Learning Outcomes

1. Medical Conditions and Their Impact on Dental Care.
3. The Special Care Needs Patient.
7. Infections, Infectious Diseases and Dentistry.

Pharmacology & Therapeutics in Dentistry

- We are all dealing with an increasing ageing population who are retaining their teeth well into old age. A large proportion of this population will be taking one or two medicines to enable them to continue with their normal daily activities.

- Certain drugs are the mainstay of dental practice. These include antibiotics, analgesics, local anesthetics, and agents to control anxiety.

Pharmacology & Therapeutics in Dentistry

- Many of our patients are medically compromised and this raises three important issues with respect to the delivery of routine dental care:

  1. Can the patients medication cause an adverse reaction in the mouth and associated structures?
  2. Can the drugs that I wish to prescribe interact with their current medication?
  3. What medical emergencies are likely to arise in this population and how should they be dealt with?

Evidence-Based Dentistry (EBD) on the Use of Analgesics

- Management of pain is a critical and challenging component in dentistry.

- Pain, is usually not adequately treated.

- Knowing how well an analgesic works and its associated adverse effects is fundamental to clinical decision-making.
**Aims of Presentation**

1. Are there **clinically important differences** in the **efficacy** and **safety** between different analgesics and techniques?

2. If there are differences, which are the ones that are more **effective** and associated with fewer **adverse effects**?

3. Which are the **effective therapeutic approaches** that could reduce the adverse effects?

**Pain Mechanisms Underlying Analgesic Efficacy**

- Oral Tissue **Insult** Activates the **Inflammatory Process** (this is inflammatory pain not nociceptive pain nor neuropathic pain)
  - Releases a large series of **pain mediators** (prostaglandins, bradykinins) → ↑sensitivity & excitation of peripheral nociceptors.
  - These usually have little spontaneous activity under normal conditions (**peripheral sensitization**).

**Chemical Mediators for Dental Pain**

(Seymour et al., 2008)

<table>
<thead>
<tr>
<th>Pain mediators</th>
<th>Source</th>
<th>Drug antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradykinin</td>
<td>Plasma kininogen</td>
<td>Non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Histamine</td>
<td>Mast cells</td>
<td>Anti-histamine</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Thromboxane acid</td>
<td>Non-steroidal anti-inflammatory drugs</td>
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<tr>
<td>Endorphines</td>
<td>Enkephalins</td>
<td>Non-steroidal anti-inflammatory drugs</td>
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<tr>
<td>Substance P</td>
<td>Primary afferent nerve</td>
<td>Opioids</td>
</tr>
<tr>
<td>Glutamate, aspartate</td>
<td>Primary afferent nerve</td>
<td>N-methyl D-aspartate receptor antagonist</td>
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**Pain Mechanisms Underlying Analgesic Efficacy**

- Repetitive **C-fiber nociceptor stimulation** from the periphery + excitatory amino acids (glutamate and aspartate) + several peptides (substance P) increase → activation of N-methyl-D-aspartate (NMDA) receptors of the postsynaptic second-order neuron in the dorsal horn.
  - This leads to increased responsiveness of neurons in the central nervous system and to **central sensitization**, which is responsible for the prolonged pain after dental surgery.

**Pain Mechanisms Underlying Analgesic Efficacy**

- The analgesic effect of NSAIDs is primarily the result of their **inhibition of the synthesis** of prostaglandins and bradykinins through the **inactivation of cyclo-oxygenase**.
  - Opioids exert at least part of their effect by inhibiting substance P release in the peripheral and the central nervous systems.

**Pain Mechanisms Underlying Analgesic Efficacy**

- Once central sensitization is established, larger doses of analgesics are required to suppress it.
- The concept of **pre-emptive analgesia** (analgesic intervention before nociception) is particularly useful because it can potentially:
  - prevent the induction of central sensitization by blocking the arrival of nociceptive input to the central nervous system and can
  - prevent peripheral sensitization by preventing the formation of pain mediators in the injured tissues.
Many dentists and patients are confused as to which analgesic is most efficacious for the pain that needs to be treated.

Frequently, the choice of analgesic is based on personal preference rather than evidence-based information.

There is a wealth of information available for the efficacy of analgesics for dental pain.

Analgesics available for dental pain management belong to two major groups: the non-opioid analgesics (e.g. NSAIDs and acetaminophen) and opioids.

Opioids

Oxycodone 15 mg is the only opioid that has a NNT close to that of NSAIDs (2-3) in the Oxford League Table – high incidence of reported adverse effects.

Oxycodone has 10 to 12 fold greater potency than codeine.

Codeine phosphate 60 mg and tramadol 50 mg have NNT of 16.7 and 8.3, respectively.

But tramadol produced dose-related analgesia.

Efficacy: NSAIDs and Acetaminophen

Traditional NSAIDs (ibuprofen, diclofenac, and naproxen) and COX-2 inhibitors (rofecoxib, valdecoxib, and lumiracoxib), do extremely well in this single-dose comparison, but they do differ in efficacy.

Results from a recent meta-analysis also indicate that NSAIDs are clearly more effective in dental surgery compared with acetaminophen, whereas their efficacy appeared to be without substantial differences from acetaminophen in general and orthopedic surgery (Ong et al. 2005).

Efficacy: Opioids

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Efficacy: NSAIDs and Acetaminophen

COX-2 inhibitors have equal or better analgesic efficacy compared with traditional NSAIDs (Ong et al. 2005).

NSAIDs vary in their time of onset and their duration of analgesic effect:

- the longer the half-life of the drug, the slower the onset of effect.
- a higher dose has a faster onset, higher peak effect, and longer duration.

It is advantageous to start with a high dose of a short half-life drug and then adjust the dose downward when analgesic efficacy has been achieved, e.g. ibuprofen.

Efficacy: Opioids

Oral opioids alone are a poor choice for acute dental pain because they provide relatively inferior analgesia and more adverse effects compared to NSAIDs.

Opioids may be used as adjunctive analgesics and can be combined with acetaminophen to increase its efficacy. For example:

- Codeine phosphate 60 mg with acetaminophen 1,000 mg increases its efficacy from a NNT of 16.7 to 2.2.
- Tramadol 75 mg with acetaminophen 690 mg increases its efficacy from a NNT of 8.0 to 3.0.
**Effects of Formulation on the Analgesic Efficacy**

- Formulations of certain analgesics can have a profound effect on their efficacy and the onset of analgesia.
- Absorption of ibuprofen acid is influenced by formulation, and certain salts of ibuprofen (e.g., lysine and arginine), and solubilized formulations have an enhanced onset of activity:
  - Ibuprofen lysine 400 mg produces faster onset and higher peak analgesia than a conventional ibuprofen. (Cooper et al., 1994)
  - Diclofenac sodium softgel has been shown to provide very rapid onset and prolonged analgesic duration compared with conventional diclofenac potassium. (Zuniga et al., 1999)

**Effects of Formulation on the Analgesic Efficacy**

- Many opioids have a short elimination half-life, which necessitates frequent administration (as frequent as every 2–4 hours).
- Sustained-release or controlled-release formulations have been developed (once-or twice-a-day dosing).
  - Sustained-release oxycodone, codeine, and tramadol have been shown to be effective for chronic pain.
  - However, sustained-release formulations usually have a slower onset of action. Timed-release formulations are of limited value for treatment of acute pain.

**Adverse Effects of Analgesics**

- Dentists need to know the likelihood of adverse effects of analgesics to assess the Efficacy: Risk ratio.
- This applies to both serious clinical effects that may cause significant morbidity or mortality, and to more trivial symptoms that may affect quality of life and drug compliance.

**Effects of Formulation on the Analgesic Efficacy**

- Failure to achieve adequate pain relief with one NSAID is followed by a trial of another NSAID from the same or different class. Good management of pain may be achieved with such a second agent. (Mehlisch et al., 1999)
- If two NSAIDs of two different classes have been tried individually, further attempts to obtain benefit from NSAIDs are unlikely to succeed. (Mehlisch et al., 1999)
- Opioids may be required when NSAIDs and acetaminophen are contraindicated, e.g. because of allergy.

**Effects of Formulation on the Analgesic Efficacy**

- Improved clinical outcomes have been documented with combinations of analgesic agents:
  - Not all combinations of dose ratios lead to enhanced analgesia or reduced adverse events.
    - Acetaminophen/NSAID combinations have been shown in RCTs to have better analgesic efficacy than the single agent alone for dental pain without an increased incidence of adverse events. (Fricke et al., 1999)
    - Acetaminophen/NSAID combination has shown to act synergistically to improve analgesia for acute postoperative pain. (Truitt et al., 2004)
  - Many studies have been able to show that a NSAID/opioid combination is better than NSAIDs alone for dental pain – combinations of ibuprofen/ codeine, ibuprofen/oxycodone, naproxen/codeine have failed to show any additive effects in many dental studies. (Shannon et al., 1997; Radden et al., 2004; Nelson et al., 2004)

**Adverse Effects of Non-steroidal Anti-Inflammatory Drugs (NSAID)**

- Minor Side Effects: nausea, vomiting, diarrhea, dizziness, and headache.
- Serious Side Effects: prolonged bleeding after surgery, kidney failure, and gastrointestinal and cardiovascular adverse effects.
- Increased risk of cardiovascular adverse events in patients taking certain NSAIDs, particularly cyclooxygenase-2 (COX-2) inhibitors (Garcia Rodriguez et al., 2005).
Gastrointestinal Risk of traditional NSAIDs

- Ibuprofen has the lowest risk among the traditional NSAIDs, diclofenac and naproxen have intermediate risks, and piroxicam and ketorolac carry the greatest risk.
- However, it should be noted that the advantage of low-risk drugs may be lost once their dosage is increased.
- Risk for GI complications increases in the following groups: ≥ 65 years, peptic ulcer disease, alcoholics, on corticosteroids, on anticoagulants, on aspirin, chronic use (risk develops in a time-dependent manner).

Therapeutic Approaches to Reduce GI Toxicity of Traditional NSAIDs

1. Use a drug other than a traditional NSAIDs when possible (e.g. acetaminophen).
2. Use the lowest effective dose because the risk is dose-dependent and the efficacy of traditional NSAIDs has a ceiling effect.
3. Anti-ulcer co-therapy and cyclooxygenase-2 inhibitors can be used in high-risk GI patients.

Use of Anti-ulcer Co-therapy

- Misoprostol (a synthetic prostaglandin E1 analogue), effectively reduces GI acid to prevent traditional NSAID dependent Gastropathy. (Sheth et al, 1999) Because of its non-specific mode of action, a significant proportion of patients reported adverse events such as diarrhea, and discontinued it.
- No evidence that the concomitant use of H2-blockers or antacids will either prevent the occurrence of GI effects or allow continuation of traditional NSAIDs when and if these adverse reactions occur. (Bagg et al, 2000)

Use of Cyclooxygenase-2 (COX-2) Inhibitors

- Evidence has shown that COX-2 inhibitors have reduced GI toxicity compared to traditional NSAIDs.
- VIGOR (Bombardier et al, 2005), CLASS (Silverstein et al, 2000), TARGET (Schmier et al, 2006), and SUCCESS-I (Singh et al, 2007) trials have provided evidence that COX-2 inhibitors minimize risk for GI events.
- A recent meta-analysis has shown that treatment with etoricoxib was associated with a significantly lower incidence of GI adverse events than was treatment with traditional NSAIDs. (Kane et al, 2007)
Evidence from several large-scale RCTs of structurally distinct COX-2 inhibitors indicated that such compounds clearly elevate the risk of MI and stroke. (REACT Trial by Ott et al, 2003; VIGOR Trial by Bombardieri et al, 2005; APPROVe Trial by Bresalier et al, 2005; APC Trial by Solomon et al, 2005)

Worldwide withdrawal of rofecoxib and valdecoxib.

Although it seems clear that COX-2 inhibitors increase the risk for CV events, the risk differs to some degree between individuals and across agents, is dose-related, and varies with the duration of therapy.

Some studies suggest celecoxib, etoricoxib, and lumiracoxib have a better safety profile than other COX-2 inhibitors, which is why these drugs have remained on the market. (Osbourn et al, 2002; Schatzkin et al, 2004).

Recent studies have shown that some COX-2 inhibitors are not associated with increased CV risks:

- The SUCCESS (Singh et al, 2004) trial found no increased CV risks with etoricoxib compared to diclofenac or naproxen in 13,773 patients with osteoarthritis.
- The TARGET (Sachse et al, 2004) trial found no significant difference in CV deaths between lumiracoxib and either celecoxib or naproxen irrespective of aspirin use in 18,305 patients with osteoarthritis.
- The MEDAL-C (Connolly et al, 2006) trial found no increased CV risks of etoricoxib compared to diclofenac in 54,701 patients with osteoarthritis.

Cardiovascular Risk of NSAIDs

The FDA (USA) and the NICE (UK) have concluded that the increased risk of CV events may be a class effect for all NSAIDs and recommended that they all will now carry stronger warnings for adverse side effects, including gastrointestinal and cardiovascular adverse effects.

These serious warnings for all NSAIDs may have been exaggerated and have definitely, and perhaps needlessly, frightened NSAID users, because current literature supports the enhanced cardiovascular toxicity of cyclooxygenase-2 inhibitors over traditional NSAIDs.

With the recent findings of cardiovascular adverse effects of COX-2 inhibitors, a potential safety concern has been raised as to whether the increased CV events would be a class effect for all NSAIDs.

No placebo-controlled RCT addressing the CV safety of traditional NSAIDs only observational studies, and comparator RCTs.

Traditional NSAIDs may increase the risk for MI (2004). In particular, diclofenac carries a higher risk than other traditional NSAIDs (because it is a more COX-2 selective); this was not the case for naproxen.

Acetaminophen has a safer profile than NSAIDs. A recent meta-analysis of 47 RCTs shows no statistically significant differences in the frequency of reported adverse effects between acetaminophen and placebo. (Barden et al, 2004)

Overdose can cause hepatotoxicity.
Severe hepatotoxicity has been reported even after therapeutic doses in patients with risk factors such as chronic alcohol consumption, human immunodeficiency virus infection, and hepatitis C virus infection.

Adverse Effects: Acetaminophen
Adverse Effects: Opioids

- Two recent meta-analyses for the adverse effects of opioids in pain management showed that about 1/3 of patients abandoned treatment because of adverse events (Moore et al., 2005; Furlan et al., 2006).
  - Dry mouth (25%)
  - Nausea (27%), and
  - Constipation (15%) were most common.
- In view of the frequency of adverse effects, softening laxatives and anti-emetics (e.g., metoclopramide) should be made available at the same time.

Adverse Effects: Opioids

- Another meta-analysis of analgesics for dental pain shows that codeine and codeine combinations were associated with a significant increase in patients suffering adverse events compared with NSAIDs alone (Barden et al., 2004).
- The frequency of adverse events with opioids is more common than with NSAIDs and acetaminophen, making them a poor choice for dental pain.

Techniques of analgesic Administration: Routes

- It is a common belief that parenteral NSAIDs would be more efficacious than the oral route.
- A meta-analysis of 26 RCTs compared the analgesic efficacy of NSAIDs given by different routes in acute and chronic pain (Tramer et al., 1998) – there was a lack of evidence for any difference in analgesic efficacy of NSAIDs given by different routes.
- The intramuscular, intravenous and rectal routes were more likely to have specific local adverse effects. The oral route should be used whenever possible!

Techniques of analgesic Administration: Timing

- Traditionally, analgesics were given after surgery when patients experienced moderate to severe pain. The nociception may be upregulated through both peripheral and central sensitizations, leading subsequently to more intense postoperative pain.
- Prophylactic Preoperative Analgesics (Pre-emptive Analgesia)
- A recent meta-analysis of 66 RCTs has concluded that pre-emptive analgesia is effective for NSAIDs but not for opioids (Ong et al., 2005).

Drug Interactions: NSAIDs

- Most NSAID interactions relate to the antiplatelet and gastrointestinal effects:
  - Aspirin – NSAIDs (in particular ibuprofen) may reduce its cardioprotective benefits and increase GI risk, diclofenac, rofecoxib, or acetaminophen do not influence the effects of aspirin on platelet function.
  - The gastroprotective benefit of COX-2 inhibitors is partially or, in some patients, totally lost if aspirin is used for cardiovascular prophylaxis.

Drug Interactions: NSAIDs

- NSAIDs antagonize the antihypertensive effects of ACE inhibitors. The risk of renal impairment or hyperkalemia is increased when patients are treated with these two classes of drugs simultaneously.
- Warfarin levels are likely to be increased if patients are treated with NSAIDs because of competition for protein-binding sites.
- Antidiabetic effects of the oral sulfonylureas are increased by the co-administration of NSAIDs.
Drug Interactions: NSAIDs

- **Corticosteroids** – risk of peptic ulceration with associated perforation and bleeding is increased in patients taking both drugs.
- **Diuretics** – nephrotoxicity is increased, which is probably the result of reduced extracellular fluid volume. The diuretic effect is antagonized and an elevation in serum potassium can occur.
- **Methotrexate** – levels of methotrexate can be increased because of the direct competition for renal excretion of the two drugs.

Drug Interactions: Acetaminophen

- It has the fewest drug interactions.
- Acetaminophen is metabolized in the liver, drugs that increase the action of liver enzymes that metabolize acetaminophen (e.g., carbamazepine) may decrease the action of acetaminophen.
- The potential for acetaminophen to harm the liver is increased when it is combined with alcohol or with drugs that also harm the liver.

Drug Interactions: Opioids

- Most opioid interactions stem from the drugs' effects on the liver enzymes, which are largely responsible for the elimination of drugs.
- These interactions can either slow down or speed up that elimination:
  - An example of the former is the sometimes-fatal interaction between pethidine and MAOI antidepressants, an interaction that can cause an extreme increase in body temperature and seizures.
  - An example of the latter is the withdrawal symptoms reported in patients maintained on methadone when they are given phenytoin.

Algorithm for Decision Making in Pain Management

- NSAIDs should be first-line analgesics, especially for severe dental pain where no contraindications exist.
- The most efficacious and least toxic agent should be used first.
- Availability, cost, and length of action.
- Mucosa-protective agents should be added for those at high risk of developing adverse GI effects because of the possibility of adverse events even in short-term use.
Take Home Message
No analgesic, dose, or combination will work for all patients.

Participation by a fully informed patient in the decision-making process is an essential element of good dental practice.

Rational prescribing will result in good pain management with minimal side effects.

Thank You