UNIT NO. 2

APPLIED PHARMACOLOGY IN PAIN MANAGEMENT

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ABSTRACT

Disease and age affect the pharmacokinetics and pharmacodynamics of agents given for pain management. Consequently smaller doses of analgesics are appropriate for the elderly. Analgesics may be classified as opioid, non-opioid and co-analgesics. The chronic pain of cancer requires a step ladder approach in the use of analgesics starting with non-opioid analgesics progressing to the opioids. Tricyclic agents, gabapentin, and corticosteroids are coanalgesics that are useful for neuropathic pain. Attention to adverse effects and drug interactions help in safe use of analgesics.

INTRODUCTION

Effective pain management requires an understanding of the changes in pharmacokinetics and pharmcodynamics as a result of disease and also ageing, the general characteristics of agents used for pain management, and the adverse effects likely to be encountered.

PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetics

Pharmacokinetics describes the steps in the handling of a drug from the point of entry into the body to its site of action. There are the four steps in the handling of a drug – absorption, distribution, metabolism and elimination. The effect of age and disease on these four steps are shown in Table 1.

Pharmacodynamics

Pharmacodynamics describes the mechanisms on which drugs exert their effects on the body. Most work on action on receptors on the cell surface or within. The receptors are coupled with effectors to result in cellular effects and pharmacologic actions. Wth age, there is altered receptor function and also impaired function at target organ resulting in altered effect of the drug on the elderly person. The ageing nervous system shows increased *susceptibility* to many commonly used drugs, such as opioid analgesics, benzodiazepines, antipsychotics, and antiparkinsonian drugs, all of which must be used with caution. Similarly, other organs may also be more susceptible to the effects of drugs such as antihypertensives and NSAIDs. The elderly are less sensitive to other drugs (e.g., beta-adrenergic agents). (Table 1).

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Pain and sites of action of common analgesics

Pain begins when local tissue damage causes the release of inflammatory substances (prostaglandins, histamine, serotonin, bradykinin, and substance P). The four physiological processes of transduction, tramsmission, modulation, and perception follow:

- Transduction. The inflammatory substances released lead to the generation of electrical impulses at the peripheral nerve endings, or nociceptors.
- Transmission. The electrical impulses are conducted by nerve fibres (A-delta and C fibres) to the spinal cord.
- Modulation. Further relay of the electrical impulses to the higher brain centres can be modified or modulated within the spinal cord before an individual perceives a painful stimulus.
- Perception. Awareness of a painful stimulus.

Sites where painful stimuli can be blocked in this complex chain of events are shown in Table 2.

CLASSIFICATION OF ANALGESIC DRUGS

Analgesics can be classified in different ways. One practical schema is to group them as:

- Non-narcotics – aspirin & other salicylates; paracetamol; NSAIDs (COX-1 inhibitor, COX-2 inhibitor).
- Narcotics – strong opioid – e.g., morphine, meperidine, fentanyl; mild to moderate opioid – e.g., codeine, diphenoxylate.
- Co-analgesics/adjuvants for neuropathic pain – tricyclic antidepressants, gabapentin, lamotrigine, corticosteroids
- Others – agents for trigeminal neuralgia, migraine, and gout.

NON-NARCOTICS

Nonsteroidal Anti-inflammatory Drugs. In contrast to opioids, the use of the NSAIDs is associated with a ceiling effect, above which dose escalations do not result in enhanced analgesia. The ceiling dose in a given individual may differ from the recommended dose by up to two-fold.

Paracetamol is similar in efficacy to aspirin, but has no demonstrable anti-inflammatory activity; it is less irritant to the stomach and for that reason is now generally preferred to aspirin, particularly in the elderly.

NARCOTICS

Morphine remains the standard of reference to which other analgesics are commonly compared. The pharmacokinetic and pharmacodynamic characteristics of a single 10 mg dose of morphine administered intramuscularly forms the basis of most tables and charts compiled to describe the relative characteristics of the opioids.

Table 1. Age And Disease On Pharmacokinetics And Pharmacokinetics

Step	Age Effect	Disease, Factor Effect	Prescribing Implications
Absorption	Rate and extent are usually unaffected	Achlorhydria, concurrent medications, tube feedings	Drug-drug and drug-food interactions are more likely to alter absorption
Distribution	Increase in fat : water ratio. Decreased plasma protein, particularly albumin	CHF, ascites, and other conditions will increase body water	Fat-soluble drugs have a larger volume of distribution. Highly protein-bound drugs will have a greater (active) free concentration
Metabolism	Decreases in liver mass and liver blood flow may decrease drug metabolism	Smoking, genotype, concurrent drug therapy, alcohol and caffeine intake may have more effect than aging	Lower doses may be therapeutic
Elimination	Primarily renal. Age-related decrease in GFR	Renal impairment with acute and chronic diseases; decreased muscle mass results in lower creatinine production	Serum creatinine not a reliable measure of renal function; best to estimate CrCl using formula
Pharmacodynamics	Less predictable and often altered drug response at usual or lower concentrations	Drug-drug and drug-disease interactions may alter responses	Prolonged pain relief with morphine at lower doses. Increased sedation and postural instability to benzodiazepines. Altered sensitivity to beta-blockers

Source: Reuben et al, 2002

Morphine is readily absorbed from the gastrointestinal tract and is metabolized in the liver. With chronic use, about 1/3 of the orally administered dose ultimately exerts an analgesic effect (oral bioavailability of 3:1). This is in contrast to the 6:1 parenteral:oral ratio determined from single dose studies for acute pain. Since parenterally administered drug is not subject to this first-pass effect, clinicians may incorrectly perceive parenterally administered opioids as more effective than opioids administered orally. The various opioids produce analgesia by similar mechanisms and when administered in comparable doses, the quality of analgesia and spectrum of side effects are similar. Nevertheless, individuals may vary idiosyncratically in their sensitivity to the analgesic effects and toxicity of the various opiods.

CO-ANALGESICS/ADJUVANTS

The so-called "adjuvant analgesics or coanalgesics" enhance opioid-mediated analgesia, or reduce opioid-mediated toxicity, or tumour effects in the control of cancer pain. Of drugs with purported co-analgesic properties, evidence most strongly supports the clinical use of selected antidepressants, anticonvulsants, oral local anesthetics and corticosteroids.

In contrast to the opioids, which are relatively useful for all types of pain, the co-analgesics are indicated only in specific settings, eg: antidepressants, anticonvulsants, and oral local anesthetics are used for neuropathic pain; corticosteroids are used for pain associated with inflammation and peritumoral edema. The dose-response relationship for these drugs and the opioids differs in important ways. The administration of a sufficient dose of an opioid invariably results in some degree of analgesia, which increases linearly with the dose in a close temporal relationship to each administration. Depending on the underlying pain mechanism and other more obscure factors, administration of the coanalgesics may or may not result in analgesia. The onset of analgesia may be delayed by days or even weeks after initiating therapy, and the quality of analgesia is less closely linked to dose increases.

CHOICE OF THERAPEUTIC AGENT IN PAIN MANAGEMENT

Non-narcotics

NSAIDs are useful in the short-term treatment of mild to moderate pain including transient musculoskeletal pain but paracetamol is now often preferred, particularly in the elderly. They are also suitable for the relief of pain in *dysmenorrhoea*. The non-steroidal anti-inflammatory analgesics are also particularly useful for the treatment of patients with chronic disease accompanied by pain and inflammation. It is also useful for treating pain caused by *secondary bone tumours*, many of which produce lysis of bone and release prostaglandins. Regular (around-the-clock or a-t-c) administration is most effective. Gastrointestinal, hematologic and renal toxicity may occur, as well as masking of fever, a particular concern in patients with reduced marrow function.

Opioid Analgesics

The progression from non-opioid analgesics to the next step of addition of mild opioid analgesics, and the next step of more potent opioids is the best strategy in cancer pain control. Oral opioid analgesics are the mainstay of therapy for patients with cancer pain requiring opioids. The introduction of transdermal fentanyl provides alternative means to control pain noninvasively. Tansdermal fentanyl it is not recommended when rapid titration is required for unstable pain.

Practical use of oral morphine. Most patients will require simultaneous treatment with two different formulations of an opioid: a long-acting (basal) analgesic administered around-the-clock (a-t-c) and a short acting analgesic, administered as needed (prn). This schema is analogous to the treatment of diabetes mellitus with long acting (NPH) and short acting (regular) formulations of insulin concurrently.

Basal (around-the-clock) Analgesia. Since most oncologic pain is constant and unremitting, a time-contingent (a-t-c) schedule

for the administration of analgesics is preferable to symptom-contingent (prn) administration. This strategy promotes consistent therapeutic plasma levels and avoids "roller coaster" or sine wave kinetics and dynamics characterized by alternating bouts of pain and toxicity. If analgesics are withheld until pain becomes severe, sympathetic arousal occurs and even potent analgesics may be ineffective. Basal analgesia is usually provided by the administration of controlled release preparations of oral morphine every 12 or 8 hours, or alternatively with transdermal fentanyl,methadone or levorphanol.

Supplemental (prn) Analgesia. In addition to the above regimen, potent short-acting opioids with minimal potential for accumulation (immediate release morphine, hydromorphone, oxycodone) are generally made available on an as-needed basis, usually at intervals of two to four hours for exacerbations of pain. Such exacerbations, referred to as breakthrough pain may be spontaneous, related to specific activities (incident pain) or, if the dose of the basal analgesic is insufficient, may occur regularly just prior to the next scheduled dose (end of dose failure). When frequent use of these rescue doses or escape doses is observed, the dose of basal analgesic should be increased accordingly. In such cases, relatively tolerant patients generally tolerate increments of 25-50% or more of their basal dose readily.

Toxicity and its management. Toxicity occurs most commonly after the initiation of treatment or a dose escalation, and is usually transient. Sudden cognitive changes in patients taking opioids chronically are unlikely to be related to opioid therapy, and other potential causes such as brain metastases or electrolyte disturbances should be considered. Sedation is most likely to emerge as a dose-limiting side effect in the elderly and in patients with relatively opioid-resistant pain problems (incident pain, bone metastases, nerve injury). Sedation can often be minimized by initiating opioid therapy at low doses and titrating upwards gradually.

Alternate Routes of Administration. There is no evidence that parenteral administration produces superior analgesia to oral administration, so treatment should be reserved for conditions that render oral administration unreliable, such as weakness, dry mouth, dysphagia, nausea, vomiting, malabsorption or obstruction. Alternate routes may also be considered when an impractical numbers of tablets must be ingested or, acutely when rapid induction of analgesia is required to treat a pain emergency.

Rectal Administration is reliable and effective, but is usually only considered practical for short term use. A continuous subcutaneous infusion (CSCI) or continuous intravenous infusion (CII) is usually instituted when parenteral opioids need to be administered chronically. Home infusion devices should be flow-calibrated, portable, battery-driven, inexpensively-leased, easily-taught, suitable for the addition of patient controlled analgesia and equipped with alarms.

Except in selected circumstances (pre-existing indwelling catheter, severe cachexia, pain emergencies) subcutaneous administration is preferred to intravenous administration because it is easier to maintain in the home and is as reliable as intravenous administration. Absorption of subcutaneously administered opioids is rapid and steady state plasma levels are generally approached within one hour. Morphine and hydromorphone are most commonly employed for subcutaneous infusions, and should ideally be concentrated to permit infusion at volumes of under 1-2 ml/hr in order to minimize tissue irritation.

Co-analgesics/Analgesic Adjuvants

The choices of coanalgesics for neuropathic pain are:

- Amitriptyline is prescribed most frequently, initially at 10–25 mg each night. The dose may be increased gradually to about 75 mg daily if required (higher doses under specialist supervision); nortriptyline, a metabolite of amitriptyline, also given at an initial dose of 10–25 mg at night may produce fewer side-effects.
- Gabapentin is licensed for the treatment of neuropathic pain.
- Capsaicin is licensed for neuropathic pain (but the intense burning sensation during initial treatment may limit use). Drugs, that are now generally reserved for use under specialist supervision include sodium valproate and occasionally phenytoin.
- Corticosteroid may help to relieve pressure in compression neuropathy and thereby reduce pain.

Table 2. Site of action of common analgesics

Site of action	Analgesics and effect
Nociceptors in skin and subcutaneous tissues – These receptors are stimulated by inflammatory substances e.g., prostaglandins	NSAIDS, e.g., diclofenac, ibuprofen, ketorolac – block pathway involved in the formation of inflammatory agents
A-beta fibres – Stimulation of these fibres inhibits transmission of pain to higher centres	Transcutaneous electrical nerve stimulation (TENS) – stimulates A-beta fibres
Primary afferent neurons (A-delta, C-fibres) – Transmit impulses from nocioceptors to the spinal cord	Local anesthetics e.g., lignocaine, bupivacaine, prilocaine, ropivacaine – block transmission along neurons.
Dorsal horn of spinal cord and higher centres – Further relay/ transmission of painful stimuli to the cerebral cortex	Opioids e.g., morphine, pethidine, diamorphine (heroin), fentanyl – act as agonists at opioid receptors (also ketamine)

Source: Fernando & Hunt, 1995

Trigeminal neuralgia can be treated with the following:

- Carbamazepine taken during the acute stages of trigeminal neuralgia, reduces the frequency and severity of attacks. Plasma-carbamazepine concentration should be monitored when high doses are given. Small doses should be used initially to reduce the incidence of side-effects e.g. dizziness.
- Gabapentin and lamotrigine [unlicensed indication] are also used in trigeminal neuralgia.

Postherpetic neuralgia follows acute herpes zoster infection (shingles), particularly in the elderly. The choice of medications are:

- Amitryptyline may be tried initially
- If amitriptyline fails to manage the pain adequately, gabapentin may improve control
- A topical analgesic preparation containing capsaicin 0.075% is licensed for use in postherpetic neuralgia.

ADVERSE DRUG REACTIONS

Non-opioid analgesic use

Aspirin. Gastric irritation may be a problem; it is minimised by taking the dose after food. Enteric-coated preparations are available, but have a slow onset of action and are therefore unsuitable for single-dose analgesic use (though their prolonged action may be useful for night pain). Aspirin displaces a number of drugs from protein binding sides in the blood. These include tolbutamide, chlorpropamide, NSAIDs, methotrexate, phenytoin, and probenacid. Corticosteroids may decrease salicylate concentration. Aspirin reduces the pharmacological activity of spironolactone, competes with penicillin G for renal tubular secretion, and inhibits the uricouric effect of sulphinpyazone and probenacid. The use of aspirin with warfarin is a special hazard because the risk of gastrointestinal bleeding is increased.

Paracetamol. Overdosage with paracetamol is particularly dangerous as it may cause hepatic damage which is sometimes not apparent for 4 to 6 days.

NSAIDs and the elderly. Bleeding associated with *aspirin* and *other NSAIDs* is more common in the elderly who are more likely to have a fatal or serious outcome. NSAIDs are also a special hazard in patients with cardiac disease or renal impairment which may again place older patients at particular risk.

Opioid Use

Toxicity and undesired effects. Direct toxic effects of opioid analgesics that are extensions of their acute pharmacological actions are respiratory depression, nausea & vomiting, constipation and urinary retention. Itching around nose and urticaria can occur (more frequent with parenteral administration).

Tolderance and Dependence. Physical dependence and tolerance are physiologic effects that are almost invariably associated with chronic opioid use, and as such can be conceived of as independent and distinct from addiction. Addiction (psychological dependence) is regarded as a psychologically-mediated disorder with possible genetic influences that occurs only rarely as a consequence of medical use, and then idiosyncratically. Physical dependence, tolerance need not be regarded as important impediments to the successful management of cancer pain.

Opioids and the elderly. The elderly are sensitive to opioid analgesics and the following may not be thought of as adverse effects, namely, confusion, unsteadiness, and falls. Constipation is a problem and prophylactic treatment is necessary when opioids are used for palliative care. The clinician should monitor for the presence of bowel obstruction and fecal impaction.

Opioid drug interactions. The following are the important ones:

- Sedative-hypnotics – increased central nervous system depression, particularly respiratory depression
- Anti-psychotic tranquilisers – increased sedation; variable effects on respiratory depression; accentuation of cardiovascular effects (antimsuscarinic and alpha-blocking actions)
- MAO inhibitors – relative contraindication to all opioid analgesics because of the high incidence of hyperpyrexic coma; hypertension has also been reported.

LEARNING POINTS

- Disease and age affect the pharmacokinetics and pharmacodynamics of agents given for pain management
- Smaller doses of analgesics are appropriate for the elderly
- The chronic pain of cancer requires a step ladder approach in the use of analgesics
- Tricyclic agents, gabapentin, and corticosteroids are are useful for neuropathic pain
- Attention to adverse effects and drug interactions help in safe use of analgesics.

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