(Table I). The following opioids will be discussed briefly: morphine, oxycodone, fentanyl and buprenorphine.

- *Morphine:* The total daily parenteral dose of *morphine* is determined. Morphine has an oral bioavailability of approximately 30%. Therefore, the total daily oral dose is approximately three times the IV dose. This oral dose is offered as a long-acting tablet containing the daily dose. These are available as 10 mg, 30 mg and 100 mg. The long-acting tablet is taken as 50% of the total dose 12-hourly. With the development of tolerance, higher doses will be required. The new dose is determined using the morphine solution/syrup (5 mg, 10 mg, 20 mg or 100 mg/5 ml). For breakthrough pain, the syrup is used. The dose is 0.2–0.5 mg/kg 4–6-hourly. The syrup is titrated up until the VAS has decreased to < 4/10 with movement. The new total daily dose is the total of the long-acting tablet plus the total of the solution. Once the total morphine dose has been established, this is replaced by a slow-release tablet with an adjusted morphine content.
- *Oxycodone:* It has an oral bioavailability of 50% (Table I). If the total IV dose is known, the oral dose is twice that amount. Half of this dose is given p.o. 12-hourly as the prolonged-release tablet (5 mg, 10 mg, 20 mg, 40 mg and 80 mg). The short-acting 5 mg tablet is used 4–6-hourly for breakthrough pain. The total daily dose is determined and the long-acting dose is adjusted accordingly.
- *Buprenorphine:* It has an oral bioavailability of 50%. The total IV dose is determined and the oral dose is twice the total IV dose. This amount is divided by 4 and taken 6-hourly. If the oral dose is known, the IV dose can be calculated (50% of the oral dose) and the IV dose per hour is calculated (total IV dose/24). The prolonged-release patch that delivers the calculated hourly dose, is used. The patches available are 5 µg/hour, 10 µg/hour and 20 µg/hour.
- *Fentanyl:* This is given IVI. The total daily dose is known, and the hourly dose can be calculated. The prolonged-release patch that delivers approximately that amount is then prescribed. These patches deliver 12 µ/hour, 25 µ/hour, 50 µ/hour, 75 µ/hour or 100 µ/hour. To adjust the patch dose, the patient must be admitted and fentanyl administered IVI using a PCA pump. The new total daily dose is determined and the most appropriate patch is applied.

13.13 Opioid tolerance

(Also see opioid tolerance in the ICU – section 13.4.1)

Opioid tolerance is a common cause for the failure of opioid analgesia. Exposure to an opioid, particularly as the sole analgesic, gives rise to pharmacodynamic tolerance (loss of activity, not due to faster drug clearance but to decreased analgesic effect). Tolerance develops to the adverse effects of opioids, namely sedation, hypoventilation and nausea, but not to constipation and miosis.

Tolerance results from alterations in G-protein coupling to the opioid receptor, changes in receptor trafficking between the neuronal surface and cytoplasm, and an increase in the number and sensitivity of NMDA receptors as a result of central sensitisation.

Tolerance in the perioperative setting can be attenuated by preventive and/or prolonged blocking of pain impulses along the pain pathway through the following non-opioid agents:

- Local analgesics as a *continuous* local, regional or neuraxial infusion.
- Paracetamol and an NSAID, used before considering opioids.
- De-escalating opioids as soon as possible.
- Multimodal analgesia (co-analgesia): apart from paracetamol and an NSAID, a combination of usually two analgesics with different pharmacodynamics (e.g. an opioid, ketamine, dexmedetomidine and a gabapentanoid).

Regarding multimodal analgesia, it is difficult to interpret studies due to the heterogeneity of the studies: number of studies included, number and type of participants, studies used different drug combination, different dose ratios. Studies also administer analgesics according to different regimens, for example, PCA of (usually) two drugs, always an opioid with a non-opioid in the same mixture, PCA an opioid with a concurrent non-opioid infusion, concurrent (in the same mixture) infusion of an opioid plus a non-opioid, concurrent (in the same mixture) infusion of two non-opioid with addition of a low-dose opioid on a prn basis, and different opioids.

Several of these combinations have been tested; anaesthesiologists, using fuzzy logic (an integration of a sound knowledge of experience), are very good at compiling these recipes. Very often, these recipes are found in meta-analyses, which often both confirm the utility of these combinations, and also point out the deficiencies of studies or the fallacies of some combinations.

Primary outcomes usually are postoperative pain intensity, opioid consumption over different periods, and patient satisfaction. *Secondary outcomes* usually include sedation, hallucinations, hypoventilation, hypoxaemia, hypotension, brady- or tachycardia, nausea, vomiting and pruritus.

Postoperative PCA opioid-dexmedetomidine combinations decrease pain intensity, opioid consumption and adverse effects, as compared to an opioid only.

An example of an opioid-dexmedetomidine PCA regimen is that of Nie et al.:

- *Mixture*: sufentanil 100 µg + dexmedetomidine 300 µg diluted to 100 ml (This is a very expensive mixture)
- *Background infusion*: sufentanil 0.015 µg/kg/h + dexmedetomidine 0.045 µg/kg/h
- *PCA dose*: sufentanil 0.023 µg/kg + dexmedetomidine 0.07 µg/kg
- *Lockout interval*: 8 minutes

An example of an opioid-ketamine PCA regimen is that of Javery et al.:

- *Mixture*: morphine 100 mg + ketamine 100 mg diluted to 100 ml
- *No background* infusion
- *PCA dose*: 1 ml
- *Lockout interval*: 6 minutes

Once opioid tolerance is diagnosed, the following steps may be taken:

- Management is similar to that of ANP, including amitriptyline or gabapentanoids.
- The patient may continue with the normal opioid dose, while additional doses are administered, either intravenously or via a transcutaneous patch.
- Opioid rotation may be applied in the tolerant patient. There are significant differences in the interaction between different μ agonists and the μ-receptor which go beyond the effect on second messenger systems after binding, including the rate of receptor trafficking, and possibly even effects on receptor synthesis and affinity. In view of this, a patient experiencing inadequate analgesia from one opioid drug may be switched to slow-release morphine, or oxycodone. Transdermal fentanyl should be avoided due to the likely development of hyperalgesia. A switch back to the previous drug may prove effective should analgesia on the new drug become inadequate over time. A patient on maintenance opioids for chronic pain in the perioperative setting should be managed with a different opioid for perioperative analgesia. The following approach to opioid rotation is used:
  - Calculate the equianalgesic dose of the new opioid based on equianalgesic tables.
  - Start the new opioid at a dose 25–50% lower than the calculated equianalgesic dose.
  - Select an appropriate dose within this window, using clinical judgment as to the applicability of the equianalgesic dose table to the specific characteristics of the opioid regimen (i.e. p.o. or IVI).
  - Reassess pain severity to determine whether an additional 15–30% dose increase or decrease should be allowed to improve efficacy or to minimise adverse effects.
  - Evaluate the response frequently and titrate dose of the new opioid up or down to optimise the effect. If supplemental doses are used, these should constitute 5–15% of the total daily dose and should be administered according to dose intervals appropriate for the particular opioid.

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