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Clinical and pharmacokinetic aspects of the combination of meperidine and prilocaine for spinal anaesthesia

The aim of this study was to determine whether the addition of a small dose of prilocaine could augment the spinal block induced by meperidine and affect intrathecal meperidine pharmacokinetic behaviour. Spinal anaesthesia was performed in 60 men scheduled for endoscopic resection of a prostatic adenoma or bladder tumour under spinal anaesthesia. They were allocated randomly to receive either 1 mg·kg⁻¹ meperidine (Group 1, n = 30), or 1 mg·kg⁻¹ meperidine plus 0.5 mg·kg⁻¹ prilocaine (Group 2, n = 30). Blood samples were collected prior to and for 24 hr after spinal injection in 24 patients (12 in each group). Plasma meperidine levels were assayed by gas chromatography. Complete motor block was achieved in all Group 2 patients, but was incomplete in seven of Group 1 (P < 0.05). The onset of both motor and sensory blocks was shorter (P < 0.01) in Group 2 and the duration was longer (P < 0.05). Coadministration of prilocaine modifies meperidine pharmacokinetic behaviour. The area under curve was 48% greater (P < 0.01) and C_{max} was higher in Group 2 than in Group 1, 145.8 ± 42.2 vs 107 ± 20.5 ng·ml⁻¹ (P < 0.001). No evidence of respiratory depression was noted in any of the patients. Despite the increase in plasma meperidine concentrations, no side effects were observed. The

plasma concentrations remained at one third to one sixth the levels reported to induce a respiratory depression. It is concluded that the addition of prilocaine to meperidine improves motor and sensory block during surgery and alters meperidine kinetics without producing major side effects.

Le but de ce travail est d'étudier si l'adjonction d'une faible dose de prilocaine améliore le bloc moteur de la péthidine et modifie sa pharmacocinétique. Soixante patients prévus pour chirurgie endoscopique sous rachianesthésie sont inclus dans l'étude. Ils sont répartis par randomisation en deux groupes : le groupe 1 (n = 30) reçoit 1 mg·kg⁻¹ de péthidine en intrathécal, le groupe 2 (n = 30) 1 mg·kg⁻¹ de péthidine associé à 0,5 mg·kg⁻¹ de prilocaine. Des prélèvements sanguins sont faits après l'injection intrathécale et pendant les 24 h suivantes chez 24 patients (12 dans chaque groupe). Le dosage de la péthidine est réalisé par chromatographie en phase gazeuse. Le bloc moteur grade 3 est présent chez tous les patients du groupe 2 mais incomplet dans sept cas du groupe 1 (P < 0,05). L'installation du bloc moteur et du bloc sensitif est plus rapide dans le groupe 2 et ils durent plus longtemps (P < 0,05). L'adjonction de prilocaine modifie la pharmacocinétique de la péthidine. La surface sous la courbe est de 48% plus grande dans le groupe 2 (P < 0,01). C_{max} est plus élevée dans ce groupe 2 : 145,88 ± 42,2 ng·ml⁻¹ que dans le groupe 1 : 107 ± 20,5 ng·ml⁻¹ (P < 0,001). Il n'y a pas de dépression respiratoire, les concentrations sanguines étant de trois à six fois inférieures à celles requises pour entraîner cette complication. En conclusion l'adjonction de prilocaine à la péthidine en rachianesthésie améliore la qualité des blocs moteur et sensitif, mais modifie la pharmacocinétique sans effet secondaire.

Key words

ANAESTHETIC TECHNIQUES: spinal;
ANAESTHETIC, LOCAL: meperidine, prilocaine;
PHARMACOKINETICS: meperidine.

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Opiates are commonly administered by intrathecal or epidural routes to produce powerful analgesia in the post-operative period as well as in chronic or cancer pain.¹ The effects of water soluble or fat soluble opiates injected intrathecally have been extensively studied.² Meperidine, a liposoluble opioid, has been administered by this route in

animals in 1978.³ A few years later,⁴ profound analgesia without motor and sympathetic blockade was achieved in cancer patients after epidural injection of meperidine. More recently, intrathecal meperidine has been used as a sole anaesthetic agent for urological,⁵ vascular,⁶ and perineal surgery.^{7,8} In a dose of $1 \text{ mg} \cdot \text{kg}^{-1}$, spinal meperidine had two advantages: firstly it induced surgical anaesthesia followed by postoperative analgesia, and secondly it provided motor blockade related to the local anaesthetic property of the drug.⁹ Nevertheless motor blockade was absent in 20% of patients¹⁰ who scored 0 or 1 according to the BROMAGE scale.¹¹

Local anaesthetic agents induce sympathetic, sensory, and motor blockade without postoperative analgesia. Prilocaine, an amide which is rapidly and completely metabolized, has been described as one of the safest agents in this class.¹² For this reason, prilocaine is commonly used in our institution.⁵ The aim of this study was to evaluate the benefit of combining spinal prilocaine and meperidine. Since changes in volume, density and pH of the solution could alter the absorption of meperidine, we also studied its pharmacokinetic behaviour.

Methods

Sixty male patients were included in the study after written informed consent had been obtained. All were of ASA I or II physical status and were scheduled either for endoscopic surgery of the prostate or for bladder tumour resection performed under spinal anaesthesia. The study was approved by our hospital ethical committee.

Patients were allocated randomly into two groups. In the first group (Group 1: control group) patients received meperidine. In the second group (Group 2: MP group) patients received spinal meperidine combined with prilocaine.

Anaesthetic procedure

Diazepam was given orally ($0.2 \text{ mg} \cdot \text{kg}^{-1}$) one hour before surgery as premedication. After infusion of 500 ml colloid solution (Plasmion®), lumbar puncture was performed with a 25-gauge needle at the L_{3-4} intervertebral interspace by the midline approach, with the patient in the sitting position. Blood pressure and heart rate (sphygmomanometer Dinamap® Critikon) were measured at five minute intervals throughout anaesthesia and surgery, and at 15 min intervals during recovery. In Group 1, meperidine $1 \text{ mg} \cdot \text{kg}^{-1}$ was administered (vials of 100 mg in a 2 ml solution of 1.014 density at room temperature). In Group 2, the same dose of meperidine was combined with prilocaine $0.5 \text{ mg} \cdot \text{kg}^{-1}$ withdrawn from vials containing 100 mg in a 2 ml hyperbaric solution (density: 1.037 at room temperature). This dose of prilocaine was determined from a previous open study as the least which induced complete spinal block. Spinal injection was performed over 30 sec

in all the patients. The mean volume injected was $1.4 \pm 0.2 \text{ ml}$ in Group 1 and $1.9 \pm 0.2 \text{ ml}$ in group 2 ($P < 0.01$).

Patients were placed in the sitting position for two minutes and then positioned on the operating table 15° head up. A Ringer's lactate solution was infused at $15 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ during surgery.

Assessment of anaesthetic blockade and monitoring

Sensory blockade (SB) was tested in the midline by pin-prick using a 20-gauge needle, above the T_{10} dermatome level. The duration of SB was assessed at the L_1 segment by repeating pin-prick every five minutes.

Motor blockade (MB) was assessed according to the BROMAGE scale;¹⁰ 0: no impairment of movement of legs and feet; 1: barely able to flex knees, no impairment of foot movement; 2: unable to flex knees, barely able to move feet; 3: unable to move feet or knees.

The MB and SB were assessed at five-minute intervals for the first 30 min following intrathecal injection, and then every 30 min until complete recovery. Respiratory rate was measured every ten minutes and blood gas measurements were performed before anaesthesia and at 1, 2, 6, and 12 hr after surgery. Patients scored their pain sensation on a visual analogue scale (VAS), graded from 0 to 10, every hour during the first 24 hr following surgery.

Pharmacokinetic study

Sampling for plasma meperidine measurement was obtained from 24 patients, 12 in each group. These patients were selected randomly from each group. The pharmacokinetic subgroups were matched in terms of age and weight with the complete groups. Using an indwelling venous catheter, blood samples of 5 ml were collected in heparinized dry tubes prior to and at 15 min, 30 min and 1, 2, 4, 6, 8, 10, 12, 16, 18, 20 and 24 hr following spinal anaesthesia. The tubes were immediately centrifuged and plasma was frozen at -20°C until the time of the assay. Meperidine plasma concentrations were assayed by gas chromatography, with nitrogen phosphorus flame ionization detection (NPFID): plasma was alkalized, extracted and centrifuged. An aliquot of the organic layer was applied to an OVI column. The sensitivity of the assay was $3 \text{ ng} \cdot \text{ml}^{-1}$. The day to day coefficient of variation was 3% in the concentration range measured. The pharmacokinetic variables of meperidine were calculated by non-compartmental analysis, using a desk-top computer and the programme PHARM;¹³ the following variables were obtained:

- $t_{1/2} \beta$ (hr): terminal plasma half-life, calculated from the formula $\text{Ln}2/\beta$ where β is evaluated from the slope of the linear regression of the logarithm of concentration versus time by means of the least square method.
- AUC ($\text{ng} \cdot \text{hr}^{-1} \cdot \text{ml}^{-1}$): area under the plasma concentra-

TABLE I Patients' demographic data and surgery: mean $\pm$ SD (range)

	Group 1 (n = 30)	Group 2 (n = 30)	
Age (yr)	66.5 $\pm$ 6.1 (55–81)	67.9 $\pm$ 5.9 (57–80)	(NS)
Weight (kg)	69.2 $\pm$ 6.0 (60–80)	70.9 $\pm$ 8.8 (59–80)	(NS)
Duration of surgery (min)	25 $\pm$ 12	30 $\pm$ 8	(NS)
Type of surgery	Prostate resection: 26 Bladder tumour resection: 4	Prostate resection: 25 Bladder tumour resection: 5	

NS: not significant.

TABLE II Feature of anaesthetic blockades of the two groups : mean $\pm$ SD (range)

	Group 1 (n = 30)	Group 2 (n = 30)	
Time to max SB extension (min)	5.6 $\pm$ 2.2 (3–10)	3.2 $\pm$ 2.2 (1–10)	$P < 0.01^*$
Duration of SB at L1 (min)	86 $\pm$ 24 (45–135)	119 $\pm$ 31.3 (65–190)	$P < 0.01^*$
Number of patients with G3 MB	23	30	$P < 0.05^\dagger$
Time to obtain G3 MB (min)	7.7 $\pm$ 2.8 (4–15)	5.4 $\pm$ 2.6 (1–10)	$P < 0.01^*$
Duration of MB (min)	91.1 $\pm$ 22 (85–125)	110.3 $\pm$ 25.3 (65–165)	$P < 0.01^*$

*Student's t test.

†Chi 2 test.

TABLE III Pharmacokinetic variables (mean $\pm$ SD)

	Group 1 n = 12	Group 2 n = 12	
$t_{1/2\beta}$ (hr)	5.4 $\pm$ 1.0	6.8 $\pm$ 1.7	$P < 0.05$
AUC $0, \infty$ (ng $\cdot$ hr $^{-1}$ $\cdot$ ml $^{-1}$)	1312 $\pm$ 311	1953 $\pm$ 679	$P < 0.05$
Cmax (ng $\cdot$ ml $^{-1}$)	107 $\pm$ 20.5	145.8 $\pm$ 42.2	$P < 0.05$
Tmax (hr)	2.8 $\pm$ 1.7	4 $\pm$ 0.8	NS
Cl/F (ml $\cdot$ min $^{-1}$)	998 $\pm$ 273	633 $\pm$ 256	$P < 0.05$

NS: non significant.

tion-time curve, extrapolated to infinity and calculated by the linear trapezoidal rule for observed data. The area beyond the last data point was estimated as the ratio of the last plasma concentration to β .

- Cmax (ng $\cdot$ ml $^{-1}$): observed peak plasma concentration, determined by visual inspection of the plasma concentration versus time profile.
- Tmax (hr): time to Cmax.
- Cl/F (ml $\cdot$ min $^{-1}$): apparent total plasma clearance, calculated as: Cl/F = Dose/AUC where F is the fraction of the drug injected which reaches the systemic circulation.

Statistical analysis

Results are expressed as mean values $\pm$ SD. Clinical features were tested by a two-tail Student t test. Differences in both motor blockade and pain scores between patients in Groups 1 and 2 were tested using the Chi-square test. Statistical analysis of the pharmacokinetic variables was performed using Mann and Whitney's non-parametric test, because of a non-homogenous variance analysis between groups. $P < 0.05$ was considered to be statistically significant.

Results

Clinical study

The demographic data are reported in Table I. In all the patients, the clinical course was uneventful. However, one patient in Group 1 demonstrated a 30 mmHg peroperative decrease in systolic arterial pressure without bradycardia, which was treated by *iv* infusion of colloid. The maximum level of analgesia was $T_{10} \pm 1.2$ (range T_7 – T_{12}) in Group 1 and $T_{11} \pm 1.4$ (range T_8 – T_{12}) in Group 2 (NS). However, in Group 2 the times of onset of both sensory and motor blockade were reduced compared with Group 1 ($P < 0.01$). The durations of both sensory and motor blockades were prolonged in Group 2 ($P < 0.01$) (Table II). Whereas all patients in Group 2 experienced grade 3 motor blockade, only 23 of 30 patients (76%) of Group 1 experienced a similar complete motor blockade ($P < 0.05$). Seven patients in Group 1 (3 grade 1 and 4 grade 2) experienced incomplete motor blockade which did however allow surgery.

Pharmacokinetic study

The mean weights of the kinetic sub-groups were compar-

FIGURE Mean values of meperidine measured plasma concentrations after intrathecal administration of meperidine alone and with prilocaïne.

able: 71.4 ± 8.7 kg in Group 1 and 66.1 ± 5.9 kg in Group 2. Mean plasma concentrations of meperidine ($\pm$ SEM) are plotted against time in the Figure. Table III shows the values of pharmacokinetic variables in each group. The addition of prilocaïne increased AUC ($P < 0.01$), $T_{1/2\beta}$ ($P < 0.05$) and C_{max} ($P < 0.01$) in Group 2 compared to Group 1.

Postoperative analgesia and adverse effects

In Group 1, 24 patients benefited from 24 hr of postoperative analgesia and scored their pain level <3 . The six remaining patients required a single additional dose of a standard analgesic: three at nine hours and three at 12 hr.

In Group 2, 26 patients experienced 24 hr of complete analgesia (VAS score <3). Four patients (two at eight hours and the other two at 12 hr) needed a single dose of a standard analgesic. There was no difference in postoperative analgesia between the two groups.

Respiratory rate always remained >12 min $^{-1}$ and $PaCO_2$ remained <42 mmHg in all the patients during the study. However, we did not monitor sedation or drowsiness in the intra- and postoperative periods. None of the patients experienced nausea, vomiting or pruritus in either group. Since all the patients had a bladder catheter in the postoperative period, urinary retention was not considered.

No headache was noted in relation to lumbar puncture.

Discussion

Our results document that intrathecal administration of meperidine 1 mg $\cdot$ kg $^{-1}$ induces a spinal anaesthetic blockade and confirms previous studies.⁵⁻⁸ Cozian *et al.*¹⁴

studying eight patients (mean age 71.4 yr, range 63–87) scheduled for transurethral resection of the prostate, reported identical features of the spinal blockade, after injection of the same dose of intrathecal meperidine. The mean onset time for analgesia to a level of T_{12} was 6.9 ± 1.9 min (range 5–10). The maximum level of analgesia was T_8 (range T_6 – T_{12}), with a mean duration of analgesia in the thoracic segments of 117.5 ± 53.9 min (range 60–240); the mean onset time for MB was 5.4 ± 3.2 min (range 2–12) with a mean duration of 133.7 ± 53.9 (range 80–210). Sangarlangham *et al.*¹⁵ compared lidocaine (5% lidocaine, 2 ml = 100 mg) and meperidine (5% meperidine, 2 ml = 100 mg) for spinal anaesthesia. The clinical features of spinal blockade were quite similar, but grade 3 MB was documented in 80% of the patients with meperidine in a dose of 1.5 – 1.6 mg $\cdot$ kg $^{-1}$. In a study performed in 111 patients,¹⁶ spinal meperidine 0.5 mg $\cdot$ kg $^{-1}$ produced similar effects but the incidence of side effects was dose-related. For example nausea and vomiting ranged from 6.3 to 55%.^{15,16} In our study, no side effects were noted. The difference between the result in our study and those of Sangarlangham *et al.*¹⁵ and Acalovschi *et al.*¹⁶ might be age-related, in that we studied older patients who less complain about side effects.¹⁴ The addition of a small dose of prilocaïne augmented the anaesthetic blockade particularly MB. However, we observed that the addition of prilocaïne to meperidine shortened the onset of action and increased the duration of both motor and sensory blockades. Previous studies during abdominal surgery demonstrated that the plasma concentrations of meperidine required to produce postoperative analgesia ranged between 400 and 700 ng $\cdot$ ml $^{-1}$.¹⁷⁻¹⁹ The much lower plasma concentrations measured in this study do not account for the low VAS scores observed in the two groups during the postoperative period.

The effect and pharmacokinetic profile of meperidine alone may be interpreted as follows. The high lipid solubility of meperidine accounts for its rapid penetration of the dura mater and its binding to opiate receptors of the spinal cord.²⁰ Absorption by epidural vessels and by the subarachnoid plexus explains the early plasma detection of meperidine. Our pharmacological results differ slightly from those previously reported.^{21,22} For example, the elimination half-life of meperidine appears to be longer.²² Differences in the mean age between the two studies may explain the difference in elimination half-life.²³

In this study, the administration of prilocaïne modified the pharmacokinetic behaviour of meperidine. However, as C_{max} but not T_{max} varies, this suggests that the rate of absorption was altered. The increase (average 40%) of meperidine AUC when given with prilocaïne may be explained by a decrease in the total plasma clearance or by an increase in the amount of drug reaching the systemic

circulation. Meperidine has a high extraction ratio and is completely metabolised in the liver.¹⁸ Therefore, its clearance depends on hepatic blood flow and, consequently, on cardiac output.²⁴ No evidence of a decrease in hepatic blood flow or in cardiac output has been observed with low concentrations of prilocaine or after spinal anaesthesia administered via L₃₋₄ space.^{25,26} A decrease in total clearance of meperidine seems, therefore, unlikely. The rate and extent of absorption of meperidine from cerebrospinal fluid (CSF) was not measured in this study as it was in the study of Burm *et al.*²⁷ concerning lidocaine and bupivacaine. However, factors such as (i) increase of C_{max} and AUC; (ii) vasodilatation of epidural vessels induced by local anaesthetic agents;²⁸ (iii) liposolubility of meperidine; (iv) increase in pH of the solution when prilocaine is added to, are likely to contribute to an increase in the passage of meperidine from CSF to the systemic circulation. The pH of commercially available meperidine solution is 5, the pH of prilocaine 6.35 and the pH of the combined bolus is 6.2 as measured by pHmetry. It is held that alkalization increases the amount of unionised local anaesthetic available for the nerve fibres.²⁹ Thus, it is reasonable to assume that the addition of prilocaine to meperidine for spinal anaesthesia increases the relative amount of unionised meperidine and consequently enhances its passage from the injection site to the blood stream. The volume effect of combining prilocaine with meperidine should also be discussed.³⁰ In fact this change in volume is small and is unlikely to have modified the results.

The intrathecal administration of opioids exposes the patient to immediate or delayed respiratory depression.^{2,31} After intrathecal meperidine administration, the risk of respiratory depression is related mainly to early absorption into the systemic circulation and to back redistribution to the CSF,³² rather than to a rostral movement of the CSF. Since, as shown in this study, the coadministration of prilocaine enhances the systemic absorption of meperidine, one could argue that it increases the risk of respiratory depression. It should be noted, however, that the maximal concentrations of meperidine always remained at only one quarter to one sixth of the levels associated with respiratory depression.³³

In conclusion, intrathecal meperidine 1 mg · kg⁻¹ allowed surgical procedures to be performed, but grade 3 motor blockade occurred unpredictably in 20% of cases. Higher doses may induce a higher incidence of side effects.¹⁵ The addition of prilocaine to meperidine augments both the motor and the sensory blocks and reduces the onset of anaesthesia. It also affects intrathecal meperidine pharmacokinetic behaviour. It should be emphasized that no excessive side effects were induced by this combination.

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