Review Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2015, Volume 3, Issue 9
ISSN: 2321–3647(online)

Relevance of Pharmacological Drug Interactions in Modern Dental Practice

Sukhwant Singh Yadav*[1], Sushma Chaurasia[2], Aishvarya Kaushik[1], Sangeeta Talwar[3]
1. MDS, Senior Resident, Department of Conservative Dentistry & Endodontics, Maulana Azad Institute of Dental Sciences, New Delhi, INDIA.
2. MDS, Tutor, ESIC Dental College, Rohini, New Delhi, INDIA.
3. MDS, Professor and Head, Department of Conservative Dentistry & Endodontics, Maulana Azad Institute of Dental Sciences, New Delhi, INDIA.

ABSTRACT

Antibiotics, analgesics and local anaesthesia are the frequently used drugs during the treatment of dental diseases. These drugs can interact to different drug classes used in different systemic conditions. Some of these interactions are adverse and life threatening to the patients. The dental practitioner should have thorough knowledge about these interactions and methods to prevent and treat the adverse effects. This article will discuss the common possible drug interactions and their adverse effects in clinical dental practice.

Keywords: Drug interactions, antibiotics, tricyclic antidepressants, NSAIDs, vasoconstrictors.

*Corresponding Author Email: sukhwant.yadav@gmail.com
Received 1 August 2015, Accepted 26 August 2015

Please cite this article as: Yadav SS *et al*., Relevance of Pharmacological Drug Interactions in Modern Dental Practice. American Journal of Pharmacy & Health Research 2015.

INTRODUCTION

Advancement in medical technology has helped people improve life expectancy. This indirectly leads to increase in patients having systemic diseases such as hypertension, diabetes mellitus in middle and old age. In the same age group, incidence of dental problems starts increasing. Dental management of medically compromised patients may need modification for certain dental procedures or medication or require special attention for their management according to their medical condition. Patient with other systemic conditions also neglect oral health as they put their most of effort in handling the other disorders such as neurological disorder, cardiac disease etc. Various kinds of medications are prescribed during the course of treatment in dental diseases/ clinics. These include antimicrobials, analgesics (NSAIDs and opoids), vasoconstrictors, local anaesthesia, sedatives etc. Two or more drugs taken simultaneously may result in increased or reduced intensity of effect produced by any of the drugs taken alone. Adverse drug interactions should be taken into consideration during dental treatment of patients as this can be life threatening so one should have adequate knowledge about it before prescribing them in medically compromised patients. This paper will review potential drug interactions in medically compromised patients pertinent to the use of various medications in dental practice.

NSAIDs

NSAIDs are used commonly to treat dental pain but their course of duration is small (3-5 days). These medicaments given in patients on anticoagulants and corticosteroids increases the risk of both GI tract ulceration and post operative bleeding[1]. Warfarin levels are likely to be increased if patients are treated with NSAIDs and anticoagulants, because of competition for protein binding sites. The co-administration of misoprostol has been shown to provide effective protection against both gastric and duodenal ulcers[2]. Patients taking aspirin are also on risk of post operative bleeding while prescribing NSAIDs for more than 5 days especially in elderly people[1]. Ibuprofen has been found to competitively inhibit the antiplatelet influence of aspirin[3, 4]. It is the only NSAID implicated in this interaction, but diclofenac and the selective COX-2 inhibitors are the only agents that have been confirmed not to interact[4]. An empiric solution to this problem is predicated on the fact that the antiplatelet influence of low-dose aspirin occurs when it contacts platelets within the hepatic portal system following absorption[5]. Simply advise the patient to take their daily aspirin upon rising and delay the first dose of ibuprofen for 1-2 hours[6]. It should be noted that aspirin is an irreversible inhibitor of platelet cyclooxygenase, whereas ibuprofen and most other NSAIDs are reversible. Hence when platelets are exposed to aspirin, they are

rendered ineffective and recovery depends on replacement, which may take 4-8 days. Platelets exposed to ibuprofen can regenerate cyclooxygenase, and the effects only last 8-12 hours. NSAIDs antagonize the antihypertensive effects of angiotension-converting enzyme (ACE) inhibitors as they leads to reduction of prostaglandins within the kidney that support its role in blood pressure regulation[7]. There is no evidence that short-term use of NSAIDs (3-5 days) carries significant risk. In the rare event that postoperative analgesics must be continued for more than 5 days, hypertensive patients should return to the office for blood pressure assessment. Other possible interactions are with oral sulfonylureas (increases the antidiabetic effects), diuretics (nephrotoxicity is increased, because of reduced extracellular fluid volume and an elevation in serum potassium can occur), selective serotonin reuptake inhibitor (SSRI) antidepressants (increased risk of GI injury) and methotrexate levels can be increased due to the direct competition for renal excretion of methotrexate and NSAIDs.

Antimicrobials

A limited class of antimicrobials are prescribed in dental practice to cure endodontic and periodontic infections. These include clarithromycin, erythromycin, ciprofloxacin, metronidazol and antifungal azolics like ketoconazol and itraconazol. The main mechanism of their interactions is microsomal enzyme inhibition and induction. 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[8]. The macrolide antibiotics erythromycin and clarithromycin are potent irreversible inhibitors of the CYP3A4 and CYP1A2 isoenzymes[9]. Normally for the interaction to appear the CYP3A4 inhibitor has to be taken for at least three to five days but an interaction has been seen on the first day of taking the medication [10]. Azithromycin a safe alternative in patients taking medicaments which could interact with the macrolide antibiotics[11]. Substrates of CYP3A4 are antihistamines H1, hypocholesterics, calcium antagonists, immunosuppresors, anticoagulants, anitepileptics, antivirals, opiate analgesics, benzodiazepines etc. When CYP3A4 inhibitors are prescribed with these medicaments, it leads to different adverse effects (Table 1). Metronidazol inhibits the activity of the enzyme acetaldehyde dehydrogenase[12]. The reaction to alcohol leads to nausea, cardiac palpitations and headache. The dentist should warn the patients not to drink alcohol during metronidazol treatment for at least three days after the final treatment[13]. Its interaction with lithium can leads to lithium toxicity with symptoms of lethargy, muscle weakness, and hand tremors. The more serious intoxications include confusion, nistagmo, ataxia, coma and circulatory collapse.

Table 1: Common drug interactions and their effects in dentistry

Drugs used in Dental clinics	Interacting drugs	Effect of drug interaction
NSAIDs	Anticoagulants, Asprin, Corticosteroids	Risk of both GI tract ulceration and post operative bleeding
	ACE inhibitors	Antagonize the antihypertensive effects
	Oral sulfonylureas	Increases the antidiabetic effects
	Diuretics	Increases nephrotoxicity
	SSRI antidepressants	Increased risk of GI injury
	Methotrexate	Methotrexate toxicity
Antibiotics (macrolide antibiotics, antifungal agents)	Inhibition of P450 CYP3A4 cytochrome enzyme	Substrate accumulation
	Antihistamines H1	Ventricular arrhythmia
	Hypocholesterics:	Diffuse myalgia, rabdomyolisis and renal failure
	Calcium antagonists	Severe hypotension and edema
	Immunosuppresors	Excessive Immuno depression and nephrotoxicity
	Anticoagulants	Increase of prothrombin time, increased bleeding risk
	Anitepileptics	Ataxia risk, vertigo, somnolence and confusion
	Antivirals	Cardiac altercation risk
	Opiate analgesics	Respiratory depression risk
	Benzodiazepines	Excessive and prolonged sedation, increased air obstruction risk in children
	Oral contraceptives	Decreased effectiveness of oral contraceptives
Metranidazole	Alcohol	Nausea, cardiac palpitations and headache
	Lithium	Lethargy, muscle weakness, and hand tremors
Macrolide antibiotics	Digoxin	Digoxin toxicity
Tetracyclines and quinolines	Dietary products containing divalent and trivalent ions	Non absorption and excretion
Vasoconstrictors	Tricyclic antidepressants	Increase in systolic arterial pressure, disrhythmia and ectopic focus in cardiac conduction
	Beta blockers	Sudden elevation of blood pressure and reflex bradycardia
	Alpha blockers	Amplify cardiovascular responses
	Digoxin, anorexics, decongestants, amphetamines	Elicit cardiotonic effects
	General anaesthetic	Cardiac dysrhythmia
	Cocaine	Increased blood pressure and cardiac dysrhythmias

Tetracyclines and quinolines, which form chelates with divalent and trivalent cations found in the diet, antiacids and vitamins. These chelates are insoluble and cannot be absorbed through the

gastrointestinal tract mucosa and the blood stream and so are excreted. A diminution of around 20% of serum concentrations of tetracycline in the presence of these cations has been observed. Tetracycline antibiotics should be taken two hours before or after food, nutrition, mineral supplements or antiacids containing calcium, magnesium, or divalent iron. In same manner quinolines also form chelates with trivalent cations like iron and zinc. Clarithromycin, erythromycin and azithromycin can inhibit the growth of intestinal bacteria. 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[14]. In these patients, prescription of these antibiotics leads to toxicity. 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[15]. Therefore there is a greater risk of bleeding which is clinically important in patients taking warfarin over prolonged periods[16]. However, none of the antibiotics used in odontology are inductors of CYP3A4 and moreover, erythromycin and clarithromycin are inhibitors of this enzyme which would raise the levels of the contraceptive[17].

The putative mechanism for this interaction relates to the ability of antibiotics to reduce normal intestinal flora that enhance bioavailability. Estrogens and progestins normally undergo enterohepatic recirculation, whereby absorbed steroids are conjugated in bile and excreted into the duodenum. Intestinal flora hydrolyzes these conjugates allowing the steroids to be reabsorbed. Most publications claiming this interaction have been either anecdotal reports or elaborate theories based on these reports. 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[18].

Vasoconstrictors

Adrenergic vasoconstrictors are commonly used with local anaesthetics to increase the duration and the quality of anaesthesia, decreases the peak plasma concentration of the anaesthetic agent and hence decreases toxic reactions. The ability of vasoconstrictors to retard the systemic absorption of injected local anaesthetic agents such as lidocaine is the basis for their widespread use[19]. Vasoconstrictors also reduce the minimum concentration of anaesthetic needed for nerve block and provide local haemostasis during surgical procedures. The addition of a vasoconstrictor to a local anaesthetic may also have detrimental effects due to drug interactions.

There are no absolute contraindications to the use of vasoconstrictors in dental local anaesthetics, since epinephrine is an endogenously produced neurotransmitter[20]. Although considered safe for dental use, the adrenergic vasoconstrictors epinephrine and levonordefrin may participate in a variety of adverse drug interactions, the most important of which involve tricyclic antidepressants, nonselective β-adrenergic blocking drugs, certain general anaesthetics and cocaine.

Certain brands of gingival retraction cord contain large amounts of epinephrine and the possibility of rapid drug absorption by abraded crevicular_tissue proscribes their use. Tricyclic antidepressants: - Tricyclic antidepressors potentiate the activity of neurotransmitters due to their capacity to inhibit the recaptation of neurotransmittors by neuronal receptors (adrenaline, noradrenaline) and serotonine. When noradrenaline is diffused a massive stimulation of the cardiovascular adrenergic receptors is produced implicating an increase in arterial pressure due to an excess of sympaticometical amines. Dysrhythmia and ectopic focus in cardiac conduction are other manifestations[21]. The administration of tricyclic antidepressors during large periods of time can produce a desensitization of vasoconstrictors and a reduction of interaction risks[22]. Vasoconstrictors like levonordephrin or norepinephrine are metabolised by COMT. Hence, COMT inhibitors lead to increase in their action by 6 folds. Alpha adrenergic antagonist like phentolamine can be used to treat this interaction. Sympathomimetic agents: - Interactions of vasoconstrictors with beta blockers are well documented in literature. Sudden elevation of blood pressure and reflex bradycardia occurs when patient taking non –selective beta blockers as epinephrine constrict arterial vessels in many organs through alpha-adrenergic stimulation[23]. Physiologic effects associated with stimulation of beta-adrenergic receptors include increased heart rate and contraction force (mediated by B1 receptors) and dilation of peripheral blood vessels (mediated by B2 receptors). Cardio selective beta 1 blockers can be used in such patients but blood pressure needs to be monitored periodically.

Peripherally-acting adrenergic blockers (guanethidine, reserpine) and alpha-adrenergic blockers (prazosin, terazosin) may amplify cardiovascular responses to vasoconstrictors. So local anaesthetic containing epinephrine should be used with caution in these patients[24]. However, risk of interaction is minimal if use of local anaesthetic is limited to 1 or 2 cartridges[25]. Vasopressors should be used with caution in patients taking sympathomimetic drugs like digoxin, anorexics, decongestants, and agents for attention deficit disorders such as amphetamines and methylphenidate (Ritalin). Epinephrine and levonordefrin cause cardiotonic effects in these

patients. Heart rate and blood pressure should be monitored baseline and after each 1-2 cartridges of local anaesthetic solution containing 1:100000 epinephrine.

CONCLUSION

A meticulous drug history should include examination of the patient's prescribed medications as well as over-the-counter (OTC) drugs and health food supplements. When prescribing a medication, one is always encouraged to check with any number of references or tables regarding risk for interactions. Nevertheless, general principles of drug interactions should be understood and the major risks for interactions should be appreciated for the principal drug classes prescribed. There is a major risk of potential pharmacological interactions with medicaments which are substrates of cytochrome 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.

REFERENCES

1. Sharpe P, Thompson J. Non-steroidal anti-inflammatory drugs. Royal Coil Anesth Bull. 2001; 6:265-268.
2. Silverstein F, Graham D, Senior J. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. Ann Intern Med. 1995; 123:241-249.
3. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med. 2001; 345:1809-1817.
4. MacDonald TM, Wei L. Effect of ibuprofen on cardio protective effect of aspirin. Lancet. 2003; 361:573-574.
5. Patrono C. Aspirin as an antiplatelet drug. N Engl J Med. 1994; 330:1287-1294.
6. Abramowicz M. Do NSAIDs interfere with the cardioprotective effects of aspirin? Med Lett Drugs Ther. 2004; 46:61-62.
7. Burke A, Smyth E, FitzGerald GA. Analgesic-antipyretic agents; pharmacotherapy of gout. In: Brunton LL, Lazo JS, Parker KL. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed. New York, NY: McGraw-Hill, 2006.
8. Gómez Moreno G, Cutando A, Arana C. Visión Odontológica de las Interacciones Farmacológicas. Granada: Grupo Editorial Universitario; 2006.

9. Hersh EV, Moore PA. Adverse drug interactions in dentistry. Periodontol 2000. 2008; 46:109-142.
10. Hersh EV. Adverse drug interactions in dental practice: interactions involving antibiotics. Part II of a series. J Am Dent Assoc. 1999;130:236-251
11. Poveda Roda R, Bagan JV, Sanchis Bielsa JM, Carbonell Pastor E. Antibiotic use in dental practice. A review. Med Oral Patol Oral Cir Bucal. 2007; 12:E186-192.
12. Fried R, Fried LW. The effect of Flagyl on xanthine oxidase and alcohol dehydrogenase. Biochem Pharmacol 1966;15:1890-1893.
13. Hersh EV. Adverse drug interactions in dental practice: interactions involving antibiotics. Part II of a series. J Am Dent Assoc. 1999; 130:236-251.
14. Stockley IH. Stockley's Drug Interactions. 6th ed. London: Pharmaceutical Press; 2002.
15. Sims PJ, Sims KM. Drug interactions important for periodontal therapy. Periodontol 2000. 2007; 44:15-28.
16. Wood GD, Deeble T. Warfarin: dangers with antibiotics. Dent Update. 1993; 20:350-353.
17. Back DJ, Orme ML. Pharmacokinetic drug interactions with oral contraceptives. Clin Pharmacokinet. 1990; 18:472-484.
18. DeRossi SS, Hersh EV. Antibiotics and oral contraceptives. Dent Clin North Am. 2002; 46:653-664.
19. Jastak JT, Yagiela JA, Donaldson D. Local anesthesia of the oral cavity. Philadelphia: Saunders; 1995:61-4. 2. Malamed SF. Handbook of local anesthesia. 4th ed. St. Louis: Mosby–Year Book; 1997:37-8, 46.
20. Pallasch TJ, Vasoconstrictors and the heart. J Cal Dent Assoc 26:668-76, 1998.
21. Weinberg MA, Fine JB. The importance of drug interactions in dental practice. Dent Today. 2001; 20:88-93.
22. Silvestre FJ, Verdú MJ, Sanchís JM, Grau D, Peñarrocha M. Effects of vasoconstrictors in dentistry upon systolic and diastolic arterial pressure. Med Oral. 2001; 6:57-63.
23. Perusse R, Goulet JP, Turcotte JY. Contraindications to vasoconstrictors in dentistry: Part III pharmacological interactions. Oral Surg Oral Med Oral Pathol 1992; 74:687-691.
24. Yagiela JA. Adverse drug interactions in dental practice: interactions associated with vasoconstrictors. Part V of a series. J Am Dent Assoc 1999; 130:701-709.

25. Budenz AW. Local anesthetics and medically complex patients. J Calif Dent Assoc 2000; 28:611-619.