5. Pharmacodynamics of opioids

Nearly all effects of the opioids (analgesia, sedation, respiratory depression) result from an interaction with a specific opioid receptor. The desired interactions of spinal opioids are those with the spinal receptors. But rostral distribution and effect on brain receptors as a source of undesired actions can neither be completely prevented nor completely excluded.

Epidural or intrathecal opioids produce a significant elevation of the pain threshold. The effect is characterized by:

- dose dependency
- stereospecificity
- highly regular structure activity relationship
- dose-dependent antagonism by naloxone.

Spinal opioids at analgesic doses, unlike local anaesthetic agents, have neither effect on the response to light touch nor do they have any direct effects on the sympathetic nervous system or voluntary motor function. However, there is clear clinical evidence that spinal opioids do not act as pure antinociceptive substances and do not only selectively block pain transmission. Side effects always appear inherent with the analgesic effect of spinal opioids (Bromage et al. 1980 c; Bromage et al. 1982 b). The degree of those side effects certainly can be different with different methods, different drugs and different doses. Therefore, the main point for the clinical practice will be to evaluate very carefully the right patient, the right drug given in the right dose and using the right technique.

5.1 Analgesia

The intensity and duration of analgesia are related to the pharmacokinetic characteristics of the opioid. In view of a good analgesic action there is an obvious advantage for morphine (low lipid solubility = long lasting effects). But regarding the safety there is a clear disadvantage for morphine (low lipid solubility = rostral spread). So, the main point for deciding is not effectiveness of analgesia but security for the patient.
As mentioned earlier, the analgesia after epidural opioids is actually a hypalgesia, not fully comparable to that obtained with local anaesthetics. The special character of hypalgesia is documented only anecdotally (Zenz et al. 1981 b). It seems that the dull pain, corresponding to the paleo-spinothalamic pathway, is more affected by spinal opioids than the sharp pain. This would imply important consequences for the postoperative period. The diffuse wound pain is clearly diminished, whereas the sharp pain (peritoneal reactions) remains fairly unaffected. This is certainly an advantage for the early diagnosis of surgical complications which, in the case of regional blocks, are masked by the completeness of analgesia. Using different opioids, there are no proven differences in efficacy if equipotent doses of different compounds are used.

The use of the visual linear analogue scale (VAS) is the most practical method for evaluating pain and pain relief (Revill et al. 1976; Scott and Huskisson 1976).

### 5.1.1 Relationship between administration route and dose

One of the most outstanding advantages of spinal administration of opioids is the long duration of action in comparison to conventional analgesia provided by parenteral administration routes (Tab. 21, 22, Fig. 28).

Comparative studies were carried out with hydrophilic opioids given at approximately equianalgesic doses epidurally (morphine 5 mg) or intravenously (morphine 5-10 mg) (Bromage et al. 1982 b; Rutter et al. 1981; Torda and Pybus 1982). A duration of the analgesic action of, respectively, 18 and 11 hours for the epidural route and 3 hours for the intravenously route were found.

For lipid soluble opioids the differences between the duration of analgesia after epidural or intravenous administration are less important (Tab. 21).

The differences in bioavailability as a function of the administration route was studied after 10 mg of morphine was injected intravenously or intramuscularly. Only 0.1% or 0.01 mg penetrates into the central nervous system. To obtain the same concentration in the CNS only 5 mg of epidural or 0.25-0.5 mg of intrathecal morphine were needed (Nordberg et al. 1984 b).

This indicates that the relative potencies of morphine for the three routes of administration are as follows:

- intravenous or intramuscular  = 1
- epidural  = 2
- intrathecal  = 20-40 (Fig. 28)

Holland et al. (1981) and Reiz et al. (1981 a) failed to obtain similar results. They estimated that the effective intrathecal morphine dose may be only 5 to 10 times smaller than the effective intramuscular dose.