Clinically Relevant Drug Interactions Associated with the Use of Analgesics in Dentistry

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ABSTRACT

An increasing number of patients on polypharmacy present to the dentist today for treatment. Analgesics are frequently prescribed. In addition to this, patients may also be taking over-the-counter medications for various reasons. Several drug interactions have been reported with analgesics prescribed for dental pain and other medications that the patient may be concomitantly on. However, not all of these drug interactions may be clinically relevant, especially in the dental setting where analgesic administration is only of a short duration, usually of 4-5 days. NSAIDs should be avoided in the elderly, in patients with renal impairment, in patients with severe congestive heart failure and over a long term. They may reduce the hypotensive effects of some antihypertensives. Preferably they should not be prescribed for patients on lithium, methotrexate, and digoxin. When used along with anticoagulants and selective serotonin reuptake inhibitors, they may potentiate gastrointestinal hemorrhage. Aspirin should be avoided in patients on sulfonylureas, valproic acid and carbonic anhydrase inhibitors. Ibuprofen should not be prescribed for high risk patients on aspirin. Paracetamol will result in increased hepatotoxic metabolites if taken by the patient who has stopped alcohol after chronic ingestion. Opioids and alcohol have a complex relationship and should be avoided. Merperidine and monoamine oxidase inhibitors can cause a significant adverse clinical interaction.

Keywords: Acetaminophen, Alcohol, Aspirin, NSAIDs, Opioids, Paracetamol

INTRODUCTION

Advances in the medical field such as early diagnosis, preventive therapy and better clinical outcomes in treating illness has resulted in an improvement in the quality of life of patients as well as a general increase in life expectancy. This manifests in the dental practice as an increasing number of patients who are undergoing concomitant therapy for other disease. Firstly, there is an increase in geriatric patients who present to the dental office. As compared to earlier times, when the geriatric population was mostly edentulous, patients now present seeking to preserve existing teeth and may also seek advanced treatment such as the placement of implants. Also polypharmacy is more common in the elderly due to comorbid conditions and age related changes in normal physiology. In addition, in younger patients, there is an increase in disease conditions such as cardiovascular disease and diabetes to name a few, most likely due to environmental and lifestyle changes. For India itself, the World health Organization estimated that 32 million people had diabetes in 2000. This was projected to increase to 69.9 million by the year 2025.[1]

Besides prescribed allopathic medication, patients may also be on over-the-counter medication, homeopathic medication, or may be taking ayurvedic, herbal or other natural remedies. These are primarily taken for general health improvement, for protecting against future disease, or for treating existing disease. The patient may not disclose this fact as the patient may not consider it relevant. Thus many patients presenting to the dentist may already be taking a variety of medications.

Toothache is a crucial symptom which may drive the patient to seek a dentist's help. Analgesics will almost certainly be prescribed, apart from any other measures to relieve the pain.

While analgesics are the most commonly prescribed drugs by the dentist, many of them come with warnings with regards to the possible interactions which can occur with other drugs. A point to be taken into consideration here is that most of these interactions have occurred when the patients have been using analgesics for prolonged periods of time. Dental management of pain usually involves only short duration of analgesic intake, usually 5 days or less. Although some caution is required, being overly cautious with the use of analgesics may prevent the patient from receiving deserved treatment.[2] Hence dentists should be familiar and attentive to these drug interactions and understand the basis on which they occur, in order to estimate the risk posed by analgesic administration to patients who are already on medication for other diseases.

NSAIDS

Nonsteroidal anti-inflammatory drugs (NSAIDs) are drugs which act by inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), which are enzymes involved in the production of prostaglandins (PG) and thromboxanes, thus inhibiting the production of these mediators. The action of drugs which are dependent on the physiologic levels of these mediators may be affected when they are used along with NSAIDS. The high plasma protein binding (PPB) ability of NSAIDS can also lead to drug interactions with other PPB drugs. There are a great number of adverse drug interactions that have been described when using NSAIDS along with other drugs, but all of these may not be relevant in the dental setting considering the short duration of medication and the low dosage.[2] The clinically relevant drug interactions that may be encountered will be discussed in the following.

NSAIDs and antihypertensives

NSAIDs have been found to interfere with those antihypertensives

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whose action depends on renal PG mechanisms to lower blood pressure.[3] These include β blockers, angiotensin converting enzyme inhibitors (ACEI), and diuretics. Other antihypertensives such as calcium channel blockers do not interact with NSAIDS.[2] β blockers produce their antihypertensive action by several mechanisms. One of them is by increasing the circulating PG. This effect is antagonized by NSAIDs, but probably not all NSAIDs.[2]

The renin-angiotensin-aldosterone system, glomerular filtration, renal tubular secretion of sodium and water, and vasodilation are regulated by PG. NSAIDs inhibit vasodilating renal PG, thereby increasing salt retention and decreasing glomerular filtration. When NSAIDs like ibuprofen and naproxen are used in patients who are also on these antihypertensive drugs, the hypotensive effect is attenuated, especially when NSAIDs are used for more than 5 days, due to inhibition of PG synthesis in kidneys. This may raise blood pressure and worsen its control, particularly in patients who already have renal problems. Increase in blood pressure has also been reported with the use of selective COX-2 inhibitors, mainly Rofecoxib. If postoperative pain medication is to be continued for more than 5 days, then the patient is to be recalled for assessment of the blood pressure. An increase of more than 10% above baseline would call for replacement of NSAIDs with acetaminophen.[3-5]

NSAIDs may reduce the action of ACEI directly, by its inhibitory action on renal vasodilatory and natriuretic PG or indirectly by interfering with ACEI induced PG production. In hypertensive patients with reduced renin production, the PG mediated ACEI action is of more value.[2] With the long term use of NSAIDS, the antihypertensive effect of ACEI have been shown to decline.[6,7] Hence hypertensive patients who are on ACEI should not be prescribed NSAIDs for more than 5 days for perioperative pain management; they can be used for 4 days or less.[6]

The effect of diuretics is reduced by NSAIDs interference with sodium secretion and plasma renin activity.[2] The combination of NSAIDs with ACEI and potassium sparing diuretics can produce hyperkalemia which can lead to bradycardia and syncope especially in elderly patients with hypertension or diabetes.[7]

When NSAIDs are used along with ACEI and diuretics there is an increased risk of acute kidney injury known as the "triple whammy" effect.[8] This occurs as all three drugs can affect the kidneys through different mechanisms. ACEI decrease glomerular filtration rate by dilating efferent arterioles. Diuretics can lead to volume depletion. When ACEI and diuretics are used together, glomerular filtration rates can no longer be sustained. Further, NSAIDs decrease PG synthesis which would otherwise maintain blood flow through the glomerulus, leading to afferent arteriolar vasoconstriction. Thus the combination can lead to acute renal failure which has been reported to cause fatalities.

Hence, patients who are already on combination therapy of ACEI and diuretics should not be prescribed NSAIDs. It should be used very judiciously in elderly patients with congestive heart failure and prior renal disease. In such patients, acetaminophen may be a better choice.[2] If NSAIDs are unavoidable, then only the lowest dose for the shortest duration may be used with great caution, with periodic monitoring of the patient.[8] Patients on these combination therapies should be advised not to self-medicate with over the counter NSAIDs.

These adverse effects of NSAIDs and antihypertensives are more commonly seen in elderly patients and those with comorbidities such as congestive heart failure, liver cirrhosis and chronic kidney disease, and with drug combinations like renin-angiotensin blockers, ACEI and diuretics along with NSIADs.[9]

NSAIDs and lithium

Lithium is the drug of choice for treating bipolar depression. Lithium has a low therapeutic index i.e. there is only a narrow margin of safety. Toxicity is more evident in patients with decreased renal function. Adverse effects of higher lithium levels are manifested as polyuria, polydipsia, nausea, vomiting, diarrhea, tremors, altered mental status and sedation. When NSAIDS are used along with lithium, they increase the concentration of lithium, which occurs due to prevention of renal PG synthesis resulting in increased lithium reabsorption. This is important especially since lithium is primarily excreted via the kidneys.[2]

The degree of interaction may differ with NSAIDS and the dose. Alterations in lithium levels is maximum with indomethacin. Piroxicam and phenybutazone which are potent PG inhibitors have also produced toxic interactions. No alteration is seen with sulindac and aspirin.[2,10]

Reports have also found that concomitant use of selective COX-2 inhibitors rofecoxib and celecoxib can lead to toxicity.[11] If NSAIDS are administered to a patient on lithium, then lithium levels are to be monitored every 4-5 days. With acute toxicity, lithium which is mainly extracellular, being a water soluble ion, is rapidly cleared by intravenous hydration and hemodialysis.[12] In cases of chronic lithium ingestion, intracellular and intracerebral concentrations are increased, which may continue to remain elevated requiring prolonged hemodialysis treatment as lithium equilibrates slowly between intra- and extra- cellular compartments.[12] In susceptible patients such as elderly patients, or those who may have impairment in kidney function, who are also subjected to polypharmacy, these interactions may be severe. Avoidance of more potent NSAIDs which have been found to increase lithium toxicity would be prudent. Other NSAIDs may be used with careful patient monitoring and only for a short duration. Lithium doses may require reduction.

NSAIDs and anticoagulants

The most frequent and grave adverse effect with the use of NSAIDs is upper gastrointestinal (GI) bleeding and hemorrhage. The bleeding is due to the harmful effects of NSAIDs on GI mucosa.[10,13] In addition to this, NSAIDs with warfarin can further produce harmful effects of bleeding in two more ways. NSAIDs displace warfarin from the PPB sites, increasing its plasma concentration, which adds to the hypothrombemic effect resulting in internal bleeding. The other is by decreasing normal platelet function.[14] Among the NSAIDs, aspirin carries a greater risk of this adverse effect as it produces irreversible platelet COX inhibition. If more than 3 gm/day of aspirin is used, it can decrease prothrombin levels and worsen bleeding problems. Thus NSAIDs, particularly aspirin, can compound the danger of bleeding with warfarin by inhibiting platelet function.[10] In addition to aspirin, mefanimic acid and ketoprofen in high doses should be avoided in patients being treated simultaneously with

warfarin, and even clopidogrel especially in the elderly.[3]

NSAIDs and methotrexate

Methotrexate is used for the treatment of rheumatic arthritis, psoriasis and cancer. Methotrexate has a low therapeutic index and can cause serious adverse effects like thrombocytopenia at higher doses. It has a better side effect profile when used at lower doses.[4] NSAIDs can decrease methotrexate renal clearance by decreasing vasodilating renal PG, thus increasing plasma concentrations of methotrexate which results in toxicity.[10]

NSAIDs are commonly prescribed for joint pain in patients with rheumatoid arthritis who are also on low dose methotrexate therapy. A review on the safety of NSAIDs used concomitantly in patients on methotrexate for inflammatory arthritis, reported that the combination of low dose methotrexate with NSAIDs, except anti-inflammatory doses of aspirin, does not produce significant clinical interactions.[15] However in such patients additional NSAIDs should be avoided for postoperative dental pain as it can lead to GI or renal toxicity of methotrexate.

For patients taking high doses of methotrexate like in the treatment of cancer, concomitant NSAIDs administration poses a significant risk and can result in renal failure or pancytopenia.[2] Ketoprofen, flurbiprofen, naproxen and ibuprofen have been implicated, even resulting in fatalities.

NSAIDs and ethanol

Alcohol and NSAIDs especially aspirin are both known to harm the gastric mucosa. Ethanol increases gastric acid secretion as well as enhances GI blood loss and extends bleeding time. Hence the ingestion of alcohol and aspirin should be separated by a period of at least twelve hours. The drug interaction may be less severe after dental procedures as NSAIDs have to be given only for a short period of time.[2,16]

NSAIDs and digoxin

Digoxin is used to treat chronic heart failure. It has a low therapeutic index and is cleared by the kidneys. NSAIDs administered to patients already on digoxin have resulted in increased plasma levels of digoxin. This is probably because NSAIDs decrease renal function. Such an action is more marked in elderly patients. However, if the patient is healthy and renal functioning is within normal limits, then simultaneous use is of little concern.[2]

NSAIDs and cyclosporine

Cyclosporine is prescribed in patients having undergone organ transplants in order to prevent organ rejection. It is also used in the treatment of rheumatoid arthritis. When NSAIDs and cyclosporine were combined, marked reductions in glomerular filtration rates and effective renal plasma flow were observed. The impairment of renal function when these drugs are used together is greater than that when either is used alone and is to a certain extent due to vasoconstriction. The concomitant uses of these increase the risk of nephrotoxicity. Although only limited evidence is available to substantiate this interaction, one should take into consideration the possibly serious adverse effects.[17]

NSAIDs and other NSAIDs

When taken for prolonged periods of time or in combination with each other, NSAIDs have been associated with nephrotoxicity. A position paper in 1996 recommended that aspirin in combination with other NSAIDs should not be taken together.[18] Combinations over longer periods should definitely be avoided, but those of a shorter durations like that in dental practice carries a lesser risk for renal damage. Nonetheless such combinations should be avoided, and NSAIDs could be prescribed either alone or in combinations with opioids for dental pain management.[2]

In addition to the risk of nephrotoxicity, the efficacy of aspirin may be reduced with concomitant administration of NSAIDs such as ibuprofen.[19] Naproxen and celecoxib and indomethacin may also interact with aspirin but to a lesser extent than ibuprofen. The decrease in aspirin efficacy could result in increased risk of myocardial infarction and stroke. If ibuprofen is to be administered, it may be done so at least 1 to 2 hours after or 8 hour before aspirin ingestion. Since aspirin has a long lasting action on platelet function, occasional use of ibuprofen only minimally attenuates the antiplatelet activity. But it would be best to avoid these drugs which have evidence of this interaction in higher risk patients, and instead prescribe drugs which are less likely to interact with aspirin such as diclofenac, meloxicam and sulindac.[3,20,21]

NSAIDs and selective serotonin reuptake inhibitors (SSRI)

Concomitant use of SSRI and NSAIDs results in increased risk of GI bleeding. When used in combination, the risk of upper GI bleeding exceeds the additive risks of the drugs when used alone. Caution is to be exercised in the patient who already has a history of GI mucosal bleeding. Thus if NSAIDs and SSRI are used then gastroprotection is required.[3,21,22]

Aspirin and sulfonylurea

The hypoglycemic effect of sulfonylurea is potentiated if aspirin is used along with it. Salicylates enhance the action by increasing insulin secretion, and decreases the plasma glucose level. Aspirin may also displace sulfonylurea from its protein binding site and increase its action. Thus in diabetic patients being treated with sulfonylureas, the use of aspirin should be avoided.[7,23]

Aspirin and anticonvulsants

Aspirin may displace valproic acid from its PPB sites as well as inhibit the metabolic pathway of valproic acid at higher concentrations. This can result in increased plasma concentration of valproic acid and resultant neurological, hematological and gastrointestinal adverse effects. The increased antiepileptic drug levels may increase toxicity but not necessarily the antiepileptic activity, thus requiring plasma concentration monitoring. Salicylates and valproate are both hepatotoxic and preferably should not be used together. Both also influence blood coagulation and platelet function. Naproxen also causes some degree of protein bound valproic acid displacement but not marked enough for a clinical effect.[2,7,24]

Aspirin and carbonic anhydrase inhibiters

Acetazolamide is a drug which acts by inhibiting carbonic anhydrase inhibitor. It is used for the treatment of glaucoma and mountain sickness. Aspirin displaces acetazolamide from its PPB site as well as inhibits its clearance. Reciprocal augmentation of both the drugs may be observed. These factors can lead to increased levels of drugs which manifests as lethargy, incontinence, confusion and metabolic acidosis. This can occur more so in the elderly and in patients with renal failure. Thus aspirin should be avoided in patients on acetazolamide.[25,26]

ACETAMINOPHEN

Paracetamol or acetaminophen is used very frequently for the management of mild to moderate pain with the advantage of fewer side effects when compared to other NSAIDS or opioids. It is considerably safe when used for a short period of time in therapeutic doses. But if used regularly over prolonged periods, then it can lead to impaired kidney function. In dentistry, drug interactions between paracetamol and alcohol are very important.

About 95% of paracetamol is converted to an inactive compound by conjugation. But 5% is converted to a highly reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI) by cytochrome P-450 enzyme CYP2E1. In patients with normal hepatic function, this NAPQI is conjugated with glutathione to an inactive metabolite and the liver is protected. (See Figure 1). If NAPQI is produced in excessive amounts, it can lead to hepatic cell death. This may occur if the patient has ingested other drugs that induce liver enzymes. Also if glutathione stores are depleted in the body, as with higher doses of paracetamol, then this NAPQI cannot be deconjugated leading to toxicity. The interaction with alcohol becomes significant as it is metabolized by the same enzymes as paracetamol. (See Figure 2). Ethanol also induces and increases levels of CYP2E1.[2,4,7,27]

When alcohol is ingested over a long period of time, due to enzyme induction, the levels of CYP2E1 is increased.[16] If ethanol is present in the body, this increased CYP2E1 will be preferentially occupied by it and will be unable to metabolize other drugs to a large extent. Thus if alcohol and paracetamol are taken simultaneously, then the level of toxic NAPQI may even be decreased. After chronic use of alcohol, if it is abruptly stopped for 12 hours and paracetamol is taken, the levels of CYP2E1 remain increased and paracetamol will now occupy the CYP2E1. Thus increased amounts of NAPQI may be produced and would be harmful. In alcoholic patients, the level of glutathione is decreased and may be insufficient to metabolize this excess NAPQI, resulting in increased toxicity. (See Figure 3). NAPQI formation will depend on how chronic the ingestion of alcohol has been and when alcohol was last consumed before paracetamol. Abrupt stoppage of alcohol and intake of paracetamol can cause a major risk. Thus if alcoholics are to be prescribed paracetamol, then the patient should not be asked to abstain from alcohol before the intake of paracetamol.[27,28] Dose reduction may be considered from 4 g to 2g.[2]

Alcohol consumption and intake of paracetamol is a matter of concern in patients who are just social drinkers, who may stop alcohol and then take paracetamol which may be in therapeutic or subtherapeutic doses. The levels of CYP2E1 may remain high for a few weeks due to enzyme induction with alcohol.[4]

If paracetamol is taken with hepatotoxic drugs or enzyme inducers, there is increased danger of paracetamol toxicity. Metoclopramide increases the absorption of paracetamol. With probenacid, the excretion of paracetamol is affected. The plasma concentrations may vary. If cholestyramine is given within an hour of paracetamol, absorption of paracetamol is decreased. Paracetamol enhances the anticoagulant effect of warfarin and the effect increases the dose. This drug interaction is seen more with a regular – daily dose of paracetamol then with an occasional dose of paracetamol. Inspite of expected drug interactions with warfarin, paracetamol still is a better choice of

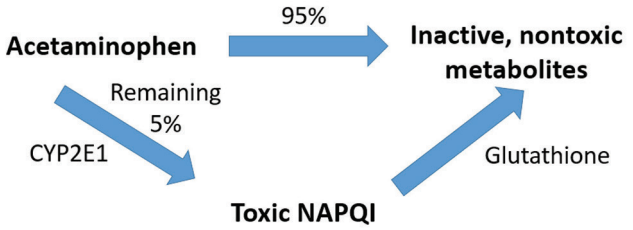

Figure-1: Metabolism of acetaminophen.

Figure-2: Metabolism of ethanol

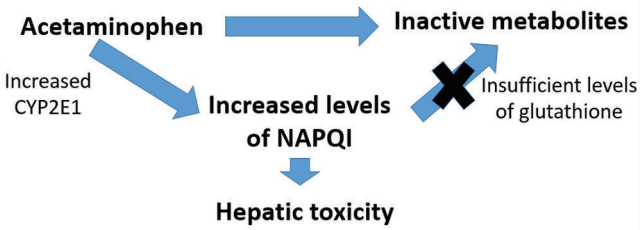

Figure-3: Metabolism of acetaminophen following chronic ingestion of alcohol.

analgesics as compared to other NSAIDs as it does not inhibit platelet function, nor does it lead to GI irritation or bleeding.

OPIOIDS

Opioids are employed in treatment of moderate to severe dental pain. They are used along with NSAIDs or paracetamol. They should never be used alone for the treatment of dental pain which is of an inflammatory nature as these drugs are not anti-inflammatory drugs. Opioids should only be used for the shortest duration of 3 days or less, only after the use of NSAIDs and/or acetaminophen is optimized.[21] The prescribing dentist should be aware of abuse with opioids. The clinical interactions of concern in dentistry is their interaction with alcohol and monoamine oxidase inhibitors.[2]

Opioids and alcohol are both known to cause CNS depression. Taking these together causes marked sedation of the patient resulting in drowsiness. Overdoses of this combination can reduce the cough reflex predisposing the patient to a risk of chocking on objects, food or fluids stuck in their airways. It may also cause respiratory depression.[16] Both alcohol and opioids are also metabolized by the hepatic system. The combination of both has resulted in slower elimination rates and higher toxicity. Opioids should best be avoided in the alcoholic patient considering the complex and multifactorial relationship that may be present with alcohol and opioid abuse.[29]

Adverse clinical interactions are seen when merperidine is administered along with monoamine oxidase inhibitor which clinically manifests as excitatory and depressive forms and even fatalities due to the excitatory effects.[30] This interaction has been postulated to occur as a result of accumulated serotonin secondary to monoamine oxidase inhibition, referred to as "acute serotonin syndrome" which clinically presents as delirium, hyperthermia and convulsions.[3] It is thus advised that patients who have been on monoamine oxidase inhibitors should not be prescribed merperidine until 2 weeks have passed.

CONCLUSION

Adverse drug interactions have been reported in dentistry with the use of analgesics, but due to the short duration of analgesic use for postoperative dental pain management, the clinically relevant interactions are limited. The risks of these adverse effects increase in the presence of comorbidities and in patients on polypharmacy. NSAIDs should be avoided in patients who are elderly, have renal or liver dysfunction, or are concurrently on long term NSAIDs. The hypertensive action of ACEI, diuretics and β blockers may be reduced if NSAIDs are used for more than 5 days. NSAIDs should never be used if the patient has severe congestive heart failure neither if the patient is on concomitant ACEI and diuretic treatment due to the possibility of the triple whammy. NSAIDs should be avoided in patients on lithium, methotrexate and digoxin as it may increase plasma levels of these drugs resulting in toxicity. When used with anticoagulants, the GI effects of NSAIDs predispose the patient to GI hemorrhage especially in the elderly, thus should be avoided. NSAIDs and SSRI also increases the risk of GI bleeding especially if the patient has a previous history of GI mucosal injury. NSAIDs prescribed in a patient on cyclosporine could increase the risk of nephrotoxicity. This risk of nephrotoxicity is also increased when NSAIDs are prescribed in combination with other NSAIDs. Ibuprofen should be avoided when the patient is on aspirin as this may increase the risk of myocardial infarction and stroke, and other NSAIDs may be considered instead. Aspirin along with anticonvulsants and carbonic anhydrase inhibitors may increase toxicity. Prescribing aspirin in patients on sulfonylureas may potentiate the hypoglycemic effect. Paracetamol is a preferred alternative to NSAIDs due to reduced side effects and drug interactions. However insufficient conjugation of its metabolite will result in increased hepatotoxicity. This risk increases when administered in patients with liver dysfunction, in undernourished patients, in the alcoholic patient or in patients treated with other hepatotoxic medications, wherein dose reductions may be considered. Opioids should be avoided with alcohol. Merperidine should not be prescribed for a patient who has been on monoamine oxidase inhibitors in the last 14 days.

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