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# *Comparative Pharmacokinetics of Spinal Opioids in Humans: A Step Toward Determination of Relative Safety*

IN A REVIEW in this journal in 1984, it was concluded that there remained many unanswered questions concerning the comparative pharmacology of spinally administered opioids.[1] In this issue of ANESTHESIOLOGY, Sjöström *et al.* report two pharmacokinetic studies which extend data previously available, disprove some data, and provide a valuable comparison of morphine and meperidine.[2,3] Data such as these, in combination with dose-response studies of analgesia and side effects, are also helpful in addressing the question of the relative safety of lipophilic compared to hydrophilic opioids. The current studies have some advantages over those previously published with respect to the specificity of the morphine assay employed, the frequency and duration of cerebrospinal fluid (CSF) sampling, and the method of CSF sampling *via* a catheter placed intrathecally at a different level than that of the spinally administered opioid.

Pharmacokinetic studies of epidural and intrathecal administration of any drug, including opioids, suffer from some limitations, as acknowledged by the current authors. When an intravenous bolus of drug is given, it is rapidly and uniformly distributed into the blood, permitting reasonably clear description of distribution and elimination phases from the blood concentration-time profile. In the case of intrathecal and epidural injection, distribution of drug does not satisfy the requirement for rapid distribution; thus, for example, absorption from the epidural space continues for an indeterminate time which clearly will overlap the time when calculations of "elimination half-life" and other parameters are made. Such data should be regarded as estimates of, rather than exact measurements of, processes such as clearance of drug from blood or CSF. Also, use of an intrathecal catheter for CSF sampling may result in leakage of CSF through the entry point in the dura; sampling of CSF would add to this "loss" of CSF, and opioid in CSF. Such losses could have played a part in the rather brief duration of postoperative analgesia. Regardless of possible influences of such factors, the data in the present study do give a precise description of the comparative time course of blood and CSF concentrations of spinally administered morphine and meperidine.

The plasma pharmacokinetic data for morphine confirm that peak concentrations are attained within 5–10 min of either epidural or intrathecal injection.[2,3] This is in contrast to earlier comprehensive plasma morphine measurements, using a radioimmune assay which co-determines morphine and its metabolites. That study reported a long delay in reaching peak morphine plasma levels after epidural and intrathecal injection.[4]

The current study of epidural administration provides support for the key role of lipophilicity in dural transfer of opioids; for the lipophilic drug meperidine, peak concentrations occurred four times more rapidly than was the case for the hydrophilic drug morphine. Similarly, CSF meperidine concentration decreased four times faster than CSF morphine concentration. However, the amount of drug reaching the CSF was similar for the two drugs, and approximated 4% of the dose injected epidurally.[2] This agrees very nicely with corresponding minimum effective epidural and intrathecal doses of 5 mg and 0.25 mg, respectively. The

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study also supports a predominantly spinal action of epidurally injected meperidine; the high CSF:plasma concentration ratio 5 min after injection in this study[2] and rapid onset of analgesia in other studies[5] indicate that onset of analgesia is predominantly due to a spinal action of the drug; the rapid decline in plasma concentration in this[2] and other studies[5] suggests that systemically absorbed meperidine could contribute to analgesia during the first hour, but not later. The transient appearance of morphine in plasma, in the current[2] and other[6,7] studies, confirms that vascular absorption of morphine contributes to analgesia for only a fraction of the analgesic interval, after epidural injection.

In both the current studies,[2,3] the rapid decline in lumbar CSF concentrations of meperidine indicated that the drug may not migrate cephaled in CSF to the brain. However, another study[7] reports that meperidine is measured in significant amounts at the C7-T1 level, and peak levels occur earlier for meperidine (1 h) than for morphine (2–3 h). As is the case in the lumbar area, meperidine concentrations at C7-T1 decline much more rapidly than those for morphine.[7] Thus, if meperidine is to cause respiratory depression, it will occur early (at about 1 h), apparently due to drug migrating to the brain as well as drug absorbed into the circulation.[8] Fortunately, it appears that meperidine is cleared as rapidly from CSF adjacent to the brain as it is from CSF in the lumbar region. However, it should be acknowledged that we know nothing at present about factors that influence the influx and efflux of opioid drugs into and out of brain; it is possible that lipophilicity may be only one of the factors involved.[8]

Variability in CSF concentrations of opioid among patients is a striking finding in both the current studies: maximum CSF concentration varied up to fivefold after intrathecal injection, and as much as sixfold after epidural administration; CSF concentrations at the time of request for additional analgesia also varied greatly.[2,3] These data point very strongly to a need to individualize dose of spinal opioid, by either route. It seems that this may be accomplished by using either an epidural or intrathecal catheter, observation of degree of analgesia and severity of any side effects, and then adjustment of subsequent doses. Infusion techniques and use of opioids with rapid onset and short-to-medium duration would seem attractive to permit flexibility of adjustment of dose rate.[8] Dose-response data now suggest that the ratio between the spinal analgetic dose and the dose that causes severe respiratory depression is not much in excess of two;[8] thus, use of a dose in an individual patient of twice that required for analgesia could lose all of the potential advantage of carefully individualized doses which the current[2,3] and prior studies suggest may produce "selective spinal analgesia."[9]

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