Visceral pain can point to injury of either hollow organs (stomach, intestines, ureter and bladder) or solid organs (or rather their capsulae). Injury is caused by stretching, distension, inflammation and ischaemia.

*Visceral pain differs from somatic pain both physiologically and clinically*. Since internal organs have a dual nerve supply (sensory autonomic as well as somatic nerve supply) ending in several spinal cord segments, visceral pain is poorly localised, diffused and referred, and is commonly accompanied by signs of activation of autonomic nerves (vagal nerve, sacral nerves and sympathetic nerves). Pain is described as poorly localised, vague, dull, deep, aching, twisting, spasmodic or cramping, or severe discomfort. *Autonomic features* include sweating, nausea, vomiting, hyper- or hypotension, and tachycardia. When visceral pathology (e.g. visceral peritonitis) spreads to structures that are innervated by somatic nerves (e.g. parietal peritoneum), visceral pain displays deep somatic pain, often accompanied by increased tone of abdominal wall muscles.

Owing to the wide innervation of internal organs, visceral pain is not only poorly localised, but also often *radiate*, making pain more unpleasant. Cardiac pain radiates to the arms (usually left), jaws or epigastrium. Blood under the right diaphragm and pathology of the gallbladder radiate to the right shoulder, and pain from a perforated peptic ulcer radiates to the back. Bladder pain radiates to the perineum, while kidney stones cause back pain.

Sometimes, pain is not felt in the area adjacent to the area of injury at all, but is *referred* to distant structures (e.g. cardiac pain may present with only neck or jaw pain and testicular pathology may only present with periumbilical pain).

## *13.2 General principles*

When treating any disease, including acute pain, the following factors should always be taken into consideration:

### 13.2.1 Anatomical consideration

Anatomical defects are congenital, iatrogenic (e.g. caused by surgery), trauma-related, neoplastic or endocrine, among others. Anatomical abnormalities may also follow pathophysiological processes, such as allergy or endocrine disease (acromegaly, goitre, diabetic arthropathy, obesity, etc.). These anatomical defects will always have some physiological consequence such as the functioning of the upper and lower airway, respiratory, CV, haemodynamic (circulatory shock, hypovolaemia, hypoproteinaemia), neurological (central and/or peripheral), haematological, renal or hepatic, among others. A typical anatomical concern in analgesia is the anatomical features that affect the airway that may cause airway obstruction (e.g., in patients with OSA).

### 13.2.2 Pathophysiological considerations

Physiological derangements may result from anatomical abnormalities, such as iatrogenic (e.g. surgery or pharmacological), trauma, neoplasms, endocrine disease, and others. Pathophysiological processes often result in anatomically identifiable complications, such as renal tubular necrosis, liver necrosis, brain ischaemia, MI, compartment syndrome, and airway and pulmonary oedema. Physiological conditions often change the volume of drug distribution as well as free drug concentrations (pharmacokinetics).

The risk of aspiration must always be considered whenever a sedative agent is administered. The trauma-related stress response as well as opioids delay gastric emptying and patients run the risk of aspirating if they regurgitate or vomit. For example, a patient who ate an hour before injury may still have a significant amount of stomach content several hours after injury.

### 13.2.3 Interventional considerations (what to do about the pain)

Interventions are pharmacological and physical (e.g. immobilisation of fractures, including the neck and facial fractures). These interventions may have anatomical effects (e.g., on the airway or vascular access) and the physiology of multiple systems, namely, CV, haemodynamic, haematological, ventilatory, renal, endocrine, etc.

*There are hundreds of drug interactions*. Therefore, clinicians must always refer to a reliable source to identify drug interactions, such as ***The South African Medicines Formulary (SAMF)***. Drug–drug interactions may be either pharmacodynamic or pharmacokinetic. Pharmacodynamic interactions refer to the enhancement or diminution of effects, such as the enhancement of opioid-related respiratory depression by sedatives. Pharmacodynamic interaction refers to the mutual effects of drugs on enteral absorption, plasma protein binding, metabolism and excretion. Regarding pharmacokinetic interactions, liver enzyme induction and suppression may affect the formation of active metabolites and drug clearance. Moreover, several pharmacogenetic effects may impact on drug activation (e.g. metabolism of codeine to morphine). The most common suppressors of cytochrome enzymes in the liver include antiretroviral protease inhibitors (ritonavir, lopinavir and atazanavir), conazole antifungal agents, cimetidine and clarithromycin.

*Drug–disease interactions* must also be considered, such as the combination of anxiolytics and opioids, SSRI antidepressants and tramadol, anti-inflammatory agents in the elderly, hypertensive vasculopath receiving an ACEI or ARA and diuretics. A patient with OSA may be very sensitive to respiratory suppression of sedatives (including all of the opioids), a patient who may develop a compartment syndrome should probably not receive a neuraxial or limb nerve block, and a patient on anticoagulants may not receive a neuraxial block or non-selective cyclooxygenase inhibitors (the traditional nonsteroidal anti-inflammatory drugs [tNSAIDs]).

*Regarding pharmacokinetics and pharmacodynamics*, remember the following principles:

- Depending on its *severity*, vital organ comorbidity affects other vital organ functions, pharmacokinetics and pharmacodynamics, which make the patient more prone to adverse effects of drugs and drug interactions.
- CV and haemodynamic disease can affect respiratory, liver and kidney function.
- Lung disease can affect haemodynamic function.
- Liver and kidney disease can affect pulmonary and haemodynamic function.
- All of the above can affect neurological and haematological function, and blood biochemistry (electrolytes, proteins).
- Metabolic diseases (including obesity) can affect all of the above.
- Physiological age (the very young and the elderly) affect all of the above.
- Pharmacological agents can affect all of the above.
- **All of the above can decrease the elimination of analgesics**, which increase its blood levels, prolong its activity and increase sensitivity (adverse effects and toxicity), as well as those of active metabolites. Keep this in mind when treating pain with any opioid, paracetamol, NSAIDs, and analgesic adjuvants (antidepressants, antiepileptics, etc.) in the patient with impaired vital organ system of any aetiology.
- Whenever possible, **multimodal analgesia** should be prescribed: a combination of drugs have the least additive effects, which allows lower doses and, consequently, fewer adverse effects.
- Since it is difficult to remember the pharmacokinetic characteristics of all drugs, clinicians must have a **source** where these characteristics can be looked up (e.g. the SAMF or package inserts).
- **Doses** are often given according to body mass. Drugs are usually tested in nonobese persons. The bodies of obese patients, however, do not only have an increased percentage of fat, but also an increased lean body mass (mainly due to an increase in muscle mass and blood volume). Some obese or overweight patients may have a normal BMI due to a loss of lean body mass (mainly bone, muscle and a decrease in blood volume). This is called sarcopaenic obesity and often occurs in the elderly, Cushing's syndrome, invalids, amputees, among others. Oedematous patients have an increased BMI in spite of a decreased percentage of fat. Athletes may have a high BMI but a low percentage of fat. Cachectic patients have a low fat and muscle mass.

  In obese patients, an adjusted body mass (ABM) is safer to use initially:

  The ABM is calculated as follows:

  DBM = Ideal body mass + 0.4(body mass – ideal body mass)

  Ideal body mass in men = Height in cm – 100 kg

  Ideal body mass in women = Height in cm – 105 kg

For example, the ABM in a woman with a mass of 100 kg and height of 1.7 m is

$$65 + 0.4(100 - 65)\ \text{kg} = 65 + 0.4(35) = 65 + 14\ \text{kg} = 79\ \text{kg}$$

### 13.2.4 Monitoring considerations

Anatomical, pathophysiological and interventional factors must always be assessed by imaging, chemical, haematological, pharmacological, pain assessment, etc.

Pain monitoring assesses the following pain characteristics: what is the location of the pain (localised or referred), what happened before the pain started (activity, visual symptoms, nausea), duration, onset (when, suddenly, gradually), constant or fluctuating, type of pain (stabbing, dull, throbbing, cramping), pain severity (pain scale), other symptoms (e.g., swelling, deformity, visual symptoms, motor or sensory symptoms, nausea, vomiting, dizziness, dyspnoea, skin discolouration or a rash), what gives relief, the effect of analgesics, and were there previous episodes?

### 13.2.5 Facilities and socioeconomical considerations

The choice of analgesia is often determined by the location (outpatient, inpatient, high dependency unit), socioeconomical factors (e.g., income, distance from health facility, housing, availability of caregivers).

*These five considerations (anatomical, pathophysiological, interventional, monitoring, and facilities and socioeconomical) never operate in isolation*. The interplay among these considerations determines the intervention (type, dose, route, etc.). In this chapter, the emphasis is on the *pharmacological intervention* in the management of *acute pain*. When treating acute pain, the practitioner must always base their choice of analgesia on the above principles, namely the pharmacokinetic and pharmacodynamic effects of the *particular anatomical, pathophysiological, and interventional factors* in a *particular patient* in *particular circumstances*.

### 13.2.6 Routes of administration of analgesics

The route of administration of analgesics is preferably either *orally (p.o.)* or *IV*. Patients who are nil per os (NPO) can receive analgesics p.o. or sublingually. *IV administration* is indicated only in patients who either cannot swallow or has a nasogastric tube in situ. *IMI* and *SC* injections are painful and drug absorption is unpredictable, especially in patients with a low cardiac output, oedema or vasoconstriction, and is contraindicated in patients receiving therapeutic doses of anticoagulants. Often, patients receive an IV infusion to keep a vein open just for IV analgesics. It is uncomfortable and increases the risk of infection and thrombophlebitis.

Generally, routes of administration other than *oral* or *topical* should be avoided, if possible. *Suppositories* should only be considered in infants and patients who are unable to tolerate

oral medication (nausea and vomiting). The use of suppositories should be avoided in young children and teenagers and needs consent from the patient or guardian. *Transdermal* formulations should not be used in acute postoperative pain, but may be used when prolonged pain is expected (e.g. cancer pain).

*Topical analgesia* is useful in treating outpatient conditions, especially superficial lesions such as abrasions and oral mucositis. This can decrease reliance on oral drug therapy.

### 13.2.7 Management of acute nociceptive pain according to the visual analogue scale

From the classification of acute pain, it should be clear that several organs (visceral, somatic, superficial, deep) and different innervations are involved. A host of neurotransmitters are involved in this circuitry. Moreover, the activity of nociception and pain experience is influenced by genetic factors, previous exposure to analgesics (tolerance and addiction) and chronic pain. If agonists, antagonists or modifiers of these transmitters were freely available, analgesia could be tailored to manage a *particular pain in a particular patient*. To date, only a handful of groups of analgesics are available. These factors form the basis of the use of different groups of analgesics simultaneously (i.e. *multimodal analgesia*).

***Only the groups of analgesics that are freely available will be mentioned, namely:***

- Paracetamol
- NSAIDs
- The steroid anti-inflammatory drug, dexamethasone
- Opioid agonists, dualists and atypical opioids, tramadol and tapentadol
- NMDA antagonists, ketamine and magnesium
- Gabapentanoids, gabapentin and pregabalin
- The $\alpha_2$-receptor agonist, dexmedetomidine
- Antidepressants

***The SAMF is indispensable for the safe prescription of drugs, including analgesics.***

***The analgesia ladder***

*Mild pain (VAS of 1–3)*

- paracetamol
- an NSAID

*Moderate pain (VAS of 4–7)*

- Paracetamol, and
- a regular NSAID, and
- an opioid.

- PCA
- Nerve block or neuraxial blockade

*Severe (VAS of 8–10)*

- Regular or continuous opioid, and
- paracetamol, and
- an NSAID, and/or
- PCA, nerve block or neuraxial blockade.
- Other adjuvants: ketamine, dexmedetomidine, pregabalin, TCAs

Each analgesic has characteristic pharmacodynamics and pharmacokinetics, and of course, also a *particular dose in a particular patient*. Regarding opioids, it is useful to regard them as morphine-like substances and to compare their potency to that of morphine. They all work to some extent on μ-receptors (agonists or dualists), but may also affect other receptors (e.g. κ-receptors) and neurotransmitters (noradrenaline, serotonin). However, the well-known adverse effects of opioids are effects on the μ-receptors.

Opioids have pharmacodynamic and pharmacokinetic characteristics that make these either very potent (doses expressed in μg, e.g. sufentanil), or weak (doses expressed in mg, e.g. tramadol). However, when given at a particular (equivalent) dose, the drug effects on the μ-receptors are similar in terms of adverse effects and addiction potential to that of morphine.

***Milligram morphine sulphate equivalents***

It is useful to have an idea of the *potency* of opioids *compared to that of morphine sulphate*. This is called the *milligram morphine sulphate equivalent (MME)*. If an opioid has a dosage interval different from that of morphine sulphate, it is more convenient to use the daily MME (DMME) and divide that dose by the number of daily doses. Doses are applicable to *nontolerant* patients. Regarding oral preparations, the dose refers to the simple not-sustained release (long-acting) preparation.

The DMME refers to the effect of 1 mg/day of a drug relative to that of morphine sulphate via the same route (Table I). For example, oxycodone has an oral DMME of 1.5. That means that 1 mg/day of oxycodone p.o. has the activity of 1.5 × 1 mg/day of morphine sulphate p.o. = 1.5 mg/day.

Since drugs have different oral bioavailabilities (the fraction of drug that reaches the systemic circulation after oral administration), an opioid may have a larger IV MME. For example, oxycodone has an IV MME of 3. That means that when given via IVI, oxycodone 1 mg/day has the effect as morphine sulphate 3 mg/day p.o. If IV morphine sulphate is to be replaced with oral oxycodone, how much oxycodone is needed? The IV MEE of morphine sulphate = 3 mg/

day IVI. Therefore, 1 mg/day of morphine sulphate IVI = 3 mg/day p.o. If the patient receives morphine sulphate 45 mg/day IVI, 3 × 45 mg = 135 mg/day p.o. is needed. What is the equivalent of oral oxycodone? The oral MME of oxycodone = 1.5. Therefore, the oxycodone dose is 135 mg/1.5 mg/day = 90 mg/day. Or, from Table I, it is seen that morphine sulphate 3 mg/day IVI = oxycodone 3 mg/day IVI. But oxycodone has an oral MME = 1.5. Therefore, the oral dose of oxycodone is 3 × 45/1.5 mg/day = 90 mg/day.

**Table I:** Oral and IV MME

| Drug | MME p.o. to p.o. | MME IV to p.o. |
|---|---|---|
| Codeine phosphate | 0.13 mg/day | Not IVI |
| Tramadol | 0.15 mg/day | 0.1 mg/day |
| Tapentadol | 0.4 mg/day | - |
| Morphine sulphate | 1 mg/day | 3 mg/day |
| Oxycodone HCl | 1.5 mg/day | 3 mg/day |
| Buprenorphine | 35.5 mg/day | 75 mg/day |

## *13.3 Acute pain in the emergency department*

In South Africa, patients with acute painful conditions may report to an outpatient or emergency department. In the private sector, these departments function in the same facility. In state hospitals, these may differ according to the grading of the hospital or clinic.

Patients usually report to the emergency department and after assessment, they are managed according to the gravity of the problem, including resuscitation, optimisation and stabilisation.

Analgesia will always form part of the resuscitation process and the choice of analgesia will be determined by anatomical and physiological findings, as well as on special investigations and the interventional options available at the particular facility. The management of acute pain due to trauma and nontrauma is similar to that of postoperative pain (see section 13.5).

Although acute pathology in different organ systems present with acute pain, the analgesics used are often similar. Some conditions, however, may need a different approach and different drugs.

Pathology may be trivial, justifying oral analgesics and discharge after minor procedures (e.g. management of minor wounds or splinting of fractures). More serious pathology or trauma may need resuscitation, admission for medical management or surgery, or be referred for further management. Recurring, intractable acute pain usually requires admission and further investigation.