Analgesic choice in dentistry
Part II: The toxicity

Abstract
Nonopioid analgesics are widely prescribed in dentistry. The first article of this series reviewed the mechanism of action of acetylsalicylic acid (aspirin), acetaminophen (paracetamol) and dipyrene; this part discusses the risks related to the use of these drugs. Paracetamol and dipyrene in therapeutic doses, unlike aspirin, do not cause nausea, do not interfere with protrombin time, do not inhibit the platelet aggregation, and do not produce as many side effects as does aspirin. The adverse reactions in relation to paracetamol seem to be restricted to situations where acute overdose occurs. In relation to dipyrene, blood dyscrasias such as the agranulocytosis are the main adverse reactions.

Key Words:
analgesics, toxicity, dentistry
Introduction
Drug prescription is an important part of dental treatment. Among the drugs used in dentistry, nonopioid analgesics are the most commonly prescribed. Several reports point out medicines as an important cause of intoxication. In Brazil, 75,717 cases of intoxication were recorded between 1994 and 1997; 2,263 out of the 22,165 cases of intoxication by medicine were related to analgesics. These drugs are equipotent in promoting postoperatively pain relief; however, they have different pharmacokinetic and pharmacodynamic characteristics, leading to special precautions in their prescription. The first article of this series reviewed their mechanism of action; this part deals with rational choice among acetylsalicylic acid (aspirin), acetaminophen (paracetamol) and dipyrone, considering and comparing their possible risks.

Aspirin
Low doses of aspirin are known to cause some adverse effects such as gastrointestinal disturbances and risk of bleeding. The most commonly reported side effect is nausea. It is important to emphasize that many procedures or illnesses might cause nausea by themselves and that the analgesics may be unjustly blamed. Aspirin significantly increases the bleeding time by inhibiting the aggregation of platelets. In a clinical study reported by Yagiela et al. (2000), the bleeding time was increased two to three times 20 minutes after a single dose of aspirin, and did not return to baseline for several days. The chronic or intermittent use of high doses of aspirin must be avoided during pregnancy, because it can affect the hemostasis mechanism of both the mother and the newborn. High doses may increase perinatal mortality, retard intrauterine growing, and cause teratogenic effects. Near to the termination, indeed in low dosages.

Patients with aspirin hypersensitivity (especially that associated with nasal polyps) may develop asthma resulting from the increased synthesis of leukotrienes when prostaglandin synthesis is inhibited. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may cause acute episodes of urticaria or angioedema. Although this is an uncommon syndrome, it is important to recognize it, since the administration of aspirin and many other NSAIDs may result in severe and possibly fatal reactions. The nonacetylated salicylate appears to be considerably less able to produce these reactions than are aspirin and other agents. Treatment of such responses does not differ from that ordinarily employed in acute anaphylactic reactions.

As a result of this wide use and ready availability, salicylate is frequently the cause of intoxication. Poisoning or serious intoxication often occurs in children and is sometimes fatal. Mild chronic salicylate intoxication is termed salicylism. The syndrome includes headache, dizziness, singing in the ears, difficulty in hearing, dimmers of vision, mental confusion, lassitude, drowsiness, sweating, thirst, hyperventilation, nausea, vomiting, and occasionally diarrhea. A more severe degree of salicylate intoxication is characterized by more pronounced Central Nervous System disturbances (including generalized convulsions and coma), skin eruptions, and marked alterations in acid-base balance. Fever is usually prominent, especially in children. Dehydration often occurs as a result of hyperpyrexia, sweating, vomiting, and the loss of water vapor during hyperventilation; its treatment is directed at cardiovascular and respiratory support and correction of acid-base abnormalities, in addition to the use of measures to speed excretion of salicylate.

The use of aspirin in children during or immediately after a viral infection has been associated with an increase in the incidence of Reye’s syndrome. This syndrome is a rare acute encephalopathy associated with fatty degeneration of the liver; although its etiology remains uncertain, it is known to occur after viral infections such as chickenpox (varicella) or influenza, and may, in mild cases, be a common cause of vomiting after such infections.

Paracetamol
Overdoses of paracetamol are an increasingly common cause of acute liver failure. The inclusion of paracetamol in numerous medications in addition to its frequent use must be a matter of concern not only for acute but also for chronic paracetamol toxicity. Paracetamol, a commonly used analgesic-antipyretic, is responsible for more hospitalizations after overdose than any other common medication. Susceptibility to the hepatotoxic effects of paracetamol is, therefore, dependent on many factors, some of which have inter-individual variability (e.g., the dose taken, genetically determined P-450 activity, GSH [reduced glutathione] availability, capacity for glucuronidation and sulfation, and regeneration capacity).

In therapeutic doses, a mild increase in hepatic enzymes may occasionally occur in the absence of jaundice; this is reversible when the drug is withdrawn. With larger doses, dizziness, excitement, and disorientation are seen. Despite these data, the ability to predict the dose taken and the length of time intake that dose required for the development of toxicity is very difficult due to inter-individual variability of paracetamol metabolism.

It is well known that paracetamol is converted by the hepatic cytochrome P450 system into reactive compounds. The reactive metabolites lead to hepatotoxicity following overdose. The most serious adverse effect of acute overdosage of paracetamol is a dose-dependent, potentially fatal hepatic
necrosis\textsuperscript{17}. Clinical indications of hepatic damage are seen within 2 to 4 days of ingestion of toxic doses. Plasma aminotransferases are elevated, and the concentration of bilirubin in plasma may be increased; in addition, the prothrombin time is prolonged. Acute renal failure also occurs in some patients\textsuperscript{18}. The main antidotal treatment is the administration of sulphhydryl compounds, which probably act by restoring hepatic glutathione levels. N-acetylcysteine is effective when given orally or intravenously\textsuperscript{14}. Despite the conversion of paracetamol into reactive compounds, hypersensitivity reactions are rare, although urticaria is produced in occasional patients\textsuperscript{18}. Possibly, the chronic use of paracetamol may result in renal disturbances, such as interstitial nephritis\textsuperscript{18}. Paracetamol, salicylamide, and fenylbutazone are the analgesic and anti-inflammatory drugs most commonly used during pregnancy\textsuperscript{19}, although there are studies reporting teratogenic effects of these drugs on renal development of human fetus. Hepatotoxicity and renal deficiency in the fetus and metahemoglobinemia and hemolytic anemia in newborn are also related to the use of such drugs during pregnancy\textsuperscript{17}. Allergy to sodium bisulphite or metabisulphite has been reported for other analgesic and antipyretic drugs marketed. Allergy to sodium bisulphite or metabisulphite has been “fresh” for long periods of time. People allergic to bisulphites (most often corticosteroid-dependent asthmatics) may develop bronchospasm, a severe response to this antioxidant drug. A history of allergy to bisulphites should alert the dentist to the possibility of this same type of response if sodium bisulphite is included in drug formulations, such as those of paracetamol drops solution and some local anesthetic solutions\textsuperscript{20}.

**Dipyrone**

Dipyrone is widely used as an analgesic in some parts of the world, including South America, South Africa, Middle East and some European countries. In other regions (like United States and United Kingdom) it has been banned because of its controversial association with agranulocytosis\textsuperscript{21}. The balance between the benefit and harm associated with this drug is particularly important to developing countries where dipyrone may be the first-line analgesic and where other drugs may not be readily available. In Brazil, media pressure has caused a recent debate; with the outcome that dipyrone remains an over-the-counter medication\textsuperscript{22}. Agranulocytosis is a potentially lethal adverse reaction of dipyrone. According to case-control studies, the frequency is low, approximately one per a million users\textsuperscript{23}. The estimated excess mortality rate due to agranulocytosis, aplastic anemia, anaphylaxis and serious upper gastrointestinal complications was 185 per 100 million for AAS, 592 per 100 million for diclofenac, 20 per 100 million for paracetamol and 25 per 100 million for dipyrone\textsuperscript{24}. Although scarce, the literature about the use of dipyrone during the first trimester of pregnancy relates that it is probably not associated with increased risk of major malformations\textsuperscript{21}. According to the Boston Study\textsuperscript{25}, dipyrone is not related to the aplastic anemia, and, when associated with agranulocytosis, its risk is 1.1 cases per million users. In a recent population-based surveillance of aplastic anemia and agranulocytosis in the metropolitan area of Barcelona, Spain, the attributable incidence of agranulocytosis by dipyrone was found to be 0.56 cases per million inhabitants; no association between aplastic anemia and the use of dipyrone was found\textsuperscript{26}. According to Ibáñez et al. (2005)\textsuperscript{26} the risk of agranulocytosis increases with duration of use and disappears 10 days after the last dose of dipyrone. In a recent meeting concerning the safety of dipyrone\textsuperscript{27}, sponsored by ANVISA, the Brazilian agency responsible for health surveillance, the following conclusions were reported:

- The efficacy of dipyrone as an analgesic and antipyretic is unquestionable;
- The risks attributed to its use in Brazil, so far, are low; published data on such risks are not enough to indicate an alteration in the current drug regulation for dipyrone (over-the-counter);
- This alteration would increase the risk of prescription of other drugs, prescribed for the same therapeutical purpose, but not as effective.
- The risks of dipyrone are similar to, or lower than those reported for other analgesic and antipyretic drugs marketed.

In relation to hypersensitivity, dipyrone is reported as a precipitant of asthma episodes in patients with intolerance to aspirin and AINES, probably due to COX inhibition; however, such risk incidence is unknown\textsuperscript{28,29}. Dental clinicians should choose the medicine based on both mechanism of action (previously discussed in the first article of this series) and toxicity, to promote a successful analgesic effect as well as comfort to the patient. Analgesics are commonly recommended for the management of mild to moderate acute dental pain and their use in dentistry should be restricted to a short-time period (1 to 3 days). In conclusion, unlike aspirin, paracetamol and dipyrone in therapeutic doses do not cause nausea, do not draw out the prothrombin time, do not inhibit the platelet aggregation, and do not produce as many side effects. They are, therefore, first-line analgesics in dentistry.

References

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