British Journal of Anaesthesia **86** (1): 120–2 (2001)

BJA

SHORT COMMUNICATIONS

Pharmacokinetic profile of epidurally administered methylnaltrexone, a novel peripheral opioid antagonist in a rabbit model

D. B. Murphy[1*], H. El Behiery[1], V. W. Chan[1] and J. F. Foss[2]

[1]Department of Anaesthesia, The Toronto Western Hospital and University of Toronto, Toronto, Ontario, Canada. [2]Department of Anaesthesia and Critical Care, University of Chicago, Chicago IL, USA

**Corresponding author: Department of Anaesthesia, Intensive Care and Pain Management,Cork University Hospital, Wilton, Cork City, Ireland*

Methylnaltrexone (MNTX) is the first peripheral opioid receptor antagonist used in man to treat acute and chronic opiate-mediated side-effects. We describe in a rabbit model the pharmacokinetics of epidurally administered MNTX 0.66 mg kg^{-1}, and we tested the hypothesis that epidurally administered MNTX does not penetrate the dura into the subarachnoid space. There were minimal concentrations of MNTX (40 ng ml^{-1}) detected in the CSF at 10 and 20 min and none thereafter in comparison with the high serum levels. The serum drug concentration–time profile fitted a two-compartment pharmacokinetic model. Further studies are warranted as epidurally administered MNTX may have the potential to reverse epidural opioid-mediated side-effects whilst preserving analgesia.

Br J Anaesth 2001; **86**: 120–2

Keywords: anaesthetic techniques, epidural; pharmacokinetics, methylnaltrexone; rabbit

Accepted for publication: August 15, 2000

Epidural opioid compounds are used for analgesia in clinical practice in patients suffering from acute and chronic pain. Common peripheral undesirable side-effects of epidural opioids include urinary retention, constipation and delayed gastric emptying, but the exact mechanisms remain unclear.[1] Epidural opioids may mediate these side-effects via a central, spinal and/or direct effect on local opioid receptors.[1] The relative contributions of each mechanism are unknown.

Methylnaltrexone (MNTX) is a quaternary opioid antagonist with limited ability to cross the blood–brain barrier. In man, intravenous MNTX has been shown to reverse morphine-induced delayed gastric emptying[2] and to reverse constipation due to chronic methadone use[3] without affecting centrally mediated analgesia. We postulated that if MNTX does not cross the dura it might have potential to reverse peripherally mediated side-effects of epidural opioids without affecting analgesia. Therefore, the purpose of this study was to describe the pharmacokinetics of epidurally administered MNTX and to test the hypothesis that epidurally administered MNTX does not penetrate the dura into the subarachnoid space (SAS).

Methods and results

With approval of the Animal Care and Research Committee of the University of Toronto, seven rabbits (3.3–3.5 kg) were anaesthetized with isoflurane in nitrous oxide and oxygen. A 22 g cannula was inserted in an ear vein and artery for blood sample collection and blood gas measurement. The trachea was intubated with a 4 mm (internal diameter) endotracheal tube and pancuronium 0.3 mg kg^{-1} was administered to produce muscle relaxation. The animals were placed prone on the operating table and the head was fixed in a modified stereotactic frame. The rabbits' lungs were ventilated (Harvard animal ventilator) to normocapnia and 10 ml kg^{-1} normal saline was administered every 30 min. The L_3 or L_4 vertebra was exposed via a midline lumbar incision by retracting the paraspinal muscles laterally. After laminectomy of one of the vertebra, a 22 g catheter was placed in the epidural space under direct vision. The cannula was inspected for the presence of CSF and aspirated. If CSF was detected the animal was discarded and replaced. After confirmation of placement in the epidural space the catheter was fixed in place with dental cement.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2001

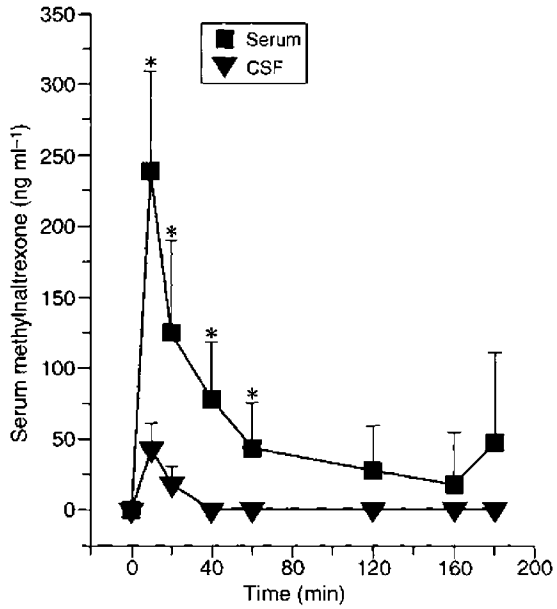

Fig 1 Plot of serum and CSF concentrations of methylnaltrexone (ng ml^{-1}) after epidural administration of methylnaltrexone 0.66 mg kg^{-1}. Data are mean (SD). *P<0.05, CSF *vs* serum (Mann–Whitney U-test).

A midline skin incision was made over the shaved back of the neck covering the occipital bone and cervical dorsum. The atlanto-occipital membrane was identified and a 22 g cannula was inserted in the base of the skull covering the cisterna magna, cephalad to the occipital–atlas junction. Spontaneous CSF flow was obtained and allowed to drain freely. The cannula was immobilized with dental cement. MNTX 0.66 mg kg^{-1} (Mallinckrodt Specialty Chemicals, St Louis, MO, USA) was administered in 1ml of normal saline via the epidural catheter and blood and CSF samples were taken 0, 3, 6, 10, 15, 20, 40, 60, 120 and 180 min after drug administration. The epidural dose of MNTX was chosen on the basis of previous results,[2,3] with the aim of administering a relatively high dose of MNTX. Animals were euthanized after 3 h by pentobarbital overdose. Blood samples were centrifuged, separated immediately and the serum and CSF sample was frozen at –80°C for later analysis by high-performance liquid chromatography. Using the modified procedure from the method of Kim *et al.*,[4] standard curves of MNTX were run for each set of samples. The lower limit of detection was 2 ng ml^{-1}. Pharmacokinetic parameters for MNTX were calculated using WinNonlin™ (2.1 Scientific Consulting, Mountain View, CA, USA).

Seven rabbits were enrolled in the study, but data from two were excluded due to difficulty in CSF or blood sampling techniques. Results are expressed as mean (SD) unless stated otherwise. The mean weight of the animals was 3.5 (0.3) kg. The serum drug concentration –time profile for each animal fitted a biexpontential function. Therefore, the disposition of epidural MNTX could be described by a two-compartment model in which the drug is eliminated from the central compartment. The mean serum and CSF MNTX concentrations determined during the duration of the study are shown in Fig. 1. There were minimal amounts of MNTX detected in the CSF at up to 20 min and none thereafter. The following pharmacokinetic data were calculated: area under the curve [AUC_{0-240} 11920 (3892) ng min^{-1} ml^{-1}], peak concentration [C_{max} 215 (35) ng^{-1} ml^{-1}], time to maximum concentration (T_{max} 10 min), total volume of distribution [Vz 5199 (1199) ml kg^{-1}], total body clearance [CL 86 (26) ml min^{-1} kg^{-1}] and β half-life [$T_{\frac{1}{2}}$ β 74.96 (35) min^{-1}]

Comment

This is the first study to describe the pharmacokinetics of epidurally administered MNTX. After epidural administration, minimal concentrations of the drug were detected in the CSF compared with plasma. Previous studies in animals and man showed the ratio of peak CSF:serum morphine levels are of the order of 35:1 after epidural morphine administration.[5] However, in this study the CSF:serum ratio was reversed to 1:5 after high-dose epidural MNTX, suggesting that high doses of epidural MNTX do not appear to cross the dural membrane significantly and would not have clinical implications. Its relative lack of dural penetration may be due to the presence of a bulky quaternary charged N_2 atom in the drug molecule. The low concentration of MNTX seen in the CNS was produced by the administration of doses very much larger than those expected to be used clinically. MNTX has significantly lower affinity for the opioid receptor than naltrexone[6] and the maximum concentration detected in the CSF is unlikely to have clinical implications. However, evaluation of this low CNS penetration would need to be studied in the clinical setting. Therefore, we postulate that, during coadministration of centrally acting opioids and MNTX in the epidural space, MNTX absorbed into the vascular compartment will act only on peripheral opioid receptor while maintaining centrally mediated analgesia.

After epidural administration of MNTX 0.66 mg kg^{-1}, peak serum values were greater than 200 ng ml^{-1}. These systemic drug levels may possibly be of therapeutic significance. In patients on chronic opioid therapy who received i.v. MNTX in doses up to 0.35 mg kg^{-1} over 1 min, rapid laxation was induced without evidence of withdrawal or diminished analgesia. Peak plasma levels of 162 (237) ng ml^{-1} were observed without side-effects in that group.[3]

In conclusion, epidurally administered MNTX does not appear to gain significant access to the CSF. Further studies are warranted as epidurally administered MNTX may have potential to reverse epidural opioid-mediated side-effects whilst preserving analgesia.

Acknowledgements

The authors wish to acknowledge the support of the Canadian Anesthesiologists' Society Award to H. El Behiery.

References

1 Chaney MA. Side effects of intrathecal and epidural opioids. *Can J Anaesth* 1995; **42**: 891–903

2 Murphy DB, Sutton JA, Prescott LF, *et al.* Opioid-induced delay in gastric emptying: a peripheral mechanism in humans. *Anesthesiology* 1997; **87**: 765–70

3 Yuan CS, Foss JF, O'Connor M *et al.* Methylnaltrexone for reversal of constipation due to chronic methadone use: a randomized controlled trial. *J Am Med Assoc* 2000; **283**: 367–72

4 Kim C, Cheng R, Corrigall WA, *et al.* Assay for methylnaltrexone in rat brain region by serum high performance liquid chromatography with colorimetric electrochemical detection. *Chromatographia* 1989; **28**: 359–63

5 Brose WG, Tanelian DL, Brodsky JB, *et al.* CSF and blood pharmacokinetics of hydromorphone and morphine following lumbar epidural administration. *Pain* 1991; **45**: 11–5

6 Brown DR, Goldberg LI. The use of quaternary narcotic antagonists in opiate research. *Neuropharmacology* 1985; **24**: 181–91

British Journal of Anaesthesia **86** (1): 122–4 (2001)

Influence of head and neck position on cuff position and oropharyngeal sealing pressure with the laryngeal mask airway in children

K. Okuda, G. Inagawa, T. Miwa and K. Hiroki*

Department of Anesthesiology, Kanagawa Children's Medical Center, 2-138-4 Mutsukawa, Minamiku, Yokohama, Japan

**Corresponding author*

We studied how head and neck position affect the cuff position and oropharyngeal sealing pressures of the laryngeal mask airways (LMAs) in children. We studied 39 non-paralyzed healthy children aged 1.5–8.0 yr, weighing 10.3–27.0 kg, managed with size 2 or 2.5 LMAs during elective surgery. Head and neck movements did not adversely affect airway patency in 97% of patients. One child developed apparent airway obstruction with head and neck flexion, which was relieved in the neutral position. Oropharyngeal sealing pressure was significantly greater during neck flexion compared with the neutral position ($P<0.02$). Fibreoptic examination revealed that the epiglottis covered a larger area of the LMA aperture during neck flexion, compared with the neutral position ($P<0.02$).

Br J Anaesth 2001; **86**: 122–4

Keywords: intubation tracheal; equipment, mask anaesthesia

Accepted for publication: August 22, 2000

The laryngeal mask airway (LMA†) is used for paediatric surgery with different head and neck positions, such as extension of the neck for adenotonsillectomy,[1] and rotation of the head for myryngotomy.[2] Studies of children with their head and neck in neutral position, assessing the position of the LMA fibreoptic[3–5] or radiological[6] examination, found that well functioning LMAs were not necessarily ideally anatomically, placed. Fibreoptic examination of the LMA position showed that the epiglottis occupied a larger area within the LMA aperture in children than in adults.[4 5] These observations suggest that head and neck movement could distort the oropharyngeal space, and affect anatomical position and function of the LMA more in children than in adults.

† LMA is the property of Intavent Limited.

A study of adult patients[7] showed little influence of head and neck position on cuff position and oropharyngeal leak pressure of the LMA, but no studies have been done in children.

We measured how head and neck movement changed the cuff position and oropharyngeal sealing pressure of the LMA in children patients.

Methods and results

After obtaining Ethics Committee approval and informed consent from the parents, we studied ASA physical status I paediatric patients who were managed with size 2 or 2.5 LMAs during elective urological surgery.

Anaesthesia was induced via a facemask with 5% sevoflurane and nitrous oxide in 65% oxygen. After