Department of Physiology and Pharmacology

Pharmacokinetic and pharmacodynamic aspects on opioid administration, morphine and ketobemidone, in the pediatric population

Akademisk avhandling

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Abstract

Opioids are the mainstay of the treatment of severe nociceptive pain in both children and adults. The studies in this thesis have focused on different aspects of opioid treatment in the pediatric population with special interest in morphine and ketobemidone. Ketobemidone has been in use for a long period of time but there has been very limited published data about the pharmacokinetics and pharmacodynamics of this drug. The aim has been to increase the knowledge of both pharmacokinetic and pharmacodynamic effects of morphine and ketobemidone.

In the sequence of studies the first one dealt with the pharmacokinetics of rectally administered morphine. Two different formulations of morphine were used and compared. Secondly the child's acceptance of the two formulations was examined from a pain perspective.

Further on, the potency of ketobemidone in children was compared to morphine in a postoperative setting using PCA as a drug delivery system.

Pharmacokinetic studies in children have been scarce despite the long time use of ketobemidone. In two studies the pharmacokinetics were explored in neonates, infants and children.

From the results the following conclusions were drawn:

- A morphine gel adapted for rectal use, with a higher pH than the regular saline solution, did not show any significant higher bioavailability but a tendency for an improved uptake. Bioavailability of rectally administered morphine is relatively low (about 30 %) and shows a large inter-individual variability in children.
- A morphine gel developed for rectal administration induces less pain in children aged 1-6 years. Most children tolerate rectal administration of morphine well when used for premedication.
- The opioid ketobemidone is equipotent to morphine when used for postoperative pain treatment. The frequency of adverse effects of ketobemidone and morphine are comparable when PCA is used for postoperative pain relief in children.
- The pharmacokinetic characteristics of ketobemidone administered in children older than 1 month appear to be similar to those in adults.
- The elimination of ketobemidone appeared to be slower in full-term neonates compared to children older than one year of age.

The analgesic effect of opioids can differ between individuals in the pediatric population to a large extent. Dose recommendations can therefore not be based solely on pharmacokinetic knowledge. The best analgesic for the patient is the one that will effectively decrease pain to a minimum or acceptable pain levels, with as little side effect as possible and without patient disagreement upon administration.

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