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## Pharmacological interactions of anti-microbial agents in odontology

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### Abstract

In this third article we describe the pharmacological interactions resulting from the use of anti-microbial agents. Although the antimicrobials prescribed in odontology are generally safe they can produce interactions with other medicaments which can give rise to serious adverse reactions which are well documented in clinical studies. Antibiotics with grave and dangerous life threatening consequences are erythromycin, clarithromycin and metronidazol and the anti-fungal agents are ketoconazol and itraconazol. Regarding the capacity of the anti-microbials to reduce the efficacy of oral anti-contraceptives the clinical studies to date are inconclusive, however, it would be prudent for the oral cavity specialist to point out the risk of a possible interaction. Therefore the specialist should be aware of possible interactions as a consequence of administering an antibiotic together with other medicaments the patient may be taking.

**Key words:** *Odontology, antibiotics, anti-fungals, erythromycin, clarithromycin, metronidazol, ciprofloxacin, ketoconazol, itraconazol, CYP3A4, CYP1A2.*

### Introduction

The duration of therapy with antimicrobial agents in odontology (except in prophylaxis of endocarditis and articular prothesis) is generally more prolonged than other types of medicaments used in odontology. Therefore this fact increases the risk of adverse pharmacological interactions in comparison with other classes of medicaments. The aim of this third article is to describe the pharmacological interactions which have major clinical repercussions resulting from antibiotics prescribed in odontology such as clarithromycin, erythromycin, ciprofloxacin, metronidazol and antifungal azolics like ketoconazol and itraconazol.

### Interaction of erythromycin, clarithromycin, antifungal azolics and metronidazol with medicament substrates of CYP 3A4

In the first article of this series we described the mechanism of the pharmacological interaction at the pharmacokinetic level in relation to metabolism. The enzymatic systems involved in the bio-transformation of the majority of the medicaments are located principally in the smooth endoplasmic reticulum of the liver, which contains an important group of oxidative enzymes called monooxidases or oxidases of mixed function. This is the location of the cytochrome family of which the P450

cytochrome system is prominent (1). The following is the nomenclature of these enzymes: CYP followed by the number representing the family of iso-enzymes, followed by a letter representing the sub-family and finally another number representing the individual gene (e.g. CYP3A4). There are more than 30 P450 cytochrome isoenzymes, the most important of which are CYP1A2, CYP2C9, CYP2D6, CYP2E1 and CYP3A4 (2). The CYP3A4 isoform is the most abundant cytochrome family in the liver and human intestine. In pharmacological interactions an induction or enzymatic inhibition can be produced at the metabolic level. During enzymatic inhibition the precipitating medicament inhibits the metabolism of the medicament objective increasing its plasma concentration and therefore a risk of toxicity. In this case the manifestations are much more immediate than in enzymatic induction (3). The macrolide antibiotics erythromycin and clarithromycin are potent irreversible inhibitors of the CYP3A4 and CYP1A2 isoenzymes which can significantly increase concentrations in blood and toxicity of other medicaments (substrates) which use this system of detoxification (Table 1) (4). Normally for the interaction to appear the CYP3A4 inhibitor has to be taken for at least three to five days beforehand although there are published cases where an interaction has been seen on the first day of taking the medication (5). While the macrolide antibiotics erythromycin and clarithromycin are potent inhibitors of CYP3A4, azithromycin is not (there are few interactions associated with azithromycin), which makes it a safe alternative in patients taking medicaments which could interact with the latter (6). This could be due to the chemical structure of azithromycin compared with erythromycin and clarithromycin. All the macrolides are composed of a macrocyclic lactone ring joined by glucoside bond to various deoxyazucar amines (7). They are classified according to the number of carbon atoms present in the lactone ring. Erythromycin and clarithromycin have 14 carbons in the ring, while azithromycin is a molecule of 15 carbons. This additional carbon is responsible for impeding it joining to CYP3A4 (8). They interact with the majority of medicament antagonists of calcium channels used for treating arterial hypertension and arrhythmia, with anti convulsives (carbamazepine) (9), with inhibitors of the enzyme 3-hydroxy-3-methyl-glutaril-coenzyme A used for treating hypercholesterolemia like atorvastine, lovastine and simvastine (with pravastine there is no interaction as it is not metabolised by CYP3A4). There are documented cases of rhabdomyolysis (syndrome due to skeletal muscle lesions) resulting from the association of simvastine with fluconazol (10) (Table 1). Interactions have also been described with cyclosporin and tacrolimus, immunosuppressive medicaments used for maintenance of solid organ transplanted patients or in the treatment of

autoimmune diseases (psoriasis, rheumatoid arthritis). Cotrimazol also raises the level of tacrolimus in renal transplanted patients. Opiate analgesics like alfentanil and inhibitors of protease (antiviral agents used for treating HIV and AIDS) like indinavir, nelfinavir, ritonavir and saquinavir (11) are CYP3A4 substrates whose levels increase when ingested together with these inhibitors (4,12). When CYP3A4 antimicrobial inhibitors are administered with warfarin an increase of prothrombin time and INR with risk of bleeding has been observed (13). Terfenadine is a promedicament which undergoes almost complete metabolism by CYP3A4 in the intestine and liver producing an active metabolite, fexofenadine which produces the desired antihistamine effect. Terfenadine is potentially cardiotoxic and if its metabolism (via the isoenzyme CYP3A4) is altered it can accumulate in the organism and produce serious cardiotoxic effects (5). Erythromycin, clarithromycin, ketoconazol and itraconazol give rise to an accumulation of initial terfenadine and its metabolite fexofenadine. Electrocardiographic changes (prolongation of QT intervals) have also been observed (14). Azithromycin (macrolide antibiotic) does not have any interaction with terfenadine nor with astemizol (15). Cisapride is a medicament used in the treatment of esophagic-gastro reflux. A possible consequence of the simultaneous ingestion of CYP3A4 inhibitors (erythromycin, clarithromycin, metronidazol antifungal agents) with cisapride is grave ventricular arrhythmias. It is very important to be aware of this interaction which is not as well known as those produced with antihistamines (5) (Table 1).

Regarding midazolam (benzodiazepine used as an oral sedative in odontology) it has to be taken into account that it is a CYP3A4 substrate which increases its blood level even with a single dose of benzodiazepine when associated with a CYP3A4 inhibitor which can result in a deep depression of the CNS (16). Ketoconazol and itraconazol have dramatic effects on these hypnotic sedatives increasing blood concentrations of oral midazolam and triazolam 15 and 27 times respectively. An intense and prolonged psychomotor alteration, up to 17 hours, accompanies these pharmacokinetic changes (5). As described the structure of azithromycin prevents this from altering the levels of midazolam. Fortunately, the benzodiazepines given orally, like midazolam and triazolam have very high therapeutic indices compared with other antianxiety-sedatory medicaments.

### **Interaction of metronidazol and fluconazol with CYP2C9 substrates**

Metronidazol and the antifungal fluconazol also inhibit CYP2C9 giving rise to an accumulation of various substrates of this isoenzyme. The CYP2C9 substrates are anticoagulants (warfarin), anticonvulsives (fenitoin, carbamazepine) (17) ARAII (losartan, ibesartan), hy-

**Table 1.** Inhibition of P450 CYP3A4 cytochrome enzyme by macrolide antibiotics (erythromycin, clarithromycin), azolic antifungal agents (ketoconazole, fluconazole) and metronidazole. Adverse reactions that can result from the inhibition of CYP3A4 which metabolises their medicament substrates.

Medicament substrates of CYP3A4 (interaction objective)	Potential Interaction
<b>Antihistamines H1:</b> cisapride, terfenadine	Accumulation of substrate leading QT intervals and ventricular arrhythmia
<b>Hypocholesterics:</b> atorvastatine, cerivastatine lovastatine, simvastatine	Accumulation of substrate leading to diffuse myalgia, rhabdomyolysis and renal failure blocking the renal tubule system by skeleto-muscular degradation products
<b>Calcium antagonists:</b> felodipine, nifedipine, amlodipine, verapamil, diltiazem	Substrate accumulation leading to increased hypersensitivity producing sever hypotension and edema
<b>Immunosuppressors:</b> cyclosporine, tacrolimus	Substrate accumulation leading to excessive Immunodepression and nephrotoxicity
<b>Anticoagulants:</b> warfarina	Substrate accumulation, increase of prothrombin and INR* time, increased bleeding risk
<b>Anitpileptics:</b> carbamazepine	Substrate accumulation, ataxia risk, vertigo, somnolence and confusion
<b>Antivirals:</b> indinavir, nelfinavir, ritonavir, saquinavir	Substrate accumulation, cardiac altercation risk
<b>Opiate analgesics:</b> alfentanile	Substrate accumulation, respiratory depression risk
<b>Benzodiazepines:</b> alprazolam, diazepam, midazolam, triazolam	substrate accumulation, excessive and prolonged sedation, increased air obstruction risk in children

\*INR: International Normalized Ratio

**Table 2.** Inhibition of CYP1A2 and 2C enzymes of P450 cytochrome by antibiotics, antifungal and antiinfection agents. Inhibition of CYP1A2 and 2C increases medicament effects with which they react.

CYTO-CHROME	INHIBITOR	MEDICAMENT OBJECTIVE OF THE INTERACTION
<b>1A2</b>	<b>Macrolide antibiotics</b> Erythromicin Clarithromycin	Teofiline <b>Antidepressors</b> Amitriptyline Clomipramine Fluvoxamine Imipramine <b>Antipsychotics</b> Haloperidol Clozapine
<b>2C</b>	<b>Azolics anti-fungals</b> Ketoconazol Fluconazol <b>Metronidazol</b>	<b>Anticonvulsives</b> Fenitoin <b>Anticoagulant</b> Warfarin

perglucemics (glipizide, gliburide, tolbutamide) and NSAIs (ibuprofen, naproxen, diclophen) (4,5,12) (Table 2). The more interesting interaction from the point of view of clinical dentistry is that of metronidazol with warfarin which significantly increases the blood levels and median life of these anticoagulants therefore giving rise to a higher tendency for hemorrhagia (18). To this we have to add the capacity metronidazol has of inhibiting the CYP2C9 enzyme which metabolises fenitoin

producing an accumulation of this antiepileptic agent resulting in an increased risk of somnolence, confusion, diplopia, ataxia and nistagmo. The antifungal fluconazol also inhibits the activity of CYP2C9 which can produce the same interactions with respect to warfarin and fenitoin (19,20). An increase has also been observed in the concentrations of carbamazepine in patients with epilepsy undergoing treatment with ketoconazol. Nistatin can be used as an alternative for oral fungal infections in patients not immunocompromised. However, realistic therapeutic alternatives do not exist for azolic antifungal treatment (12). As metronidazole is generally used for the anaerobic component of oral infections together with penicillin which treats the aerobic, clindamycin can be used as an alternative for these mixed infections. It is advisable that before prescribing metronidazol or fluconazol to dental patients undergoing long-term treatment with warfarin and fenitoin to consult a specialist in these medicaments (4,15). Another potential interaction, where the clinical significance is unclear, is the capacity of fluconazol to diminish the metabolic activity of CYP2C9 of the promedicaments losartan (an ARAII, medicament reference of this group) of its active metabolite E-3174, potentially diminishing its anti-hypertensive action (21) (Table 2).

**Interaction of ciprofloxacin and erythromycin with CYP1A2 substrates**

The antibiotics, ciprofloxacin and erythromycin are inhibitors of the CYP1A2 isoenzyme, of P450 cytochrome which can reduce biotransformation and increase blood

levels of medicaments which are substrates of CYP1A2 such as tacrine, antihistamines (teofilin) antidepressors (fluvoxamine, imipramine) and anti psychotics (haloperidol, clozapine) (1,4) (Table 2). Tacrine, a medicament used for treating Alzheimer, is an inhibitor of acetylcholinesterase, leading to a rise in the concentrations of acetylcholine. The high levels of tacrine resulting from excessive activity of muscarine and nicotine receptors with consequent excess saliva, tears, sweating, gastrointestinal hypermobility, bradycardia, miosis, muscular cramp and excitation of the CNS (22). The accumulation of teofiline implicates excessive blockage of receptors of phosphodiesterase and adenosine which gives rise to tachycardia and other dysrhythmias, tremors and convulsions (1,4,23). The potential interaction produced with fluvoxamine and imipramine antidepressors results in an excess of anticholinergic activity and alpha 1 blockage, clinically leading to xerostomia, increase of intraocular pressure, tachycardia and dysrhythmias, sedation, confusion, constipation and orthostatic hypertension. Haloperidol and clozapine, substrates of CYP1A2 increase their concentration which can lead to an excessive anticholinergic, antidopaminergic effect and alpha 1 blockage which can provoke xerostomia, sedation, tachycardia, constipation, extrapyramidal and orthostatic hypotension (4,12).

#### **Interaction of metronidazol with alcohol and lithium**

Metronidazol can interact with both alcohol and lithium. These two interactions are of special interest above all because of the toxicity that can result with lithium.

##### *Metronidazol with alcohol*

Metronidazol, just like disulfiram (antabus effect) inhibits the activity of the enzyme acetaldehyde dehydrogenase leading to an accumulation of acetaldehyde in patients consuming alcohol (24). The clinical ability of metronidazol to produce similar reactions to disulfiram in patients consuming alcohol is based on various studies showing an incidence in 2% of the population studied. The reaction leads to nausea, cardiac palpitations and headache. The odontologist should warn the patients not to drink alcohol during metronidazol treatment for at least three days after the final treatment (2, 3,9).

##### *Metronidazol with lithium*

Intoxications have been produced by lithiums a consequence of metronidazol prescription. Lithium is used for treating manic-depressive pathologies (bipolar), and more frequently during the maniac phase but always under strict control and monitoring because of its low therapeutic index. It is important to be aware of signs of acute intoxication by lithium: lethargy, muscle weakness, and hand tremors. The more serious intoxications include confusion, nistagmo, and ataxia. Coma and circulatory collapse are more grave processes which can result from this toxicity (3,5). This grave interaction

has been demonstrated and is potentially life threatening. Because of its low therapeutic index high levels of lithium can produce an alteration of renal function, sometimes in the form of insipid diabetes.

#### **Interaction of tetracyclines and quinolines with cations**

There are two groups of antibiotics, tetracyclines and quinolines, which form chelates with divalent and trivalent cations found in the diet, antacids and vitamins. These chelates are insoluble and cannot be absorbed through the gastrointestinal tract mucosa and the blood stream and so are excreted. Consequently the antibiotic or cation has no activity.

##### *Tetracyclines with cations*

Antibiotics of the tetracycline group like tetracycline, doxycycline and minocycline form insoluble complexes called chelates when administered, via the same route, at the same time or almost the same time as divalent cations (1,5). Therefore the bivalent cations like calcium, magnesium, bismuth, iron, zinc and aluminium (found daily in diets, in antacid products and vitamins) alter the absorption of tetracycline molecules by the gastrointestinal tract (1). If doxycycline is taken with milk or antacids it will form a chelate and the calcium and doxycycline will not be absorbed in the gastrointestinal tract and will be excreted in the faeces (12). A diminution of around 20% of serum concentrations of tetracycline in the presence of these cations has been observed. This is a known and well documented interaction. In these cases it would be prudent to avoid simultaneous ingestion of tetracycline and multicationic products by spacing out both these ingestions (5,15,25). Tetracycline antibiotics should be taken two hours before or after food, nutrition, mineral supplements or antacids containing calcium, magnesium, or divalent iron. This is of interest in children because of the importance of calcium for growth and development of bones and teeth, and in women to prevent osteoporosis especially as many foodstuffs are enriched with calcium thus giving rise to this potential pharmaco-alimentation interaction (12).

##### *Quinolines with cations*

The antibiotics of this group of quinolines, like ciprofloxacin also form chelates with trivalent cations like iron and zinc. In studies on hospitalised patients receiving medication via the enteric tube, it has been observed that when the quinoline antibiotic is administered in this way the concentrations reaching the blood stream are very low or null. Accordingly the administration of quinoline antibiotics should be separated from the ingestion of supplements containing zinc or iron by at least two hours.

*Interaction of erythromycin, clarithromycin and azithromycin with digoxin*

Digoxin is absorbed favourably when administered orally (approximately 75%). Clarithromycin and erythromycin can produce toxicity by digitalics in patients with a rapid increase of blood levels of digoxin (3,5). Approximately 10% of the population has intestinal bacteria (*Eubacterium lentum*), which metabolises a large portion of digoxin diminishing its bio-availability and consequently need larger doses for maintenance during treatment (1). In these patients clarithromycin, erythromycin and azithromycin can inhibit the growth of these intestinal bacteria by sufficiently increasing the levels of digoxin (4). As digoxin has a very low therapeutic index prescription of these antibiotics should be avoided in patients taking digoxin.

### Interaction of antibiotics with oral anticoagulants

Generally, antibiotics alter the normal intestinal flora. This flora is important in preventing overgrowth of opportunistic infections in the gastrointestinal tract and is essential for the production and/or absorption of some nutrients, vitamins and medicaments. When this flora diminishes gastrointestinal discomforts can appear (nauseas, vomiting) as well as lesser ability of producing vitamin K and to recycle and absorb some hormones like estrogens at the enterohepatic level. Intake of antibiotics supposes lesser absorption of vitamin K and consequently a decrease in the production of vitamin K dependent coagulation factors, VII, IX, X and probably V (12). Therefore there is a greater risk of bleeding which is clinically important in patients taking warfarin over prolonged periods (20, 26). Warfarin and dicumarol are competitive antagonists for vitamin K dependent coagulation factors and have a low therapeutic index (1). The administration of other medicaments, like wide spectrum antibiotics, can raise this antagonistic activity which in turn produces a serious increase in the blood and a threat for the patients' life (12). As reported

previously antimicrobial inhibitors of CYP3A4, when administered to patients taking warfarin there is an increase of INR and major risk of bleeding. It is suggested that wide spectrum antibiotics like tetracycline, amoxicillin, ampicillin and clarithromycin can reduce the endogenous levels of vitamin K and raise the effects of oral anticoagulants by altering the normal intestinal flora which vitamin K produces (1). Apparently the ability of these antibiotics to increase the anticoagulatory activity is relatively rare and unpredictable (5). When the longer the patient is undergoing treatment with antibiotic the greater the risk of bleeding. Wide spectrum antibiotics can be prescribed to patients taking warfarin (patients with normal ingestion of vitamin K) but they should be advised to look for signs of bleeding and consult the doctor immediately (5,12,18).

### Interaction of antibiotics with oral contraceptives

One of the widely discussed interactions is the ability of certain antibiotics to reduce blood concentrations and the efficacy of oral contraceptives. The two components of contraceptive pills, semi-synthetic estrogens (estradiol ethinil or mestranol) and semi-synthetic progestones (progestines) are CYP3A4 substrates (1,3,5). It has been shown that rifampicin (aminoglycosides used for tuberculosis treatment) and its analog rifabutine significantly reduces blood levels of the contraceptive as they are potent inducers of the CYP3A4 isoform. Rifampicin is a potent inducer of the P450 hepatic cytochrome, and increases the metabolism of many medicaments including oral contraceptives (1). However, none of the antibiotics used in odontology are inducers of CYP3A4 and moreover, erythromycin and clarithromycin are inhibitors of this enzyme which would raise the levels of the contraceptive (27,28). Cases have been published of contraceptive failure after antibiotic therapy with penicillin, tetracyclines, metronizadol, erythromycin and

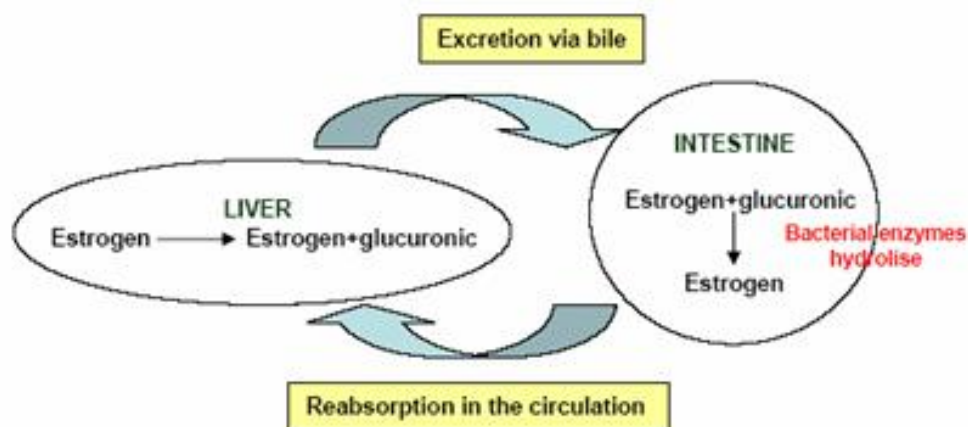


Fig. 1. Pharmacological bases of antibiotics interaction with oral contraceptives.

cefalosporins (29). However, clinical studies have not shown any significant reduction clinically or statistically in blood levels of contraceptives and neither its efficacy (5,15). The most accepted theory to explain the mechanism of sporadic cases of contraceptive failures is based on the ability of the antibiotics to inhibit the enterohepatic recirculation of the estrogen component of the contraceptives (3,30) (Fig.1). The intestinal bacteria hydrolyse glucuronic acid of the sulphate groups (SO<sub>4</sub>) of the estrogen component, liberating the liposoluble and active part that can be reabsorbed by the intestine and pass on to the blood circulation. In the presence of antibiotics the enteric bacteria are markedly reduced which produce a reduction of the reabsorbed estrogen which is then excreted (3). The levels of estrogen fall, restoring the capacity to ovulate. In theory this enterohepatic recirculation can be inhibited by antibiotics that destroy the bacteria of the colon implicated in the process of deconjugation (Fig.1). The failure of oral contraceptives in women who simultaneously take antibiotics could indicate, or form part of, the normal proportion of failures of these medicaments, or that it is a relatively rare interaction that cannot be detected in clinical trials. However, it would be prudent for the dentist to warn the women undergoing treatment with contraceptives of the possible interaction when prescribing antibiotics. Also it would be advisable to recommend other methods of contraception (while continuing oral contraceptives) during antibiotic therapy for at least one week after the last dose of antibiotic (30).

## Conclusions

The antibiotics the odontologist prescribes that present major risk of pharmacological interaction with serious and dangerous life threatening adverse reactions are erythromycin, clarithromycin, ciprofloxacin and metronidazol and also the anti fungal azolics, ketoconazole and itraconazole. This is because these antimicrobial agents are potent inhibitors of various P450 cytochrome isoenzymes. Consequently there is a major risk of potential pharmacological interactions with medicaments which are substrates of these isoenzymes and could lead to an increase of the substrate in the blood stream. Substrates of medicaments which have low therapeutic index have special clinical repercussions because small variations in their concentration could produce toxic effects. Thus the importance of suspecting the appearance of serious pharmacological interactions when prescribing antimicrobial agents in odontological practice.

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