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Effects of Meperidine Spinal Anesthesia on Hemodynamics, Plasma Catecholamines, Angiotensin I, Aldosterone, and Histamine Concentrations in Elderly Men

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Intrathecal opiates produce a segmental, profound, and long-lasting analgesia.¹⁻⁴ Meperidine is the only narcotic that has been shown to be effective intrathecally as an anesthetic for surgery.^{5,6} This is probably because, as a phenylperidine derivative, meperidine has a close structure and acts similarly to local anesthetics.⁷ However, the hemodynamic consequences of its use by the intrathecal route are not described. Furthermore, meperidine elicits histamine release after iv administration and reduces systemic vascular resistance and mean arterial blood pressure.⁸ For these reasons, we investigated the effects of meperidine spinal anesthesia on hemodynamics, plasma catecholamines, renin activity, and aldosterone and histamine concentrations in elderly patients.

MATERIALS AND METHODS

Eight patients scheduled for transurethral resection of the prostate were included in this study. Their mean age was 71.4 yr (range 63-83 yr). Their mean weight was 65.7 kg (range 55-72 kg). All were in ASA Class I or II and did not take any drugs known to influence the cardiovascular and neuroendocrine systems. The protocol was approved by our Human Investigation Committee. Informed consent for the investigation was obtained from the patients after they received a detailed description of the procedure.

Premedication consisted of diazepam 10 mg po 1 h prior to insertion of the catheters under local anesthesia. Monitored variables consisted of heart rate (HR); systolic (SAP) and diastolic (DAP) radial arterial pressures; right atrial (RAP), pulmonary arterial (PAP), and pulmonary

capillary wedge pressures (PCWP); and thermodilution cardiac output (CO) measured in triplicate using 5 ml iced injectate with a 7 F thermister-tipped Swan Ganz[™] catheter. All pressures were referenced to the level of the right atrium and recorded. Derived hemodynamic variables included mean arterial pressure ($MAP = (SAP - DAP)/3 + DAP$), cardiac index ($CI = CO/body\ surface\ area\ [BSA]$), stroke index ($SI = CI/HR$), and systemic vascular resistance index ($SVRI = (MAP - RAP) 80/CI$). Arterial blood samples were obtained for measurements of pH_a , Pa_{CO_2} , Pa_{O_2} , HCO_3^- at the time of hemodynamic determinations. Simultaneously, arterial blood samples were drawn for determination of plasma renin activity (PRA) and aldosterone, catecholamines, and histamine levels. Blood samples were immediately centrifuged at 4° C for 10 min at 3000 rpm and plasma was stored at -80° C until subsequent analyses. PRA was measured according to the method of Haber *et al.*⁹ using an angiotensin I radioimmunoassay kit (SB-Ren-1, CEA SORIN). Aldosterone was measured using an aldosterone radioimmunoassay kit (SB-Aldo-H, CEA SORIN) according to the method of Mayes *et al.*¹⁰ Norepinephrine (NE) and epinephrine (E) plasma concentrations were measured, according to Brown and Jenner,¹¹ with a double-isotope enzymatic assay with a sensitivity of 1.5 pg/ml for both E and NE. The coefficients of variation were 3.1% and 3.3% for NE and E, respectively (intraassay) and 4.2% and 4.5% (interassay).¹² Plasma histamine levels were measured by a double-isotope enzymatic assay according to the method of Shaff and Beaven.¹³ The sensitivity of the method was 100 pg/ml. The coefficients of variation were 9.7% and 10.2% for intraassay and interassay, respectively.

Lumbar puncture was performed with the patient in the sitting position on the operating table. A 25-g spinal needle was introduced through the third or fourth lumbar vertebral interspace. After obtaining clear spinal fluid, the analgesic, meperidine hydrochloride (1 mg/kg) solution in 1 ml of 30% dextrose in water, was injected at a rate of approximately 0.2 ml/s without barbotage. The 2-ml ampul of meperidine for parenteral use containing 50 mg/ml was diluted just before administration. The patient was maintained in the sitting position for 5 min after the injection and then placed in the lithotomy position. The operating table was horizontal during the

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TABLE 1. Hemodynamic and Blood Gas Data (mean \pm SD)

	Control	8 min Post Meperidine Spinal Injection	During Resection	2 h Post Spinal Injection	ANOVA
Heart rate (beats/min)	70 \pm 5	64 \pm 5	62 \pm 14	62 \pm 10	NS
MAP (mmHg)	99 \pm 17	77 \pm 7 \ddagger	74 \pm 7 \ddagger	72 \pm 11 \ddagger	<0.001
RAP (mmHg)	5.6 \pm 1.7	2.2 \pm 1.7 \S	3.0 \pm 1.8 \S	6.0 \pm 1.3	<0.001
mean PAP (mmHg)	13.6 \pm 2.8	9.4 \pm 2.6*	11.2 \pm 2.7	12.2 \pm 2.9	<0.05
PCWP (mmHg)	6.5 \pm 1.9	3.9 \pm 2.8	3.6 \pm 2.3*	6.1 \pm 2.6	<0.05
CI (l \cdot min ⁻¹ \cdot m ⁻²)	3.13 \pm 0.69	2.94 \pm 0.60	2.86 \pm 0.56	2.82 \pm 0.89	NS
SI (ml \cdot beat ⁻¹ \cdot m ⁻²)	45 \pm 11	47 \pm 12	48 \pm 14	47 \pm 18	NS
SVRI (dyn \cdot s \cdot cm ⁻⁵ \cdot m ⁻²)	2605 \pm 733	2170 \pm 394	2139 \pm 459	2220 \pm 680	NS
PaO ₂ (mmHg)	94 \pm 12	85 \pm 12	75 \pm 9 \ddagger	77 \pm 9*	<0.02
PaCO ₂ (mmHg)	38 \pm 5	42 \pm 5*	46 \pm 7*	47 \pm 5*	<0.05
pH	7.40 \pm 0.01	7.36 \pm 0.02 \ddagger	7.35 \pm 0.02 \S	7.35 \pm 0.02 \S	<0.001

See "Materials and Methods" for abbreviations.

NS = Not significant.

* $P < 0.05$ when compared with control values (Student's t test).

$\ddagger P < 0.02$ when compared with control values (Student's t test).

$\ddagger P < 0.01$ when compared with control values (Student's t test).

$\S P < 0.001$ when compared with control values (Student's t test).

whole procedure. The cephalad spread of analgesia was studied by pin prick using a short bevel 25-g needle with the skin at the shoulder as the reference point. The level of sympathetic block was evaluated by lightly spraying the skin with ethyl chloride to find the place where the sensation of cold was no longer obtunded.¹⁴ Motor nerve block was evaluated using Bromage's score (0–3).¹⁵ Testing was initiated 2 min after injection, immediately after placing the patient in the lithotomy position, and continued at 2-min intervals for 20 min. Intraoperatively, lactated Ringer's solution was infused iv. Regression of sensory anesthesia and motor blockade after surgery was tested at 30-min intervals during 4 h. The occurrence of pruritus, nausea, vomiting, and both early and late respiratory depression was noted. Study was performed with patients breathing room air spontaneously.

Complete hemodynamic measurements and blood sample collections were made while the patients were in the lithotomy position: 1) 20 min after placement of the catheters, prior to intrathecal injection; 2) 8 min after the injection of meperidine before surgery; 3) during transurethral resection; and 4) in the recovery room 2 h after meperidine injection.

All values are reported as mean \pm SD. Analysis of variance was used to search for significant hemodynamic and biologic changes during the study. A probability of $P < 0.05$ was regarded as statistically significant. When analysis of variance revealed significant effects, Student's t test was used to make multiple comparisons. Unpaired t test was used to compare mean onset time and mean duration of blocks. Linear correlations were examined using the least-squares method.

RESULTS

The mean onset time for analgesia to a level of T-12 was 6.9 ± 1.9 min (range 5–10 min). The mean time until

the maximum spread of analgesia was 14.7 ± 2.0 min. The maximum level of analgesia was T-8 (range T-6–T-12). The mean duration of analgesia in the thoracic segments was 117.5 ± 53.9 min (range 60–240 min) but prolonged analgesia of perineal area was observed during at least 4 h. The mean onset time for motor block was 5.4 ± 3.2 min (range 2–12 min). Its mean duration was 133.7 ± 41.0 min (range 80–210 min). Its degree was variable, ranging from 1 to 3 according to Bromage's score. The mean onset time for sympathetic block was 5.4 ± 2.0 min. Its mean spread was approximately two segments higher than sensory block. Its mean duration was 80.6 ± 31.2 min ($P < 0.02$ vs. mean duration of motor block). In all patients the operative procedure was completed without the need of supplementary analgesia. Intraoperatively, five patients complained of pruritus localized to the face. One patient complained of nausea that responded to administration of crystalloids iv. About 3 h after meperidine injection, three patients complained of itching that was generalized to the whole body surface although more intense in the face, groin, and flexor surfaces. This side effect was not considered to be particularly distressing by any patient and consequently was not treated. Slight sedation was seen in all patients. No clinical sign of ventilatory depression was observed during the procedure, but significant variations in arterial blood gas tensions and pH (table 1) occurred. These changes remained 120 min after meperidine spinal injection.

The hemodynamic data are summarized in table 1. Control values were within normal limits. The slowing of HR was not significant. MAP decreased significantly throughout the study when compared with control values, whereas CI was unchanged and SVRI decreased, but not significantly. SI was unchanged, whereas RAP, mean PAP, and PCWP decreased significantly. The decrease of PCWP at 8-min after meperidine spinal injection was not significant. PCWP remained significantly lower than con-

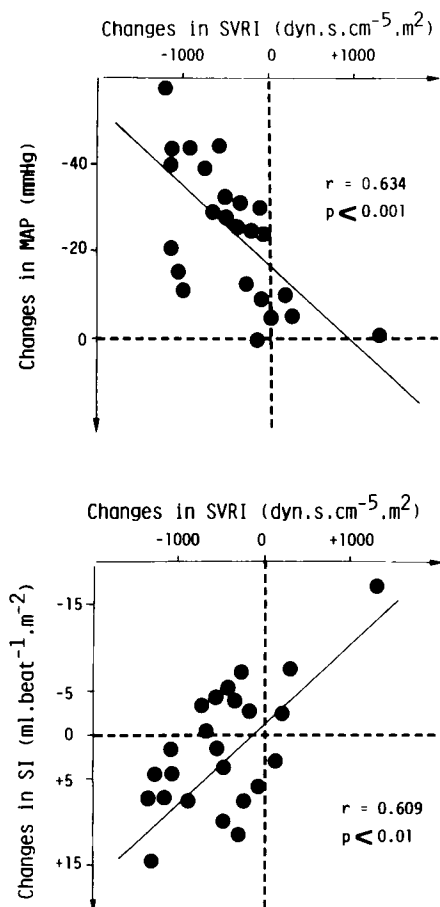


FIG. 1. Scatter plot and regression line of changes in SVRI versus changes in MAP (top) and versus changes in SI (bottom) for eight patients.

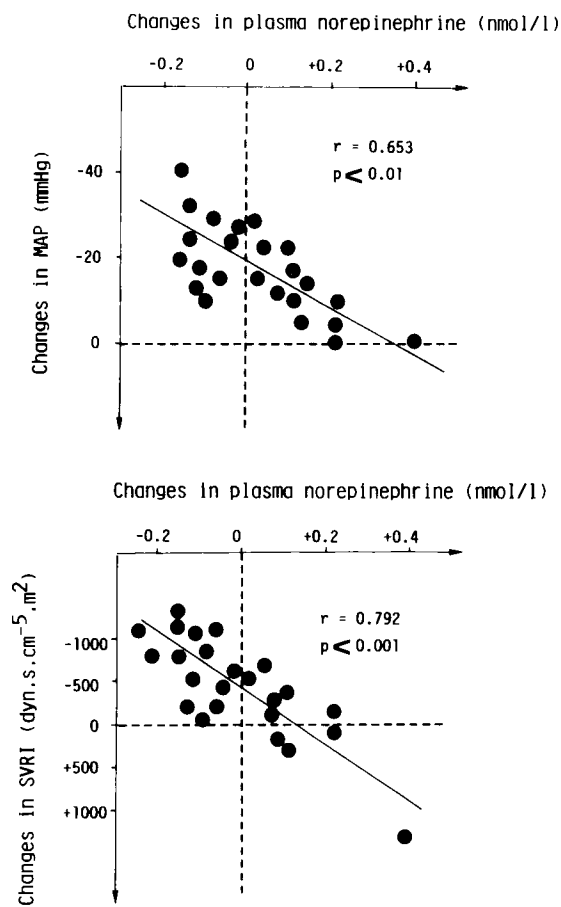


FIG. 2. Scatter plot and regression line of changes in plasma norepinephrine versus changes in MAP (top) and versus changes in SVRI (bottom) for eight patients.

tol values during the surgical procedure despite 250 ml to 1000 ml lactated Ringer's infusion. Correlation study showed that changes in MAP were linked to changes in SVRI ($P < 0.001$, fig. 1) but not linked to changes in CI. Furthermore, individual changes in SI were linked to changes in SVRI ($P < 0.01$, fig. 1).

Plasma E, plasma NE, PRA, plasma aldosterone, and histamine did not change significantly (table 2). However, correlation studies showed that individual changes in plasma NE were linked to changes in MAP ($P < 0.001$,

fig. 2) and to changes in SVRI ($P < 0.001$, fig. 2). No correlation was found between plasma E, PRA, plasma aldosterone, or histamine and changes in MAP or SVRI.

DISCUSSION

Intrathecal meperidine (1 mg/kg) is effective as the sole agent for spinal anesthesia in patients undergoing transurethral resection of the prostate. The mean times

TABLE 2. Plasma Catecholamines, Renin Activity, and Aldosterone and Histamine Concentrations before and after a Spinal Meperidine Injection (1 mg/kg), during Surgical Manipulations, and 2 h after Spinal Injection (mean \pm SD)

	Control	8 min Post Meperidine Spinal Injection	During Resection	2 h Post Spinal Injection	ANOVA
Plasma epinephrine (nmol/l)	0.100 \pm 0.033	0.125 \pm 0.049	0.109 \pm 0.053	0.077 \pm 0.028	NS
Plasma norepinephrine (nmol/l)	0.402 \pm 0.062	0.458 \pm 0.159	0.381 \pm 0.132	0.421 \pm 0.222	NS
Plasma renin activity (ng \cdot ml ⁻¹ \cdot h ⁻¹)	1.36 \pm 0.85	1.53 \pm 1.17	1.66 \pm 1.22	1.28 \pm 1.13	NS
Plasma aldosterone (nmol/l)	0.297 \pm 0.097	0.402 \pm 0.174	0.559 \pm 0.348	0.492 \pm 0.319	NS
Histamine (ng/ml)	0.66 \pm 0.11	0.71 \pm 0.12	0.62 \pm 0.16	0.67 \pm 0.14	NS

NS = not significant.

of onset of sympathetic, sensory, and motor blocks were not statistically different, but in our routine practice, onset time for motor block seems to be faster than for sensory block. The level of sensory block was always below T-6. Prolonged postoperative analgesia in the perineal area was observed following the regression of analgesia in the thoracic segments, so that the total duration of analgesia largely exceeded the duration of motor blockade. No supplementary administration of narcotic analgesics was needed either during the operative procedure or the immediate postoperative period. Mechanisms of motor block may be: 1) a direct action of meperidine on spinal grey matter is probable because the fast speed of block; 2) a mediation by opiate receptors in the ventral horn of the spinal cord and on motor fibers may be evoked (but Faden and Jones¹⁶ demonstrated that motor dysfunction following intrathecal administration of peptides belonging to the dynorphin family was not reversed or blocked by naloxone); and 3) a local anesthetic action on axonal membrane in the anterior spinal nerve roots is not excluded because local anesthetic action of meperidine.

During meperidine spinal anesthesia, incomplete sympathetic denervation resulted in a 25% decrease in MAP linked to a slight peripheral vasodilatation, whereas CI remained constant. Venous return decreased despite the lithotomy position and iv administration of crystalloids, but the combined decrease in preload and afterload of the heart allowed an unchanged SI. The explanation for the absence of increase in the HR in spite of hypotension may involve several factors: 1) The baroreceptor reflex function in man is impaired by age¹⁷ during hypotension. 2) The role played by the removal of the cardiac accelerator tone can be eliminated because the cardiac accelerator fibers arise from the first four thoracic spinal segments, and in all patients in our study, the level of sympathetic denervation was below T-4. 3) Vascular absorption of meperidine after subarachnoid injection has been demonstrated (unpublished data); however, such blood concentrations (100 to 200 ng/ml) do induce tachycardia.¹⁸ The spinal cord may be affected in two ways: systemically by vascular absorption, and supraspinally by an ascent of the drug through cerebrospinal fluid (CSF) circulation. Perhaps the bradycardia produced by meperidine is in part produced *via* actions on the opiate receptors in the medulla oblongata and the vagal system as suggested for other narcotic analgesics.¹⁹ 4) A controversial cause of bradycardia is the diminished venous blood flow to the right side of the heart that modifies the hydrostatic pressure within the right atrium. Venous return to the heart affects HR through intrinsic chronotropic stretch receptors located within the wall of the right atrium and in the great veins. A decrease in right atrium pressure is associated with a reflex decrease in HR, an increase in pressure with a reflex increase in HR.^{20,21} This Bainbridge reflex²²

remains debated²³ since cardiac output can respond to changes in venous return independently of sympathetic and parasympathetic innervation of the heart.²⁴ Changes in body position effect changes in HR during spinal anesthesia even in the absence of changes in the level of sympathetic denervation.

We observed no modification in mean plasma NE levels during meperidine spinal anesthesia. Block of preganglionic fibers to the adrenal medulla have little influence on circulating levels of NE because relatively little NE is normally secreted by the gland. The strong correlation between NE release in both vascular resistance and arterial pressure indicates that the block of NE release was related to the hemodynamic effects rather than a normal release from unblockade upper regions; in addition, this correlation suggests that there were differences in plasma NE levels even if mean levels did not change. Moreover, the absence of significant increase of NE during the surgical procedure is an argument in favor of a stress-free anesthesia. No significant modification in plasma E was observed despite the decrease of MAP during the study. Similar results are reported by Shimosato *et al.*²⁵ following induction of tetracaine continuous spinal anesthesia with sensory level at T4–T7 without surgical stimulation. The level of sympathetic paralysis obtained by meperidine spinal anesthesia (T4–T10) prevented reflex increases in blood epinephrine concentration during hypotension and surgical manipulations. These effects were expected because the adrenal medulla is innervated by preganglionic sympathetic fibers arising from T10–L2. No significant modification of PRA was observed during meperidine spinal anesthesia as described by Oyama *et al.*²⁶ during amethocaine spinal anesthesia. This lack of increased renin release despite the decrease of MAP may be due to the blockade of renal sympathetic afferents considered to be necessary for normal response to postural hypovolemia and hypotension.²⁷ Despite the fact that the renin–angiotensin–aldosterone system plays an important role in the maintenance of intravascular fluid volume and arterial pressure, meperidine spinal anesthesia did not stimulate aldosterone secretion. But, PRA did not increase during anesthesia and during surgery so that the linkage between the renin–angiotensin system and secretion of aldosterone is not apparent. Finally, hypotension did not reflect an acute reduction in intravascular fluid volume due to histamine-induced vascular smooth muscle relaxation.

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