Opioids

Besides the type of injury occurring in particular sports, sports injury is characterised by *repeated injury and pain*. The prescription of opioids every time an athlete seeks help, should therefore be done with circumspection to prevent abuse of opioids. All opioids are habit-forming and related to the number (milligrams) of MMEs – not the type of opioid (so-called weak and potent opioids). When prescribing opioids, the MME for the different opioids should be kept in mind to prevent inadvertent overdosing when switching between opioids.

The use of NSAIDs for sports injuries is controversial. Taking into account the (probable) effects of NSAIDs on healing, paracetamol and opioids are the only analgesics useful for the management of acute sports-related pain. However, the adverse effects of NSAIDs have not been demonstrated to impact significantly on the outcome, and are often prescribed. Paracetamol and the NSAID must be taken around the clock, while the opioid must be reserved for breakthrough pain. Physical measures are opioid-sparing (e.g. limb elevation and cold therapy to decrease swelling). A prescription for more than five days is usually unnecessary and it should never be prescribed for longer than 10 days without a review.

13.3.4 The discharge prescription from the emergency department

A patient should not receive a prescription for analgesics without a diagnosis. If a diagnosis is not clear, the patient must be referred for further evaluation as either an in- or outpatient. If the doctor is of the opinion that it is safe to discharge the patient, they must be advised on the symptoms to look for and instructed to return if necessary.

A prescription consisting of paracetamol and an NSAID is usually safe. The drugs should be taken around the clock for approximately 24 hours and longer if necessary. An opioid may be added for breakthrough pain or when NSAIDs are contraindicated. The number of opioid tablets/capsules should not exceed 10 units containing approximately 5 mg MMEs. This practice may decrease the availability of unused opioids that can land up in the hands of people who misuse opioids.

13.4 The intensive care unit

The duration of sedation and analgesia in the intensive care unit (ICU) should be limited to decrease the duration of ventilatory support and limit the complications thereof. To this end, the availability of well-trained staff, good monitoring and resuscitation equipment allow for more potent agents to be used more safely.

- *Multiorgan physiological derangements* may develop or exist in most patients. These abnormalities affect pharmacokinetics to some extent or may be aggravated by analgesics. Owing to large organ reserves, biochemical indicators may be within normal limits, but show a downward trend or deteriorate rapidly once the reserve has been exhausted. For example,

serum creatinine and the glomerular filtration rate (GFR) remain within the normal range in the presence of a severe renal insult. In fact, the baseline GFR may remain within the normal range until as much as 50% of nephrons have been lost.

- *Liver function* is determined by liver perfusion and hepatocyte volume and function. Low liver perfusion and hepatocyte dysfunction commonly occur, impairing excretory, anabolic and catabolic liver functions. These may be due to preadmission conditions (trauma, medical conditions), or pre-, intra-, or postoperative insults. *Hypoalbuminaemia* is very prevalent and may indicate a decrease in anabolic liver function, but is often a finding in several clinical situations, including catabolic states, systemic inflammation disorders (including sepsis), nephrotic syndrome, GI protein loss, and HIV infection.
- *A low plasma albumin* concentration increases the free (active) fraction of most analgesics, while loss of hepatocytes decrease the clearance of several analgesics. *Clearance from the plasma* is not only affected by metabolism and excretion, but also by redistribution to muscle and fat. Apart from remifentanil that is metabolised rapidly, it should be appreciated that the longer a sedative is infused, the longer the patient will take to wake up after termination of infusions (up to several days). This also accounts for propofol infusions.
- *Ventilated patients are unable to verbalise their pain*. It is often difficult to differentiate between discomfort caused by ventilatory failure (dyspnoea, hypoxaemia, hypercapnia), the endotracheal tube, artificial ventilation, awkward body posture, withdrawal of opioids or ethanol, and surgical and nonsurgical pain. All these factors can cause restlessness and haemodynamic instability (e.g. tachycardia and hypertension). Therefore, all the nonnociceptive elements of care must be attended to before resorting to analgesics.
- *When the presence of moderate to severe pain is unlikely*, nonanalgesic interventions (including sedatives) may suffice. However, when pain and discomfort is the likely cause of restlessness, analgesic-based sedation (*analgosedation*) is preferred to hypnotic-based sedation (*hypnosedation*).
- *Non-pharmacological interventions can affect both pain level and pain perception*. These include nursing care, pressure care, devices, masks, oxygen gas flow, humidification, physiotherapy, secretion formation, noise levels, day-night routines, visits and sleep. If pain is the likely main cause of restlessness, it is a wise policy to administer *analgesics before sedatives*, which should reduce the risk of inadequate pain control in sedated patients. All opioid analgesics have sedative properties and may address the sedative component adequately. Usually, morphine sulphate is the preferred analgesic in mechanically-ventilated patients, often in combination with the short-acting benzodiazepine, midazolam or propofol.
- Patients may receive analgesics p.o. or via nasogastric tube, but GI motility may be unpredictable, which may affect absorption.

13.4.1 Analgesics used in the ICU

Paracetamol

Paracetamol should be used for pain and fever, if not contraindicated. Paracetamol forms the basis of analgesia in the ICU. The dose of paracetamol is 15 mg/kg 6-hourly by any route, but should be decreased in patients with liver and renal impairment and elderly patients. Paracetamol has a plasma protein binding of < 50%. Therefore, free drug concentrations are less affected by hypoalbuminaemia.

NSAIDs

NSAIDs should probably not be used in the ICU setting. For a discussion of paracetamol and anti-inflammatory drugs, see section 13.5.

Opioids

Opioids are the most important analgesics in ICU. These can be given intravenously or enterally, but must be administered IV if it forms part of sedation. Opioid analgesia is usually started by titration to effect. The analgesic is administered as boluses, every 5 minutes until the VAS is < 3/10. This is followed by an infusion, the effect of which must be monitored regarding pain, sedation and haemodynamic effects.

Analgesia and sedation should be monitored. Not only using a pain scale, but also by keeping an eye on haemodynamic changes. Haemodynamic suppression (due to central sympatholysis) usually correlates with the analgesic/sedative effect (e.g. hypotension and bradycardia) when sedation is too deep, and vice versa. When analgesia is inadequate, a bolus of approximately 15% of the hourly dose is administered over 30 minutes, while the infusion rate is increased by 15–20% until a new steady state is reached. Similarly, when analgesia/sedation is too deep, the infusion is decreased by 15–20% until a new steady state is reached.

Tolerance of all opioid agonists develop and is a normal physiological phenomenon. It should be taken into account if a patient needs higher doses of opioids or becomes restless when weaned from an opioid infusion. Tolerance to the analgesic effect of opioids should not be overlooked and is managed by administering a muscle relaxant or restraining the patient.

Tolerance manifests as opioid-induced hyperalgesia (OIH) in the postoperative period and doses need to be increased to maintain adequate analgesia and sedation, while it manifests as opioid withdrawal syndrome (OWS) when an opioid infusion is stopped. OWS occurs in adults and in more than 50% of children. The degree and manifestation of tolerance (dose needed, OIH and OWS) vary and are probably determined by pharmacogenetic factors. The potent

shorter-acting opioids such as fentanyl and remifentanil are often used in the ICU and have often been implicated in the development of tolerance.

OWS manifests as severe restlessness and haemodynamic instability when the infusion of a potent opioid is stopped. It can be prevented by decreasing opioid infusion rates over several hours or days, while the drug that the patient is being weaned from is replaced by an infusion of a longer-acting opioid such as morphine sulphate (opioid rotation). The infusions should be titrated downward using the 20%-rule. For example, if the infusion runs at a rate of 10 ml/h, it is changed to 8 ml/h for 6 hours → 6.4 ml/h for 6 hours → 5 ml/h for one hour → 4 ml/h for 6 hours → 3 ml/h for 6 hours → 2.4 ml/h for 6 hours → 2 ml/h for 6 hours → stop. The longer the patient has received an opioid, the longer the weaning period should be and could even last days.

Tolerance to the analgesic effect of opioids may be overcome by using the dualist (partial μ agonist) buprenorphine instead of the pure μ agonist or by adding low dose ketamine or dexmedetomidine. The dose of buprenorphine is 0.2–0.4 mg sublingually or 0.3 mg IV 6-hourly. Since buprenorphine binds strongly to μ-receptors, its effect on respiration is not readily reversible by naloxone.

Morphine sulphate

Morphine sulphate is an effective analgesic and, in combination with paracetamol, forms the basis of analgesia in the ICU. It is cheap, readily available, and the agent with which most practitioners have the most experience. Its length of action is well-suited to this environment. Morphine sulphate is titrated at a dose of approximately 50 μg/kg every 5 minutes until the VAS is < 3. In a patient with a mass of 70 kg, this is about 3 mg every 5 minutes. This is followed with an infusion of 50–300 μg/kg/hour.

Morphine is metabolised in the *liver* to the active metabolite morphine-6-glucuronide (M6G) and other nonactive metabolites, all of which are excreted by the *kidneys*. Approximately 10% of morphine is excreted unchanged in the urine. Morphine has a half-life of about 2 hours. However, M6G is twice as potent as morphine and has a longer half-life. Therefore, the dose of morphine should be adjusted in patients with decreased liver and kidney function of any cause. Both morphine and M6G have low plasma protein binding (15–30%), which make their effects more predictable in the presence of low plasma protein concentrations.

When morphine is contraindicated, the short-acting potent opioids alfentanil, fentanyl, sufentanil and remifentanil can be used. The analgesic potencies of alfentanil, fentanyl, remifentanil and sufentanil relative to that of morphine are approximately 10, 100, 100 and 1 000 times more potent, respectively. Alfentanil, fentanyl and sufentanil are all cleared by the liver and can accumulate in patients with liver impairment.

Fentanyl and remifentanil

Fentanyl and remifentanil can be used as morphine alternatives. These opioids are similarly titrated intravenously. Although these work quicker, better analgesia is not offered than morphine after about 30 minutes. Since these are highly plasma protein bound, dosages should be lowered in hypoproteinaemic patients.

Fentanyl is effective after 1–2 minutes. The initial bolus dose in nontolerant patients is 1–2 µg/kg, followed by an infusion of 1–1.5 µg/kg/h (up to 10 µg/kg/h in tolerant patients). Fentanyl is metabolised in the liver and has no active metabolites. Therefore, it accumulates in patients with liver impairment but usually not in patients with kidney failure. Fentanyl has a plasma half-life of 2–4 hours. Since fentanyl has a long context-sensitive half-time, the duration of action increases as infusion time increases.

Remifentanil is cleared by nonspecific esterases, which makes it independent of renal and liver function. It has no active metabolites. Remifentanil works within 1–3 minutes. The LD is 1 µg/kg and the maintenance dose (MD) is 0.05–2 µg kg/min (3–120 µg/kg/h). Remifentanil is ideal for infusions in the ICU since it has a short half-life (3–10 minutes) and a constant context-sensitive half-time of approximately 3 minutes.

Remifentanil is useful for analgosedation in ventilated patients and when performing uncomfortable or painful procedures. It can be used in combination with propofol for analgosedation. The dosages of remifentanil plus propofol sedation are 0.025–0.200 µg/kg/minute and 5–50 µg/kg/minute, respectively. Both remifentanil and propofol are very expensive. In addition, a propofol infusion should not be used for longer than three days because of the risk of propofol infusion syndrome.

Dexmedetomidine

Dexmedetomidine is a selective α_2 agonist with hypnotic and analgesic properties synergistic with that of opioids. It is an opioid-sparing adjunct to opioid-based analgosedation. Dexmedetomidine improves analgesia in opioid-tolerant patients (e.g. patients with major burns and in patients with a history of substance addiction). Dexmedetomidine and clonidine are useful in the management of OWS. However, evidence does not support the routine use with opioids. It is a useful analgosedative for short stressful procedures, such as fiberoptic bronchoscopy and tracheal intubation.

Adverse effects include hypotension and bradycardia. Abrupt cessation of an α_2 agonist infusion can result in life-threatening hypertension and, rarely, withdrawal syndrome. The rapid administration of a bolus can cause severe hypertension and bradycardia.

The LD is 1 µg/kg over not less than 10 minutes. However, an LD may be omitted when converting from another sedative to dexmedetomidine. The maintenance infusion dose is 0.2–0.7 µ/kg/h and should not be used for more than 24 hours. The dose should be decreased in the presence of hepatic impairment, elderly patients, and when used concomitantly with anaesthetics, hypnotics or opioids.

When used in ventilated patients, it is unnecessary to wean the patient from dexmedetomidine since it can be continued after extubation. This makes dexmedetomidine a useful drug during weaning analgosedatives such as morphine, fentanyl and remifentanil.

Ketamine

Ketamine is a pluripotential agent with several mechanisms of action and, consequently, applications. It is analgesic and hypnotic, and useful in painful procedures such as burn dressings and gaining venous access, especially in children. The pharmacodynamic characteristics that come in handy in the ICU scenario include the following:

- It is an indirect NMDA receptor antagonist in dorsal spinal ganglia. This anti-NMDA effect mediates (potentiates) opioid-mediated antinociceptive effect (analgesia) and reduces OIH. The hypnotic effect of ketamine results from a combination of NMDA channel blockade and activation of cation channels at supra spinal sites.
- Ketamine suppresses induction of nitric oxide (NO) synthase and protein expression by endotoxin. This results in an anti-inflammatory effect in sepsis, as well as a reduction of OIH.

Ketamine causes dose-dependent profound analgesia, catalepsy, amnesia, sedation and anaesthesia. Its sedative properties differ from that of other sedatives in that it produces a dissociative state; patients appear to be awake, but are detached from their surroundings and their eyes often remain open.

Ketamine increases muscle tone, causes minimal respiratory suppression, is a bronchodilator, and increases salivation and tracheobronchial secretions. Since airway reflexes remain intact, laryngospasm occurs more commonly. Different from other analgosedatives, it increases blood pressure and heart rate. Adverse effects of ketamine include delirium, hallucinations, nausea and vomiting.

Ketamine is metabolised in the liver and has an active metabolite that is excreted by the kidneys. Therefore, dosages should be adjusted in patients with decreased liver and kidney function. Ketamine has a low plasma protein binding (about 30%). Therefore, free plasma concentrations are less affected by low plasma protein concentrations.

Ketamine can be administered p.o., IM and SC. The dosage via these non-IV routes is 5–10 mg/kg. The oral bioavailability is 20%. The oral route (often combined with midazolam 0.2–0.5 mg/kg) is often used in children. This oral combination produces sedation within about 20

minutes and usually allows for painful procedures such as venous cannulation. IV ketamine of 1–2 mg/kg and 0.1–0.2 mg/kg produces anaesthesia and sedation, respectively. These IV dosages are effective within 1 minute and the effect lasts for up to 10 minutes. IM and SC administration produce deep sedation or anaesthesia within 10 minutes, which lasts up to 20 minutes. The analgesia and psychological adverse effect of ketamine lasts longer than the sedative effect.

Ketamine infusions are used in the ICU, usually in selected patients (e.g. to decrease delirium in ventilated patients). The sedation dose is 0.1–1.0 mg/kg followed by 0.125–0.5 mg/kg/h (usually 0.2 mg/kg followed by 0.2 mg/kg/h).

Caution should be exercised in patients with ischaemic heart disease, significant hypertension and psychotic states. In spontaneously breathing patients, ketamine should be used cautiously if there is increased intracranial pressure. However, this applies to all sedatives. In ventilated patients who maintain $PaCO_2$, ketamine can be used safely, usually in combination with other sedatives such as midazolam or propofol.

Ketamine is often used as co-analgosedative with other agents in nonventilated and ventilated patients. This includes ketamine-midazolam and ketamine-propofol. The dose of midazolam when used as monosedative in ventilated patients is an LD of 10–50 µg/kg over several minutes, which may be repeated every 5–15 minutes until the required level of sedation is reached. The MD is 20–100 µg/kg/h infusion. A low dose ketamine-midazolam infusion of ketamine (≤ 0.25 mg/kg/h) with midazolam (7–15 µg/kg/h) reduces morphine requirements.

Propofol

Propofol is commonly used as a sedative in the ICU. The dose of propofol sedation in the ICU is 5 µg/kg/min for 5 minutes. This is titrated upwards with approximately 20% every minute until an adequate level of sedation has been reached. The MD is 5–50 µg/kg/min IV titrated to response. Cognisance should be taken of the danger of propofol infusion syndrome and prolonged emergence with prolonged administration.

Numerous mg:mg combinations of ketamine and propofol (ketofol) have been described, varying from 1:10–1:1, but the optimum dose of combinations remains unclear.

Drug combinations in the ICU

The principle with respect to combinations of analgosedatives and hipnosedatives is that these *combinations should be regarded as a drug with unique characteristics and adverse effects*. Furthermore, *the effect* of a combination should be assumed to be at least a synergistic effect of these combinations (i.e., 2 + 2 = an effect of $(2 + 2)^2 = 16$) while an *additive* effect is produced

when 2 + 2 = 4. When synergism is assumed, the dose can be titrated to the required endpoint of sedation or analgesia.

Several binary drug combinations have been reported in the literature and are widely used. These combinations give rise to several caveats.

- Firstly, numerous dose combinations on numerous patient profiles formed part of study protocols, and are therefore difficult to apply universally.
- Secondly, the pharmacokinetics of the drugs used in these combinations differ, resulting in different times to maximal effect of the individual drugs. Consequently, a clear effect of the combination ('new drug') may be delayed. Moreover, the effect of the drugs may dissipate at different rates when the infusion is stopped.
- Thirdly, there may be physicochemical incompatibility of the different agents in the same syringe or the same infusion line. Incompatibilities may manifest as precipitation of the drugs, which may make the solution cloudy or degrade components (propofol containing mixtures obscure precipitation). The absence of any visible change does not necessarily exclude incompatibility. Precipitation is impossible in propofol combinations. Propofol is compatible with fentanyl, alfentanil, sufentanil and ketamine; however, propofol is incompatible with remifentanil and midazolam. Ketamine is compatible with propofol, midazolam, morphine sulphate, fentanyl and sufentanil.

13.5 Postoperative pain

Failure to treat postoperative and posttraumatic pain adequately result in increased psychological and physiological stress and contributes to the development of *chronic pain*. Perioperative clinicians are the most experienced in the management of postoperative pain and their experience in this scenario has been extrapolated to guide pain control in most other medical scenarios, including the outpatient department, emergency department, and the ICU.

Day case surgery also warrants specific mention. The incidence of severe pain following these surgeries is approximately 5%. However, inadequate pain control is common because of concerns of administering powerful agents to patients who will be discharged soon, and reluctance on the part of staff to delay the discharge process. Orthopaedic, plastic surgery, laparoscopic procedures and hernia repair are common scenarios in which pain control is often inadequate. Patients with an increased BMI, and procedures that requires longer GA, are risk factors for the development of severe pain.

The use of multimodal analgesia, including local and regional anaesthesia, is strongly advocated in the day case scenario where possible. This means that analgesics of different classes or pharmacodynamics are co-prescribed. These different drugs may have additive or synergistic effects, which allows for lowering the doses of the different analgesics (e.g. opioid-sparing).