration of tricyclic antidepressors during large periods of time can produce a desensitization of vasoconstrictors and a reduction of interaction risks (6).

However, there are experimental studies in both humans and animals which show a significant interaction between tricyclic antidepressors and adrenergic vasoconstrictors (13) and have identified various unpublished tricyclic antidepressor-epinephrine interactions. The most important changes produced as a result of this interaction are a significant in-

crease in systolic arterial pressure, disrhythmia and ectopic focus in cardiac conduction (14). Normally in odontology it is important to find out beforehand if the patient is being treated with tricyclic antidepressors and then to assume the existence of an active pharmacological interaction between tricyclic antidepressors and vasoconstrictors (15). Preventive measures include previous aspiration to discard intravenous injection and the use of phelypresine as a sure alternative to other sympatheticomimeticos in these patients.

Vasoconstrictors like levonordephrin or norepinephrine should never be used. Likewise gum cleaning filaments impregnated with epinephrine should not be used because of the possibility of rapid absorption across the gum grooves and adjacent tissues (16). It is recommended not to use more than 1:100,000 concentration of epinephrine in local anaesthetics and the dose of local anaesthetic should be 1/3 the normal dose for patients not taking tricyclic antidepressors. Additional injections can be safely administered after 30 minutes. The epinephrine dose should not be more than 0.054 mg (three phials of 1:100,000) (3). It is an established interaction and potentially dangerous for life and capable of causing permanent damage (13). If this reaction is produced it can be controlled via an alpha adrenergic antagonist like phentolamine.

Interaction of vasoconstrictors with beta blockers

Beta blockers act by antagonizing the beta adrenergic receptors. They are commonly used for treating hypertension, angina, and cardiac arrhythmia. They act by competitively blocking the stimulation of beta receptors by endogen catecholamines, epinephrine and norepinephrine. They also block the stimulation when exogenic adrenergic medicaments are administered. The specificity of its action on beta receptors could be non selective (blocking beta 1 cardiac receptors and beta 2 in blood vessels) and cardio selective beta 1 (preferentially blocking beta 1 receptors at the cardiac level (1,3).

When epinephrine is absorbed at the systemic level it is not a pure vasoconstrictor as it acts on alpha 1 and beta 2 adrenergic receptors. However, if a beta blocker is active and produces a systemic absorption of epinephrine then the effects of the beta 2 vasodilators of epinephrine are blocked and can only act on alpha 1 receptors. Propranolol is the beta blocker the odontologist has to take into consideration when using epinephrine in local anaesthetics. Propranolol, blocks beta 2 vasodilatator receptors which are found on the walls of the vessels of the skeletal muscles and other tissues suggesting that epinephrine acts at the vessel level as a pure stimulant of alpha adrenergic receptors (5,17).

Studies have shown an increase in systolic and diastolic arterial pressure of 15-33 mmHg and 14-21 mmHg respectively in hypertensive patients who were on propranolol treatment during intravenous infusion with 0.016-0.032 mg epinephrine, equivalent to one or two phials of odontological local anaesthetic with 1:100,000 epinephrine. When these same patients are treated with metoprolol (cardio selective beta blocker) infusions of epinephrine only provoke an increase of systolic arterial pressure of 5-11 mmHg and does not produce any change in diastolic arterial pressure (2). Similarly in healthy 38-46 year old subjects previously treated with propranolol when carrying out intravenous infusion with 0.015 mg of epinephrine a pronounced hypertension is produced with reflex bradicardia. The peripheral resistance which normally falls after administering a moderate dose of epinephrine increases and this produces an increase in a dose dependent arterial pressure and a slowing down of cardiac reflex. Metaprolol does not have this effect. However, both selective and non-selective beta blockers reduce the elimination of epinephrine and norepinephrine in the blood stream which could lightly increase arterial pressure. The pharmacological interaction between non- selective beta blockers and epinephrine used in local anaesthetic has been shown (2,13). Although local anaesthetics with epinephrine injected intradermally produce slight pharmacological interactions, intravenous injection of a small quantity of epinephrine, such as 15 micrograms, equivalent to 5/6 phial of 1:100,000 epinephrine, can produce a bradicardia reflex. Adverse reactions including cardiac arrest following injection the equivalent of 2 phials of 2% lidocaine with 1:50,000 epinephrine have been reported as being a consequence of an interaction between non selective beta blockers and epinephrine. Epinephrine and levonordephrine can be used in patients taking beta blockers. However, the doses used are minimal: ½ phial of local anaesthetic with 1:100,000 epinephrine and carefully injected to avoid administering it intravascularly (13). It is recommended to continue monitoring the patient as follows: inject the patient, wait five minutes and if there is no change in cardiovascular parameters the anaesthetic can be repeated at 5 minute intervals with continuous monitoring. More than 0.04 mg of epinephrine or 0.2 mg of levonordephrine should not be administered (2 phials of 1:100,000 epinephrine or 1:20,000 levonordephrine) (1). Cleaning gum filaments impregnated with epinephrine should also be avoided in these patients. Given the potential danger of this pharmacological interaction and the large number of existing publications one should always take this into account before beginning dental treatment with local anaesthetics with vasoconstrictors (3,18,19).

Interaction of vasoconstrictors with general anaesthetics

Halothane, thiopental and barbiturates with very short activity are general anaesthetics that are able to increase the disrhythmic effects of dental vasoconstrictors. Halothane is the most problematic. The mechanism by which these general anaesthetics increase disrhythmic activity of the vasoconstrictors appears to be due to the simultaneous stimulation of both medicaments with alpha and beta receptors (1). Epinephrine and levonordephrine are able to activate both receptors and unchain disrhythmic episodes during general anaesthesia.

Generally, when carrying out odontological treatment under general anaesthesia the odontologist should inform the

anaesthetist that on administering a local anaesthetic with vasoconstrictor he should take into consideration the dose limit recommended for the vasoconstrictor according to general anaesthetic procedures: halothane (2 micrograms epinephrine/kg), enfluorane (3.5 micrograms epinephrine/kg, isofluorine (5.5 micrograms epinephrine/kg) (1,3). Regarding this interaction a death resulted using a gum cleaning filament impregnated with epinephrine during an odontological treatment under general anaesthetic. This reinforces the general prohibition of the use of epinephrine in a concentrated form where there is a possibility of a potential pharmacological interaction (20).

Interaction of vasoconstrictors with cocaine

Cocaine was introduced in medicine in1884 as the first local anaesthetic. It was mixed with epinephrine in 1903 to increase the clinical efficacy of cocaine. In 1924 use of these medicaments was stopped as the result of various deaths produced. Actually cocaine is used as topical anaesthetic in mucous membranes and more so mixed with epinephrine for nasal surgery. Certainly illegal use is much more extended. Cocaine presents a pharmacological complex as an anaesthetic as it blocks the nervous conduction a similar way to lidocaine. As a stimulant, it inhibits the recaptation (via presynaptic nervous terminals) of norepinephrine, dopamine and serotonin (Figure 3). This activity, similar to tricyclic antidepressors potentiates the adrenergic effects of vasoconstrictors (Figure 2). There is evidence that cocaine can increase the liberation of adrenergic neurotransmittors and intensify the postsynaptic response. It also blocks the cardiac muscarine receptors and produces a central alteration in the activity of the autonomic central nervous system. All of which can additionally contribute to exaggerated responses on injecting vasoconstrictors in local anaesthetics used in odontology (21). The potential pharmacological interaction between vasoconstrictors and cocaine was clearly shown in both human and animal experiments (13). There is a well documented case of a myocardial infarction in a young healthy adult administered an injection of lidocaine with epinephrine after a topical application of cocaine for nasal surgery (8,22). Deaths have also been reported both in medicine and odontology as a result of the combination of vasoconstrictors and cocaine (23). The most important problem for odontologists is the fact that he is unaware that the patient requesting surgical treatment in out-patients is taking drugs. Therefore it is essential to be aware of possible signs of cocaine abuse, lesions in nasal walls and skin lesions. Dental treatment including the use of vasoconstrictors should be avoided for at least 48 hours after the last intake of cocaine because of agitation, hypertension and cardiac arrhythmia. Patients with cardiopàthy associated with cocaine or suspected of being under the influence of cocaine should be treated in hospitals as in-patients.

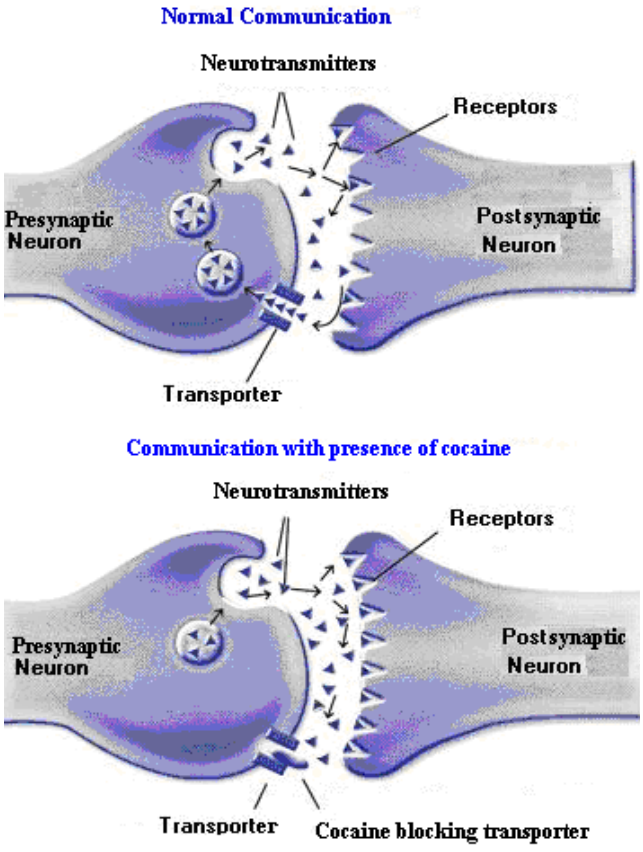

Fig. 3. Mechanism of the action of cocaine

Interaction of vasoconstrictors with blocking adrenergic neuron

Guanethidine and guanadrel are medicaments that block adrenergic neurons. It inhibits the liberation of norepinephrine via the sympathetic nervous terminals (13). Prolonged use of these medicaments in treating arterial hypertension can result in adrenergic receptors to be hyper-regulated by the body in order to restore normal neurotransmission. An increase in the number of receptors and/or sensitivity could produce a hyperresponse to adrenergic vasoconstrictor. Blocked neurons can also increase the effect of epinephrine via a mechanism of competitive inhibition of the recaptation neuronal system. Blocking adrenergic neurons are used infrequently. However, in patients under treatment with these blockers the dose of epinephrine should not exceed 0.054 mg followed by careful aspiration. Levonordephrine and norepinephrine should be avoided (2,8).

Interaction of vasoconstrictors with thyroid hormones

Thyroid hormones are produced by the thyroid glands. They are responsible for the increase of basal metabolism, which is essential for fetal development and proper functioning of cardiovascular, skeleto-muscle and hematopoietic systems as well as for corporal response regarding production of heat, oxygen consumption and the regulation of other hormonal systems. There are three circulating hormones: T4 (tetraiodotironine or tyroxine), T3 or triodotironine and

reverse T3 (biologically inactive). The plasma levels of these hormones are maintained stable throughout life, except during the neonatal period and sometimes during the use of some medicaments in some illnesses. Hypothyroidism is the reduction of thyroid hormone levels which can be asymptomatic giving rise to multiple symptoms and signs of diverse intensity in the whole organism. Untreated hypothyroidism carries a high mortality risk. The substitution of thyroid hormones is normally carried out with oral levothyroxine. Hyperthyroidism is a pathology caused by oversecretion of thyroid hormones (free T4, or free T3 or both) resulting in abnormally raised levels of plasma. The main cause is Grave´s disease or diffuse toxic goitre, toxic thyroid adenoma, toxic multinodular goitre and sub-acute thyroiditis. Inappropriate use of tyroxine and other preparations of thyroid hormones can cause cardiovascular changes as a result of increased concentrations of epinephrine (tachycardia, disrhythmia, pulse alterations or myocardial ischemia). For many years it was thought that the thyroid hormone and epinephrine interacted synergically to create these effects. However, evidence accumulated over the last decades show that the hemodynamic response to epinephrine and norepinephrine are nor significantly altered in patients with hyperthyroidism. Patients with large quantities of thyroid hormones in the blood stream develop cardiovascular pathologies as a result of the overstimilation of myocardial metabolism (24). Therefore it is recommended that adrenergic vasoconstrictors are used with caution in patients with evidence of excessive thyroid stimulation when being treated (13).

Interaction of vasoconstrictors with monoaminooxidase inhibitors (MAOI)

The efficacy of MAOI antidepressors (isocarboxazides, phenylzine, tranylcypromine, furazolidine, antimicrobial agents and seligilinine, -antiparkinson) is comparable to tricyclic antidepressors, but there are patients who respond better to these, similar to those patients who suffer the so-called ¨"atypical depression" or accompanied by intense anxiety or phobias. It is also used in depression resistant to other antidepressors (1). Traditional MAOI are non-specific irreversible inhibitors. Actually non-selective reversible inhibitors have been developed with less cardiovascular risks (although not as effective as the irreversibles) (Table 2). MAOI blocks the intraneuronal degradation of the norepinephrine in sympathetic nerves by MAO thus increasing the quantity of neurotransmittors capable of being liberated by adrenergic medicaments by indirect activity such as amphetamine, pseudofedrine (commonly found in nasal decongestions) and tyramine (amino acid present in various foods like cheese). Accordingly the capacity of MAOI to totally and non-selectively inhibit MAO favors the accumulation of exogenic vasopressor amines, which appears as a hypertensive crisis on consumption of these medicaments or food rich in tyramine. However, the frequency and seriousness of this phenomenon is less than previously thought. MAOI has already been implicated in interactions with various adrenergic amines resulting from its activity (avoiding the metabolism of metabolised medicaments by MAO) suggesting the existence of a potentially dangerous interaction between these antidepressors and vasoconstrictors in odontological use. However, clinical studies in human and animals have shown that cardiovascular interactions between MAOI and dental vasoconstrictors are not produced (8,13,25). Neither have pharmacological interactions between the selective inhibitors of the recaptation serotonin (Table 2) and odontological vasoconstrictors been shown (26).

Interaction of vasoconstrictors with cathecol-o-methyltransferase inhibitors

Treatment of Parkinson´s disease has incorporated new medicaments such as tolcapone (Tasmar®) and entacapone (Comtan®) used together with levadope/carbidope. On reversibly blocking the cathecol-o-methyltransferase enzyme the inactivity of peripheral levodope is inhibited. The inactivity of epinephrine and levonordephrine administered exogenically, as they are substrates for cathecol-o-methyltransferase, can also be inhibited. These medicaments are relatively new and should be used cautiously in local anaesthesia (27). The European Agency for Medicaments (EAM) withdrew tolcapone for producing fulminating hepatitis, rabdomyolisis and malignant neuroleptic syndrome. Previously, in a switch study against entacapone, a non-significant tendency was observed but beneficial for tolcapone. Data available are insufficient to know the risk-benefit relationship (28). In odontologically managing these patients it is recommended to initially administer a phial of lidocaine with epinephrine 1:100,000 and to monitor the arterial pressure and cardiac frequency of the patient before administering an additional injection of local anaesthetic with vasoconstrictor (2).

Interaction of vasoconstrictors with digital glucosides

Digoxin is the most frequently used cardiotonic glucoside in the treatment of insufficient cardiac congestion. Digoxin is a classical vegetal cardiotonic therapeutically used since Gallic times (29). In insufficient cardiac congestion therapy it is a medicament in the second line after diuretics and inhibitors of enzyme converters of angiostensine-aldosterone. Although this improves tolerance of diuretic requirements and reduces exacerbations of insufficient cardiac congestion, it has a narrow therapeutic margin (with the consequent danger of digital intoxication) (3) and an adverse critical effect like ventricular arrhythmias, which raises the risk of acute myocardial infarction (1,30). Patients undergoing treatment with digoxin are more fragile as a result of their basic pathology when undergoing dental treatment. Therefore the use of vasoconstrictors in these patients should be carried out cautiously as excessive doses of epinephrine or levonordephrine can induce a disrhythmic activity. Careful aspiration prior to administering local anaesthetic should be carried out as well as limiting the dose of epinephrine or levonordephrine from 0.04 to 0.20 mg respectively (1,3).

Conclusions

The odontologist should be aware of the importance of identifying and preferably preventing the appearance of pharmacological interactions and the possible consequent adverse reactions during bucal cavity treatment. Correct medical history with special note of medicament taken by the patient is essential in preventing pharmacological interactions. Administration of local anaesthetics with vasoconstrictors can produce severe repercussions. It is also important to know the mechanisms by which these interactions can be produced in order to avoiding them. The sympatheticomimetical effect of epinephrine in local anaesthetics can be intensified by the simultaneous administration of tricyclic antidepressors and non-selective cardio beta blockers, which could lead to increased arterial blood pressure. Certain general anaesthetics, like halothane, can sensitize the heart to catecholamines thus induce arrhythmias after administration of anaesthetic with epinephrine. Treatment of patients with cocaine addiction (including use of vasoconstrictor) should be avoided for at least 48 hours after the last cocaine intake.

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