Title : ARTERIAL AND VENTRICULAR CEREBROSPINAL FLUID PHARMACOKINETICS AFTER INTRATHECAL MEPERIDINE IN MAN

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INTRODUCTION : Intrathecal anesthesia with meperidine alone seems to be an interesting technique in perineal surgery. It has been shown indeed that (i) meperidine induces a motor block related to its local anesthetic properties in the operative period (ii) it also causes a long lasting and potent pain relief in the postoperative period. However there is a putative risk of respiratory depression related to opioids properties. Although respiratory depression is more commonly observed with hydrophilic opioids such as morphine rather than with meperidine, the mechanism of this depression remains unclear and thus limits the use of such a technique. To further investigate the mechanisms of meperidine-induced respiratory depression, we compared meperidine pharmacokinetics both in the arterial blood and in the ventricular cerebrospinal fluid (VCSF).

METHODS : Five severe head-trauma patients (30.4 ± 8 years old) with intracranial pressure monitoring had to be operated on a lower limb fracture between the 5$^{th}$ and 10$^{th}$ day of evolution, once clinical status (Glasgow Coma Scale = 7 ± 1) and ventricular pressure (8.2 ± 2.5 mmHg) allowed such a surgery. After approval of the Ethics Comittee, all patients were anesthetized for this surgery by means of intrathecal administration of meperidine 1 mg.kg$^{-1}$ (2 ml ampul, 50 mg per ml, baricity 1014). Meperidine concentration was determined in the arterial blood and simultaneously in the VCSF (using monitoring catheters) and by means of gas chromatography every 2 hours up to the 16$^{th}$ hours after administration. An additional determination was obtained at the end of the first hour. Pharmacokinetics data were computed using the SIPHAR$^{R}$ software. Resultats are given as mean ± SEM.

RESULTS : The clinical course was uneventful for all patients. On the figure are plotted mean meperidine concentration in the blood as well as in the VCSF versus time. VCSF/blood concentration ratio significantly increased with time (r = 0.85) from 0.23 ± 0.03 at the first hour to 0.36 ± 0.16 at 16$^{th}$ hour. Pharmacokinetics data are given in the table.

DISCUSSION : Our results show that VCSF meperidine concentration is directly related to that in the blood. Respiratory depression is thus likely to be dependent upon the meperidine blood concentration. The analgesic effect of intrathecal meperidine is related to its liposolubility (allowing a high concentration ratio in the spinal cord) and not to its blood transport as the blood concentration was always lower than that currently admitted to induce systemic analgesia (1). Whereas intramuscular injection of the same dose of meperidine as that used in this study does not allow surgery, it is notewortly that both VCSF and blood concentrations were similar to those observed after intramuscular injection (2). Among the 3 hypothesises that have been put forward to explain increase in VCSF concentration of an opioid administred intrathecally (i.e. rostrocaudal movement, systemic vascular absorption and redistribution, movement up Batson's perivertebral plexus), the systemic vascular pathway seems to play a major role for meperidine. As respiratory depression occurs for a meperidine blood concentration higher than 800 ng.ml$^{-1}$ (3) the benefit-risk ratio of this technique was in this study of about 2. It is concluded that side effects of this technique and namely respiratory depression would be diminished if vascular absorption and redistribution could be reduced.

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| | BLOOD | | VENTRICULAR CSF | |
|---|---|---|---|---|
| | Mean | SEM | Mean | SEM |
| $T_{\frac{1}{2}}$ el (h) | 3.14 | 0.4 | 2.72 | 0.3 |
| Cmax (ng.ml$^{-1}$) | 335 | 103 | 64.5 | 14.9 |
| Tmax (h) | 1 | 0.29 | 1.4 | 0.24 |
| AUC (ng.ml$^{-1}$.h) | 1476 | 244 | 379 | 90.7 |
| Cl tot (l.kg$^{-1}$.h$^{-1}$) | 0.75 | 0.12 | 3.52 | 1 |
| Vd (l.kg$^{-1}$) | 3.33 | 0.63 | 12.4 | 2.3 |

*Elimination half live ($T_{\frac{1}{2}}$ el) maximum concentration and time to reach maximum concentration (Cmax, Tmax). Area under the blood and VCSF concentration time curve (AUC). Total clearance (Cl tot) and volume of distribution (Vd)*