HORMONAL AND METABOLIC RESPONSES TO CHOLECYSTECTOMY: COMPARISON OF EXTRADURAL SOMATOSTATIN AND DIAMORPHINE

J. P. DESBOROUGH, S. A. EDLIN, J. M. BURRIN, S. R. BLOOM, M. MORGAN AND G. M. HALL

Opioids have been shown to produce effective analgesia when given extradurally [1]. Extradural opioids reduce the cortisol response after operation, probably as a result of the excellent analgesia which is produced [2, 3]; otherwise they appear to have little effect on the metabolic and hormonal response to upper abdominal surgery.

The tetradecapeptide somatostatin has been shown to be an effective analgesic when given by the extradural route for treatment of acute and chronic pain [4, 5]. Somatostatin exists in the central nervous system [6] and is found in high concentrations in the dorsal horn of the grey matter in the spinal cord [7]. The analgesic action may be mediated through opioid receptors [8]. It is known also to inhibit the secretion of growth hormone, glucagon and insulin [9].

The aims of the present study were threefold: to determine the extent of the absorption of somatostatin from the extradural space into the circulation; to investigate the effects of any absorption of somatostatin on the hormonal and metabolic response to upper abdominal surgery; and to compare the effects of somatostatin with a standard extradural analgesic, diamorphine.

PATIENTS AND METHODS

Twenty-four patients presenting for elective cholecystectomy were admitted to the study,

which had been approved by the Hospital Ethics Committee. They were otherwise healthy and not receiving any therapy known to interfere with the metabolic or hormonal responses to surgery. The nature of the study was explained to the patients and informed consent obtained. Patients were allocated randomly to one of three groups. A control group received a general anaesthetic without an extradural. A second group received the same general anaesthetic together with extradural diamorphine 0.1 mg kg⁻¹, and a third group also received the same general anaesthetic and extradural somatostatin 1 mg as a bolus

SUMMARY

We have studied the metabolic and hormonal responses to surgery, and the pain scores and analgesic requirements in 24 patients undergoing cholecystectomy, allocated randomly to three groups to receive either general anaesthesia alone, or general anaesthesia with extradural diamorphine 0.1 mg kg⁻¹, or general anaesthesia with extradural somatostatin to a total dose of somatostatin 3 mg. The only significant effect of extradural diamorphine was a decrease in the glucose response to surgery. Somatostatin 3 mg by the extradural route caused a significant increase in the concentration of circulating somatostatin which resulted in a significant decrease in plasma growth hormone and insulin after 60 min of surgery, together with an increase in plasma glycerol concentration. Patients in the diamorphine group required significantly less i.v. analgesia in the postoperative period than the other two groups. Intraoperative somatostatin failed to provide any postoperative analgesia.
injection followed by an infusion of 1 mg h⁻¹ for 2 h.

All patients were premedicated with papaveretum 10–20 mg and hyoscine 0.2–0.4 mg 1 h before operation. When the patient arrived in the anaesthetic room a central venous catheter was inserted percutaneously from a vein in an antecubital fossa to allow blood sampling and administration of i.v. fluids and drugs. After the patient had rested for 10 min a control venous blood sample was obtained.

Patients in the extradural groups were placed in the lateral position and a catheter inserted into the extradural space at the T6-7 or T7-8 space. The patients received either diamorphine 0.1 mg kg⁻¹ dissolved in water to a concentration of 1 mg ml⁻¹ or somatostatin 1 mg dissolved in 0.9 % sodium chloride 5 ml followed by an infusion of somatostatin 1 mg h⁻¹ for 2 h or until the end of the operation, whichever occurred first.

Anaesthesia was induced in all patients with a sleep dose of thiopentone and the trachea was intubated following administration of pancuronium 0.1 mg kg⁻¹. The lungs were ventilated with 70 % nitrous oxide and 0.5 % halothane in oxygen. Ventilation was adjusted to maintain end-tidal $P_{CO_2}$ at 4.0–4.5 kPa throughout the anaesthetic. During surgery, 0.9 % sodium chloride was given i.v. at a rate of 6 ml kg⁻¹ h⁻¹. This was reduced to 2 ml kg⁻¹ after operation.

Venous blood samples were collected at the start of surgery and at 30, 60, 90, 120, 240 and 360 min after surgery had commenced. Heart rate and mean arterial pressure were recorded at the same time.

After operation the patients were observed closely in the recovery area and analgesia was provided by the i.v. administration of morphine 5 mg on demand. The amount of morphine given in the period up to the 360-min sampling time was recorded. Analgesia was measured using a 10-cm linear analogue scale [10]. The patients were instructed in the use of this during the preoperative visit. In patients with extradurals the extent of sensory loss to pinprick and temperature was assessed at 120, 240 and 360 min after the start of surgery.

All patients with extradurals received 0.5 % plain bupivacaine 3 ml through the catheter at the end of the study (360 min after the start of surgery), to confirm the correct sitting of the catheter in the extradural space.

Blood samples were analysed in duplicate for glucose, lactate and glycerol, and haematocrit by methods described previously [11]. Growth hormone (GH) [12], insulin [13], cortisol [14], glucagon [15] and somatostatin [16] concentrations were measured by radioimmunoassay. The intra-assay and interassay coefficients of variation were 6.4 % and 5.8 % for cortisol, 5 % and 7.3 % for GH, 8.5 % and 10.2 % for insulin and 7.9 % and 9.0 % for glucagon, respectively.

Somatostatin measurements were undertaken in a single assay, the intra-assay coefficient of variation was 9.6 %.

Results are presented as mean values (SEM) or median (range) for pain scores. Within-group comparison of metabolites, hormones and physiological data was undertaken by two-way analysis of variance and Dunnett's test and between group differences by one-way analysis of variance. Data not distributed normally were analysed by Mann–Whitney $U$ test and Wilcoxon rank test (insulin, somatostatin and GH). Pain scores and mean doses of morphine given after operation were evaluated using the Kruskal–Wallis test.

**RESULTS**

One of the patients allocated to the diamorphine group had a vagotomy and pyloroplasty in addition to cholecystectomy, and required transfusion for blood loss of 1000 ml. The results from this patient were excluded.

The mean age, weight and percentage of body fat [11] were comparable in the three groups of patients. The duration of surgery in the diamorphine group was significantly longer.

**Table I. Details of patients studied, mean values (SEM)**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Diamorphine</th>
<th>Somatostatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>45.1 (5.3)</td>
<td>46.2 (4.5)</td>
<td>43.5 (3.9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.4 (2.6)</td>
<td>65.8 (3.5)</td>
<td>65.8 (4.6)</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>27.5 (1.5)</td>
<td>26.8 (1.5)</td>
<td>26.5 (1.5)</td>
</tr>
<tr>
<td>Sex (F:M)</td>
<td>6:2</td>
<td>5:2</td>
<td>7:1</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>66.7 (6.0)</td>
<td>97.8 (8.8)</td>
<td>71.6 (6.6)</td>
</tr>
</tbody>
</table>
TABLE II. Pain scores (median (range)) at 240 and 360 min after start of surgery, and mean (SEM) dose of morphine received up to 360 min. *Diamorphine v. control and somatostatin

<table>
<thead>
<tr>
<th></th>
<th>Pain score</th>
<th>Dose of morphine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>240 min</td>
<td>360 min</td>
</tr>
<tr>
<td>Control</td>
<td>3.5 (2-6)</td>
<td>6.0 (3-10)</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>3.0 (0-6)</td>
<td>3.0 (0-5)</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>5.0 (2-7)</td>
<td>5.5 (4-8)</td>
</tr>
<tr>
<td>P*</td>
<td>ns</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

(P < 0.05) than in the other two groups (table I).

Six of the patients in the somatostatin group received 3.0 mg of somatostatin; the other two patients received 2.5 mg. No side effects were observed in any patient who received extradural somatostatin. Two patients in the diamorphine group required i.v. naloxone 20 μg and 80 μg, respectively, because of inadequate ventilatory effort after antagonism of neuromuscular block at the end of surgery. These two patients did not require supplementary analgesia in the recovery period.

Details of the pain scores and analgesic requirements are shown in table II. Pain scores at 120 min could not be assessed statistically as insufficient patients were able to complete the linear analogue scale. There was no difference between the pain scores at 240 min, but at this time seven of eight patients in the control and somatostatin groups had received at least one 5-mg dose of i.v. morphine compared with only two of seven patients in the diamorphine group. At 360 min the pain scores were significantly less (P < 0.05) in the diamorphine group than in the other two groups. Similarly, morphine requirements were significantly less (P < 0.02) in the diamorphine group (2.1 mg) compared with the control (8.8 mg) and somatostatin groups (9.4 mg). No sensory loss to pinprick or temperature was elicited during the postoperative period in any patient who received somatostatin. However, areas of cutaneous hypoalgesia corresponding to dermatomes T5–T10 were demonstrated in the patients who received extradural diamorphine at 120, 240 and 360 min after the start of surgery.

Plasma somatostatin (fig. 1)

There was no change in plasma concentration of somatostatin in either the control or the diamorphine group. However, in the somatostatin group there was a 15-fold increase in circulating somatostatin to 394 pmol litre⁻¹ after 60 min of surgery (P < 0.05) and this persisted for the duration of the extradural infusion. The increase in somatostatin concentration was significantly different from the pre-induction value at 0, 30, 60, 90 and 120 min after the start of surgery (P < 0.05). There was a significant difference from the control group of patients at 0 and 30 min (P < 0.05), 60 min (P < 0.01) and at 90 min (P < 0.05).

Plasma growth hormone (fig. 2)

In the control group, plasma concentration of GH increased from 0.8 μU. litre⁻¹ to 10.2 μU. litre⁻¹ after 30 min of surgery (P < 0.05) and this significant increase was maintained until 240 min after surgery started. There was a similar significant increase in plasma GH in the diamorphine group at 30, 60, 90, 120 and 240 min (P < 0.05).
In the somatostatin group, however, there was a significant decrease in GH concentration from 5.6 μg litre⁻¹ to 1.0 μg litre⁻¹ after 60 min of surgery (P < 0.05). Plasma GH then increased to 16.5 μg litre⁻¹ after 240 min, but this was not significantly different from the preinduction value. There was a significant difference in GH concentrations between the control and the somatostatin groups at 60 min (P < 0.01) and at 240 min (P < 0.05).

Plasma insulin (fig. 3)

Plasma insulin concentration did not alter significantly in either the control or the diamorphine groups of patients. In the somatostatin group, insulin concentration decreased from 11.3 μg litre⁻¹ to 5.9 μg litre⁻¹ after 60 min of surgery (P < 0.05), but then returned to the preinduction value by 120 min. There was a significant difference in the insulin concentration between the control and the somatostatin groups of patients at 60 min (P < 0.05) and was not significant. There was no difference in plasma concentrations of glucagon between the three groups.

Plasma glucagon (fig. 4)

In the control group there was no significant change in plasma glucagon concentration. The diamorphine group showed an increase in glucagon from 4.5 pmol litre⁻¹ to 6.7 pmol litre⁻¹ 240 min after surgery started (P < 0.05). In contrast, there was a decrease in glucagon from 5.2 pmol litre⁻¹ to 3.2 pmol litre⁻¹ in the somatostatin group after 60 min of surgery, but this was not significant. There was no difference in plasma concentrations of glucagon between the three groups.

Plasma cortisol (fig. 5)

Plasma cortisol concentration increased in the control group of patients from 303 nmol litre⁻¹ before surgery to 750 nmol litre⁻¹ after 60 min (P < 0.01), and continued to increase after operation to 1163 nmol litre⁻¹ after 240 min (P < 0.001). The increase in cortisol concentration was slower in the diamorphine group of patients and was
Blood glucose (table III)

In the control group of patients, blood concentrations of glucose increased from 3.82 mmol litre⁻¹ to 7.09 mmol litre⁻¹ after 120 min (P < 0.01). Circulating glucose increased from 4.25 mmol litre⁻¹ to 4.97 mmol litre⁻¹ after 120 min in the diamorphine group and this change was not statistically significant. In the somatostatin group glucose increased from 4.56 mmol litre⁻¹ to 7.22 mmol litre⁻¹ after 120 min of surgery (P < 0.01). Blood concentrations of glucose differed significantly between the control and the diamorphine groups at 60, 90, 120 and 240 min (P < 0.05).

Blood lactate (table III)

Blood concentrations of lactate did not alter significantly from preinduction values in either the control or the somatostatin groups of patients. In the diamorphine group lactate concentration decreased from 1.11 mmol litre⁻¹ to 0.62 mmol litre⁻¹ after 360 min (P < 0.01). There was no difference in blood lactate concentrations between the three groups of patients.
RESPONSES TO CHOLECYSTECTOMY

Plasma glycerol (table III)

There was no significant change in plasma glycerol in either the control or the diamorphine group of patients. In the somatostatin group, however, glycerol increased significantly from 131 μmol litre⁻¹ to 281 μmol litre⁻¹ after 60 min of surgery (P < 0.05) and then returned to pre-induction values at 360 min. There was no significant difference in plasma concentrations of glycerol between the three groups.

Haematocrit (table III)

The haematocrit declined in all three groups, but there was no significant difference between the groups.

Arterial pressure and heart rate

There was no significant change from preinduction values in mean arterial pressure and heart rate in any of the three groups of patients. At 240 min, mean arterial pressure in the diamorphine group was significantly greater than in the control group (P < 0.05) and in the somatostatin group (P < 0.01), and at 360 min it was greater in the control group than the somatostatin group (P < 0.05). Heart rate was significantly higher in the control group compared with the diamorphine group at 0 min (P < 0.05), 60 min (P < 0.01) and at 90 min (P < 0.05), and was also significantly higher than in the somatostatin group at 60 min (P < 0.01).

DISCUSSION

In this study, somatostatin given extradurally as a bolus injection of 1 mg, followed by an infusion of 1 mg h⁻¹ for 2 h, failed to provide adequate analgesia after cholecystectomy. We cannot exclude the possibility, however, that extradural somatostatin may have resulted in transient block of nociceptive stimuli during operation and immediately after operation. Our results are in contrast with previous studies in which analgesia was achieved after operation using a bolus dose followed by an infusion of somatostatin [4,5,17].

Chrubasik and colleagues [5] studied eight patients, after a variety of surgical procedures; postoperative analgesia was produced with a bolus dose of somatostatin 250 μg followed by an infusion of 125 μg h⁻¹. Thirty minutes after the injection, mean upper and lower levels of analgesia to pinprick were T6 and T12, T7 and L1 and T7 and T12, respectively. In our study we did not demonstrate any cutaneous analgesia in the patients who received somatostatin.

Somatostatin has been shown to produce analgesia in animal models. This was demonstrated before clinical trials by an increase in pain threshold to a standard test in rats by the intrathecal administration of somatostatin 10 μg [4]. In more recent animal studies [19,20], however, the analgesic action of somatostatin has been associated with toxicity. In the study by Gaumann and Yaksh [19], intrathecal somatostatin 10 μg and 30 μg had no analgesic effect on thermal stimulation in rats, and 30 μg had no effect on chemical stimulation. The intrathecal injection of somatostatin 100 μg produced some analgesia, although it was invariably associated with a temporary or permanent effect on hind limb motor function, including flaccid paralysis. Similar effects were found by Mollenholt and colleagues [20] who showed analgesic effects after the intrathecal injection of 10 μg, but not somatostatin 1.5 μg in rats. No motor effects were seen in these animals, but rats given somatostatin 20 μg and 30 μg intrathecally developed hind limb paralysis. The 1.5-μg intrathecal dose which had no analgesic effect in the rat was felt to be similar on a dose to body weight ratio as the 250-μg bolus which was shown to be analgesic in clinical trials in man [5].

The opioid receptor activity of somatostatin has been studied extensively in animal preparations. Terenius [8] demonstrated its affinity for opioid receptors and suggested that partial agonist-antagonist activity was present. More recent animal studies [21, 22] have shown somatostatin
to be a selective antagonist at mu opioid receptors. Thus the pharmacological basis for the use of somatostatin as an extradural analgesic in man is tenuous and possible toxic effects suggest that its further use in clinical practice is unjustifiable.

In the present study, as in others [5,18], the infusion of somatostatin into the extradural space had no deleterious effects on the cardiovascular system. Somatostatin is known to reduce splanchnic blood flow [23], but is effects on systemic haemodynamics and portal pressure remain controversial. In one report [24] of 10 patients with liver cirrhosis and portal hypertension receiving somatostatin 250 µg i.v. as a bolus followed by 125 µg infused over 30 min, mean arterial and pulmonary artery mean pressure increased together with a transient reduction in portal pressure. These findings were postulated to be the result of transient vasoconstriction.

Extradural somatostatin is thought to have no deleterious effects on the control of ventilation [18]. Obvious clinical respiratory depression was not demonstrated in any patient receiving extradural somatostatin in our study. This is in contrast with the use of extradural opioids.

Extradural diamorphine 0.1 mg kg⁻¹ reduced the hyperglycaemic response to surgery and also delayed the cortisol response both during and after operation. This finding is in agreement with the effects of extradural opioids demonstrated previously [2,3,25,26]. The injection of somatostatin 1 mg into the extradural space followed by an infusion of 1 mg h⁻¹ for 2 h produced an increase in plasma somatostatin which was maximal at 60 min. This was associated with a reduction in plasma concentrations of GH, insulin and glucagon at 60 min, although this only reached statistical significance for GH and insulin. The increase in plasma concentration of glycerol after 60 min of surgery in the somatostatin patients may have resulted from the suppression of insulin secretion, as this hormone is a potent inhibitor of lipolysis. A study of the hormonal effects of the subcutaneous injection of somatostatin 250 µg showed a transient reduction in plasma insulin [27]. During a continuous i.v. infusion increasing from 125 µg h⁻¹ to 750 µg h⁻¹ over 2 h, plasma concentrations of insulin and glucagon were both reduced significantly, but basal GH values were unaffected.

In conclusion, the administration of somatostatin 3 mg into the extradural space gave rise to a 15-fold increase in plasma somatostatin. This was associated with a reduction in plasma GH, insulin and glucagon values during surgery, together with a transient increase in lipolysis. Extradural somatostatin failed to provide analgesia.

REFERENCES
17. Chrubasik J, Meynadier J, Scherpereel P. Somatostatin versus morphine in epidural treatment after major ab-
dominal operations. *Anesthesiology* 1985; 63 (Suppl.): 237.