EFFECT OF POSTOPERATIVE EXTRADURAL MORPHINE ON ADH SECRETION

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Surgery is known to disturb body water homeostasis, as a result of the hypersecretion of antidiuretic hormone (ADH) (Le Quesne and Lewis, 1953). High concentrations of plasma and urine ADH both during and after surgery have been documented previously by bio- or radioimmunoassay (Moran et al., 1964; Haas and Glick, 1978). Furthermore, it has been demonstrated that nociceptive stimulation is the main mechanism implicated in ADH hypersecretion (Morgan and Zimmermann, 1967; Ukai, Morgan and Zimmermann, 1968). This ADH hypersecretion can be blocked either by extradural bupivacaine or by large doses of morphine i.v. (Philbin and Coggins, 1978; Bonnet et al., 1982).

The effect noted during surgical procedures is in sharp contrast to the stimulation of ADH secretion observed in laboratory animals following an injection of morphine (De Bodo, 1944; Vandeputte, Van Messon and Peeters, 1980). Although extradural morphine is administered frequently in the period after operation, to provide analgesia, side effects have been described—including oliguria and water retention (Bromage, Camporesi and Chestnut, 1980; Chauvin et al., 1982a).

The following study was performed to assess whether extradural morphine could induce ADH secretion, and to assess if this ADH secretion could be related to morphine itself or to an incomplete blockade of neurosensory afferent pathways.

PATIENTS AND METHODS

Seventeen patients undergoing knee ligamentoplasty (performed under tourniquet) were included after informed consent had been obtained. None had any previous history of renal, cardiac, hepatic or endocrine disease. Premedication consisted of atropine 0.5 mg and diazepam 10 mg i.m. 1 h before surgery. An extradural catheter was introduced through the T2-T3 space on the arrival in the operating room and 0.5% bupivacaine 15—20 ml was injected to obtain analgesia to the T8–T10 level. An i.v. infusion of 500 ml of a colloid solution was commenced just before the induction of the extradural anaesthesia, and was followed by an infusion of an isotonic saline solution (5 ml min⁻¹) during and following the operation. At the end of the surgical procedure the patients were allocated randomly to one of three groups. In the first group (n = 6) analgesia was maintained with 0.5% bupivacaine 10 ml injected via the extradural catheter every 2 h until the 6th hour after operation. In the second group (n = 6) received further injections of bupivacaine; thereafter patients in group I (n = 6) received an extradural injection of morphine and in patients in group II (n = 5) both bupivacaine and morphine, were administered extradurally. In group I, plasma ADH values remained unchanged throughout the study. In contrast, in the two groups of patients receiving extradural morphine a delayed and stepwise increase in plasma ADH concentration was documented. These results indicate that extradural morphine induces ADH secretion and suggest that this effect is the consequence of the migration of morphine to the brainstem.

SUMMARY

The effect of extradural morphine on antidiuretic hormone (ADH) secretion was assessed for the first 6 h after surgery in three groups of patients. Surgery was conducted under extradural bupivacaine; thereafter patients in group I (n = 6) received further injections of bupivacaine, patients in group II (n = 6) received an extradural injection of morphine and in patients in group III (n = 5) both bupivacaine and morphine, were administered extradurally. In group I, plasma ADH values remained unchanged throughout the study. In contrast, in the two groups of patients receiving extradural morphine a delayed and stepwise increase in plasma ADH concentration was documented. These results indicate that extradural morphine induces ADH secretion and suggest that this effect is the consequence of the migration of morphine to the brainstem.
group (group II, n = 6), analgesia was produced by a single extradural injection of morphine hydrochloride 0.1 mg kg⁻¹ diluted in 10 ml of isotonic saline solution and given 3 h after the last bupivacaine injection. In order to distinguish the effect of analgesia on ADH secretion from that of the specific effect of morphine, a third group (group III, n = 5) received both bupivacaine (as in group I) and morphine (as in group II) extradurally.

In all patients, blood samples were collected to allow measurement of plasma ADH, on arrival in the operating room but before extradural anaesthesia had been performed (t₀), at the end of the surgical procedure after either morphine or bupivacaine had been injected (tᵢ), and then hourly for 6 h. In groups II and III, additional blood samples were withdrawn 15 and 30 min after the extradural morphine injection. Blood samples, collected in chilled glass tubes, were centrifuged within 10 min at 3000 rev min⁻¹ and -4 °C for 10 min. The plasma samples were acidified to pH 4.5 with hydrochloric acid 1 mol litre⁻¹ in dry tubes and stored frozen at -20 °C. Plasma ADH concentration was measured in duplicate for each sample using a previously described radioimmunoassay technique (Thibonnier et al., 1981). Plasma concentrations of sodium and potassium, and plasma osmolality were measured by flame photometry and Fiske osmometry, and respiratory rates and analgesia were monitored hourly during the period after operation. Pain was evaluated by the patients themselves using the scale: 0 = no pain; 1 = no pain but some discomfort; 2 = mild pain; 3 = moderate pain; 4 = severe pain; 5 = intractable pain.

Results were expressed as mean ± SEM. Statistical analysis used the Wilcoxon test for intra-group variations and the non-parametric Fisher permutation test for inter-groups comparisons.

RESULTS

Patients. Details of the patients are presented in table I. In all three groups, arterial pressure, heart rate and respiratory rate remained constant. Sodium and potassium concentrations, and plasma osmolality were not significantly different from control values during the 6 h of the study (table II).

Degree of pain. No patient complained of pain before the first extradural injection after surgery of either bupivacaine or morphine. Effective analgesia, lasting throughout the period of study, was obtained in each group, the pain score never being greater than 1 in any patient.

Plasma ADH concentration. Initial plasma ADH concentrations were identical in the three groups.

### Table I. Details of patients and duration of surgical procedure (mean±SEM)

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Duration of procedure (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>M/F</td>
<td>25±1.7</td>
<td>66±4.1</td>
<td>50±6.9</td>
</tr>
<tr>
<td>II</td>
<td>2/4</td>
<td>24±1.3</td>
<td>62±7.1</td>
<td>67±6.6</td>
</tr>
<tr>
<td>III</td>
<td>3/2</td>
<td>21±1.8</td>
<td>65±3.0</td>
<td>72±6.6</td>
</tr>
</tbody>
</table>

### Table II. Arterial pressure, heart rate, plasma electrolyte concentrations and osmolality values in the three groups of patients (mean±SEM). t₀=control before surgery; tᵢ=after operation before injection of analgesic; t₆=6 h after surgery

<table>
<thead>
<tr>
<th>Group</th>
<th>Arterial pressure (mm Hg)</th>
<th>Heart rate (beat min⁻¹)</th>
<th>Sodium (mmol litre⁻¹)</th>
<th>Potassium (mmol litre⁻¹)</th>
<th>Osmolality (mosmol litre⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>116±7.3</td>
<td>86±4.5</td>
<td>139±0.8</td>
<td>4.2±0.12</td>
<td>287±4.0</td>
</tr>
<tr>
<td>II</td>
<td>122±5.7</td>
<td>83±4.9</td>
<td>139±1.2</td>
<td>4.1±0.10</td>
<td>284±1.6</td>
</tr>
<tr>
<td>III</td>
<td>110±4.1</td>
<td>83±2.8</td>
<td>138±0.8</td>
<td>4.2±0.10</td>
<td>283±1.2</td>
</tr>
</tbody>
</table>

Results were expressed as mean ± SEM. Statistical analysis used the Wilcoxon test for intra-group variations and the non-parametric Fisher permutation test for inter-groups comparisons.
and were within the normal range for our laboratory (Thibonnier et al., 1981). No significant changes had occurred at the end of the surgical procedure. In group I patients (who received bupivacaine only) there were no changes in plasma ADH concentration throughout the study. In contrast, stepwise increases in plasma ADH concentration occurred in groups II and III (extradural morphine, alone or with bupivacaine) (fig. 1, table III). In these two groups, plasma-ADH concentration began to increase 3 h after the extradural morphine injection and the values measured at 4, 5 and 6 h were significantly greater than those at f and f1. Furthermore, the ADH concentrations observed in group III (who received morphine and bupivacaine) were significantly higher than those of group I at 4 and 5 h.

**Side-effects.** All patients in group I complained of leg weakness; facial itching was observed in four patients in group II and in two in group III; one patient in group II and three in group III complained of nausea; transient urinary retention was noted in four patients in group I, four patients in group II and three in group III.

**DISCUSSION**

Our study confirms that extradural morphine and bupivacaine produce effective analgesia after an especially painful orthopaedic surgical procedure. In addition, our results document an increase in plasma ADH concentrations under extradural morphine despite efficient analgesia. In contrast, the plasma ADH concentrations remained stable when analgesia was provided by extradural bupivacaine. The low plasma ADH values observed at the end of the surgical procedure confirm that extradural bupivacaine achieves a blockade of ADH secretion during surgery, as previously described (Bonnet et
al., 1982). Furthermore, the blocking effect of the extradural bupivacaine was prolonged throughout the study by repeated injections following surgery (group I patients). This effect has been demonstrated previously and attributed to blockade of afferent nervous pathways (Ukai, Moran and Zimmermann, 1968; Bonnet et al., 1982).

Extradural morphine has been reported to induce potent, selective, long lasting analgesia (Bromage, Camporesi and Chestnut, 1980). In our study, inadequate relief of pain sedation was not the cause of the increase in plasma ADH. Other nervous pathways, such as sympathetic afferents, blocked by extradural bupivacaine, but not by morphine, could be implicated in the ADH secretion. In fact, a significant increase in plasma ADH concentrations occurred in group III patients who received both analgesic drugs. Thus, the stimulation of ADH secretion can be attributed to the extradural administration of morphine itself.

Philbin and Coggins (1978) showed that a surgically induced increase in plasma ADH concentration was partially suppressed by the administration of increasing doses of morphine. This may not necessarily conflict with our own data. In their study, very high ADH concentrations were described, but the surgical procedures involved were more major. The analgesic effect of morphine is to reduce this plasma concentration, but to a range still higher than the one we measured in our patients. In such conditions, the stimulatory effect of morphine may be masked. In contrast, stimulation of ADH secretion is produced by extradural morphine. This ADH secretion could be induced either by systemic absorption of morphine or by diffusion through the cerebrospinal fluid to the brainstem. Plasma morphine concentrations are known to increase within 15 min of extradural administration of morphine (Chauvin et al., 1982a). At that time our measurements indicate that ADH concentrations do not increase. The appearance of morphine in the cerebrospinal fluid at brainstem level is said to be delayed and thereafter to increase steadily (Drayer and Rosembaum, 1978; Bromage et al., 1982); the delayed and progressive increase in plasma ADH observed in our patients strongly suggests that ADH secretion is the consequence of migration of morphine within the CSF from the lumbar area to the brainstem.

The secretion of ADH induced by extradural morphine could be mediated by the opiate receptors located in the hypothalamus or the neurohypophysis (Simantov and Snyder, 1977). Experimental data reported in laboratory animals also suggest that β-endorphin could increase ADH secretion (Weitzman et al., 1977). However, contradictory data are reported, with the results depending on the route of administration, the nature of the opiate analogue used and the laboratory animal species studied (Van Wimersa Greidanus et al., 1978; Grossman et al., 1980; Lightman, Langdon and Forsling, 1980; Reid et al., 1981). Discrepancies in the ADH response to the administration of morphine observed during anaesthesia could be explained by different routes of administration and the effects of other causes of stimulation. Finally, this study was conducted over a relatively short period of time and no significant changes in plasma sodium concentration or osmolality were noted.

However, hypersecretion of ADH could be one of the possible mechanisms behind the retention of water observed during extradural morphine analgesia.

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REFERENCES


