EFFECT OF INTRATHECAL MORPHINE ON THE ADRENOCORTICAL AND HYPERGLYCAEMIC RESPONSES TO UPPER ABDOMINAL SURGERY

R. DOWNING, I. DAVIS, J. BLACK AND C. W. O. WINDSOR

It has been suggested that postoperative morbidity may be decreased if the normal endocrine and metabolic responses to surgery are suppressed by an appropriate anaesthetic technique (Kehlet, Brandt and Rem, 1980). The adrenocortical and hyperglycaemic responses to lower abdominal surgery can be prevented by large i.v. doses of opiates (Hall et al., 1978), and by neural blockade with extradural analgesics (Kehlet, 1982; Moller et al., 1982). However, this latter procedure has either no effect on, or only attenuates, the adrenocortical response to upper abdominal surgery, despite complete suppression of the hyperglycaemic response.

Intrathecal morphine produces analgesia for up to 36 h and, notwithstanding the recognized complication of respiratory depression, has been used widely to relieve postoperative pain. Since the influence of intrathecal morphine on the endocrine response to surgery has not been investigated, we have studied its effect upon adrenocortical and hyperglycaemic responses in patients undergoing cholecystectomy.

PATIENTS AND METHODS

Healthy female patients, none of whom suffered from an endocrine disorder, were admitted for elective cholecystectomy and gave their informed consent to participate in the study which was approved by the Hospital Ethics Committee. Each patient received diazepam 10 mg by mouth as premedication and was randomly allocated to one of two groups: group A (10 patients) received preservative-free morphine 0.8 mg injected intrathecally via the L2-3 space using a 25-gauge spinal needle, 15 min before the induction of anaesthesia; analgesics were not given during the operation. Group B (10 patients) received papaveretum i.v. intermittently during the operative procedure. All patients were anaesthetized using Althesin, and nitrous oxide in oxygen. Alcuronium was administered to provide neuromuscular blockade. All operations were started at 2.00 p.m. and comprised a subcostal, muscle-cutting incision, cholecystectomy, cholangiography and insertion of a subhepatic drainage tube. Patients who underwent exploration of the common bile duct were excluded from the study.

Both groups of patients were nursed for 24 h in a high dependency unit after the completion of surgery; respiratory and heart rates, arterial pressure and the presence or absence of pain were recorded hourly. Nurses in attendance were allowed to administer a single injection of papaveretum 5 mg i.m. to patients in group A, but were instructed to call the anaesthetist if additional injections were necessary; patients in group B were prescribed paraveretum 10, 15 or

SUMMARY

Changes in plasma cortisol concentration and serum glucose concentration were measured in a group of 10 patients given intrathecal morphine 0.8 mg before cholecystectomy and the results compared with those from a control group of 10 patients receiving papaveretum i.v. during the operative procedure. Intrathecal morphine had no effect upon the hyperglycaemic response to surgery, but attenuated the increase in serum cortisol concentration.
Table I. Details (mean ± SD) of the two groups of patients

<table>
<thead>
<tr>
<th></th>
<th>Group A (Intrathecal morphine)</th>
<th>Group B (Controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47.5 ± 5.4</td>
<td>42.7 ± 15.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.5 ± 10.5</td>
<td>64.5 ± 13.8</td>
</tr>
<tr>
<td>Duration of operation (min)</td>
<td>70.0 ± 12.5</td>
<td>64.0 ± 13.7</td>
</tr>
<tr>
<td>Estimated blood loss (ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 250</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>250–300</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Perioperative fluid replacement</td>
<td>735.0 ± 62.6</td>
<td>744.0 ± 72.9</td>
</tr>
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20 mg 3 or 4 hourly i.m. All patients were nursed in a general surgical ward after 24 h and were given injections of papaveretum 10, 15 or 20 mg 3 or 4 hourly i.m. as required to control pain. Postoperative fluid replacement comprised water 50 ml h⁻¹ by mouth during the first 24 h, increasing to 100 ml h⁻¹ between 24 and 48 h, supplemented with lactated Ringer’s solution 2 litre/24 h i.v. for 48 h.

Serum glucose and plasma cortisol concentrations were estimated from venous blood samples obtained before operation, at 30 and 60 min during the operation and 4, 24 and 48 h after the completion of surgery. Glucose concentration was measured by a standard glucose oxidase method and cortisol concentration by a modified fluorimetric method (Mattingly, 1962).

Results were analysed using the Wilcoxon rank sum test for unpaired data. Statistical significance was assumed when \( P < 0.05 \).

Results

Details of the two groups of patients are shown in table I; there were no significant differences in the variables studied. The mean (±SD) dose of papaveretum given in the perioperative period to patients in group B was 16.8 ± 2.3 mg per patient.

Control of pain

All patients in group B complained of pain during the first 24 h after surgery, compared with six patients in group A. The total dose of papaveretum given to patients in group B during this period was 500 mg compared with only 80 mg to four patients in group A. During the subsequent 24 h, 270 mg and 190 mg were given to patients in groups A and B, respectively. The implications of this pattern of opiate requirements by patients receiving intrathecal morphine have been discussed elsewhere (Downing et al., 1985). No patient who received intrathecal morphine developed respiratory depression.

Serum glucose concentration (fig. 1)

Mean ± SD serum glucose concentration increased to a maximum value of 5.6 ± 0.8 mmol litre⁻¹
60 min after skin incision in patients given intrathecal morphine. A maximum value of 5.5 ± 1.0 mmol litre\(^{-1}\) was recorded 4 h after completion of the operation in control patients. There were no significant differences in the serum glucose concentrations recorded in the two groups throughout the study period.

**Plasma cortisol concentration** (fig. 2)

Plasma cortisol concentrations increased throughout the operation in both groups. However, the patients given intrathecal morphine showed an attenuated postoperative response when compared with the control patients: mean ± SD values recorded at 4 h following surgery were 895 ± 259 nmol litre\(^{-1}\) in group A compared with 1333 ± 171 nmol litre\(^{-1}\) in group B (P < 0.01).

**DISCUSSION**

The possibility that the metabolic and endocrine responses to major surgery are responsible for such life-threatening complications as thromboembolism and stress ulceration is an attractive, albeit unproven hypothesis (Kehlet, Brandt and Rem, 1980). Although these responses probably represent homeostatic mechanisms by which the patient adapts to the stress of surgery, considerable interest has centred on the investigation of those anaesthetic techniques which attenuate or abolish them. Serum glucose and cortisol concentrations have been used most commonly as indices of surgical stress and several researchers have demonstrated suppression of the increases in these concentrations during lower abdominal surgery in association with large doses of i.v. opiates (Hall et al., 1978) and extradural analgesia (Kehlet, 1982; Moller et al., 1982). However, changes in these variables during upper abdominal surgery have received comparatively little attention. It is apparent from the few published studies that extradural blockade producing sensory analgesia to at least T4 can completely suppress the hyperglycaemic response (Traynor et al., 1982; Asoh et al., 1983), but the effect of upper abdominal surgery upon the increase in cortisol concentration is uncertain. Bromage, Shibata and Willoughby (1971) failed to show an effect on serum cortisol concentrations of extensive extradural analgesia, whereas Rutberg and colleagues (1984) demonstrated a significant decrease in the plasma concentrations of cortisol after cholecystectomy in patients given extradural bupivacaine and general anaesthesia when compared with those receiving general anaesthesia alone.

Asoh and co-workers (1983) suggested that suppression of hyperglycaemia after upper abdominal surgery reflects the maintenance of insulin sensitivity, while the discrepancy between the results obtained using extradural analgesia in upper and lower abdominal surgery has been explained on the basis of vagal stimulation (Bromage, Shibata and Willoughby, 1971). However, this has not been substantiated in studies in which the vagus nerves have been infiltrated with local anaesthetic or divided during cholecystectomy (Traynor et al., 1982) or gastrectomy (Tsuji et al., 1983), respectively.

We have shown that intrathecal morphine 0.8 mg had no effect on the increase in serum glucose concentration, but attenuated the increase in plasma cortisol concentration in patients undergoing cholecystectomy. This dose of morphine was chosen for the investigation as it seemed likely to be both effective and, as we have demonstrated, free of the risk of respiratory depression. Nevertheless, this dose of morphine was not ideal—six patients experienced pain within 24 h of operation, four of whom were given papaveretum. Therefore, inadequate inhibition of somatic afferent pathways is the most likely explanation for our findings, although the role played by afferent autonomic pathways is uncertain. Larger doses of intrathecal morphine will undoubtedly produce a greater degree of analgesia (Samii, Chauvin and Viars, 1981) and, as a consequence, may completely inhibit the metabolic responses to upper abdominal surgery, but we believe that the attendant risks of such larger doses argue strongly against their use to gain what is at present only theoretical benefit from suppression of the stress response to surgery.

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**REFERENCES**


