EFFECTS OF THE EXTRADURAL ADMINISTRATION OF LOCAL ANAESTHETIC AGENTS AND MORPHINE ON THE URINARY EXCRETION OF CORTISOL, CATECHOLAMINES AND NITROGEN FOLLOWING ABDOMINAL SURGERY

N.-C. HJORTSØ, N. J. CHRISTENSEN, T. ANDERSEN AND H. KEHLET

Surgical trauma elicits endocrine and metabolic changes characterized by an increase in the secretion of cortisol and catecholamines, and a net loss of protein. The release mechanisms of this response remain to be defined completely, but pain and other afferent neurogenic stimuli from the site of the operation play a dominant role (Kehlet, Brandt and Rem, 1980). Thus, afferent neurogenic blockade with extradural analgesia using local anaesthetic agents has been demonstrated to inhibit or prevent most of the classical endocrine–metabolic changes following lower (gynaecological) abdominal surgery, and procedures on the lower extremities (Kehlet, 1982). In contrast, extradural analgesia is less efficient in modifying the response associated with major upper abdominal surgery (Bromage, Shibata and Willoughby, 1971; Menzies Gow and Cochrane, 1979; Kossman et al., 1982; Seeling et al., 1982; Traynor et al., 1982; Tsuji, Asoh et al., 1983). Extradural analgesia with morphine alone leads only to a minor suppression of the stress response during the intra-operative and immediate postoperative periods (Christensen et al., 1982; Cowen et al., 1982; Jørgensen, Andersen and Engquist, 1982). However, the relationship between the relief of postoperative pain during extradural analgesia with local anaesthetics and morphine and the stress response has not been evaluated.

The purpose of this investigation was to study the correlations between the relief of pain obtained by an extradural analgesic regimen using local anaesthetics plus morphine, and the urinary excretion of cortisol, catecholamines and nitrogen during the first 4 days after major abdominal surgery in patients on a fixed nutritional intake.

PATIENTS AND METHODS
Twenty patients undergoing elective major abdominal surgery were randomized into two groups. One group (10 patients: seven colonic resections and three gastric resections) had general anaesthesia with low-dose fentanyl (initial dose 0.007 mg kg⁻¹, maintenance dose 0.002 mg kg⁻¹ h⁻¹) and nitrous oxide in oxygen. Systemic morphine in doses of 6–10 mg every 4–6 h was given routinely to alleviate
Table 1. Clinical data (mean±SEM) in patients undergoing major abdominal surgery during general or extradural analgesia

<table>
<thead>
<tr>
<th></th>
<th>General anaesthesia (n=10)</th>
<th>Extradural analgesia (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>3:7</td>
<td>7:3</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>70±5</td>
<td>65±3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161±3</td>
<td>172±3</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>61±4</td>
<td>66±3</td>
</tr>
<tr>
<td>S-albumin (mmol litre⁻¹)</td>
<td>455±23</td>
<td>447±22</td>
</tr>
<tr>
<td>S-Transferrin (mmol litre⁻¹)</td>
<td>31.2±1.7</td>
<td>30.9±3.0</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>189±18</td>
<td>156±18</td>
</tr>
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P (between groups) ns ns <0.02 ns ns ns ns ns

pain after operation. The other group of 10 patients (eight colonic resections, one gastric resection and one cholecystectomy) received the same general anaesthetic technique with, in addition, extradural analgesia (1.5% etidocaine) used during the operation in a dose sufficient to provide sensory analgesia (pin prick) from T4 to S5 before skin incision. The extradural regimen was continued into the period after operation: 3 h after skin incision bupivacaine 10 ml (0.5% without adrenaline) was given and thereafter bupivacaine 5 ml every 4 h for 24 h. In addition, extradural morphine 4 mg was administered every 12 h from 3 to 72 h after skin incision. Thereafter, the patients received systemic morphine 6–10 mg on request.

Clinical data for the two groups are shown in table 1.

None of the patients had liver or renal disease as verified by routine laboratory tests, and none showed signs of endocrine disease or was receiving hormone treatment. None of the patients had infective or surgical complications during the 4-day study period.

All patients received 10% dextrose 1000 ml and 1000 ml of an aminoacid–glucose solution (Vamin-glucose) i.v. on the day of operation and on each of the following 3 days. This regimen provided 200 g of glucose and 70 g of aminoacids (nitrogen 9.4 g) daily. In addition, sodium chloride and potassium chloride solutions were given i.v. to maintain fluid and electrolyte balance. Oral intake of fluid during the first 4 days after operation was restricted to tap water.

Urine was collected in 24-h periods (the bladder was catheterized in all patients) and the concentrations of creatinine, urea (routine laboratory methods), cortisol (radioimmuno-assay-kit, Amer-Sham), adrenaline, noradrenaline (double-isotope derivative technique) (Christensen et al., 1980) and nitrogen (Kjeldahl-technique) were measured.

Pain was assessed by the patients 24, 48, 72 and 96 h after skin incision, using an arbitrary scale from 0 to 10 (worst pain). Patients were asked to rate the average pain experienced during the preceding 24 h. The experimental programme was approved by the ethics committee for Copenhagen Hospitals. Informed consent was obtained from all patients.

Student’s t-test and linear regression analyses were used, and a P-value less than 0.05 considered significant.

![Pain scores during the first 4 days after major abdominal surgery in patients receiving general anaesthesia and routine systemic morphine intermittently for pain relief, and in patients receiving a combination of general anaesthesia and extradural analgesia during surgery and extradural analgesia with local anaesthetics plus morphine for pain relief after operation.](image)
TABLE II. Postoperative changes (mean±SEM) in rectal temperature and urinary excretion of creatinine in patients undergoing major abdominal surgery with general or extradural analgesia

<table>
<thead>
<tr>
<th></th>
<th>Before op.</th>
<th>Days after operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>General anaesthesia</td>
<td>36.8±0.1</td>
<td>37.7±0.2</td>
</tr>
<tr>
<td>Extradural analgesia</td>
<td>37.0±0.1</td>
<td>37.5±0.2</td>
</tr>
<tr>
<td>Urinary creatinine excretion (mmol)</td>
<td></td>
<td>7.98±0.7</td>
</tr>
<tr>
<td>General anaesthesia</td>
<td>—</td>
<td>11.02±1.4</td>
</tr>
<tr>
<td>Extradural analgesia</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

RESULTS

Postoperative pain scores were significantly lower, during the first 3 days after operation, in the patients receiving the extradural analgesic regimen compared with patients receiving routine management with systemic morphine (fig. 1).

Rectal temperature increased ($P < 0.05$) slightly during the first 3 days after operation, but there was no difference ($P > 0.4$) between the groups (table II).

Urinary excretion of creatinine remained constant throughout the first 4 days after operation in both groups and there were no differences ($P > 0.2$) between the groups (table II). In the individual patients the variability in the creatinine excretion was less than 15% between days, indicating that urinary sampling was sufficient.

The cumulative 4-day postoperative excretion of cortisol (fig. 2) was insignificantly lower (8.2±2.0 μmol) in the extradural group compared with the group receiving anaesthesia plus systemic opiates (10.0±1.5 μmol). The difference in cortisol excretion between the groups was most pro-

![Graph showing cortisol excretion](image-url)

**Fig. 2.** Urinary excretion of cortisol (mean values ± SEM) after major abdominal surgery in patients receiving general anaesthesia plus routine intermittent morphine for pain relief, and in patients receiving general anaesthesia and extradural analgesia during surgery plus extradural analgesia with local anaesthetics and morphine in the period after operation. There were no differences ($P > 0.05$) between the groups in any endocrine–metabolic variable either on separate days or on the cumulative excretion values.
nounced during the first 2 days, but also failed to achieve significance on separate days. On all days cortisol excretion was greatly increased above normal mean values (0.1 µmol/24 h).

Cumulative urinary excretion of noradrenaline (fig. 4) was lower (not significant) in the extradural group (1.3 ± 0.2 µmol) than in the general anaesthesia group (1.9 ± 0.2 µmol), and again there were no significant differences between the groups on the separate days. Noradrenaline excretion was increased above normal mean values (0.18 µmol/24 h) on all days in both groups.

Cumulative urinary excretion of adrenaline (fig. 3) was lower (not significant) in the extradural group (0.29 ± 0.05 µmol) compared with the general anaesthetic group (0.34 ± 0.07 µmol), and there were no significant differences between the individual days. Adrenaline excretion was increased above normal mean values (0.04 µmol/24 h) every day in both groups.

Urinary excretion of nitrogen (fig. 5) was almost identical in the two groups, both with regard to cumulative values and values on the individual days. The cumulative 4-day nitrogen balance was negative.
in both groups (-0.25 ± 0.19 mol in the extradural group and -0.34 ± 0.18 mol in the general anaesthetic group) (P > 0.7). The relationship between the cumulative urinary excretion of nitrogen and the urea concentration was linear and similar in the two groups (r = 0.91, P < 0.001).

There were no relationships (P > 0.05) between the daily pain scores and the urinary excretion of cortisol (r = 0.18; 0.01; 0.01; 0.16), adrenaline (r = 0.05; 0.13; 0.07; 0.23), noradrenaline (r = 0.21; 0.42; 0.25; 0.28) or nitrogen (r = 0.26; 0.01; 0.09; 0.02) on days 1, 2, 3 and 4, respectively. Similarly, there were no correlations between the cumulated 4-day pain scores and the urinary excretion of cortisol, adrenaline, noradrenaline and nitrogen (r = 0.2; 0.03; 0.35; 0.17, respectively).

**DISCUSSION**

The results show that an extradural analgesic regimen with local anaesthetics plus morphine provides adequate relief of pain after major abdominal surgery, and is superior to the "routine" management of pain using the intermittent administration of systemic morphine.

Although these findings are in accord with several recent studies, it was surprising that the pain relief achieved did not decrease the catabolic response to surgery, as assessed by the 4-day postoperative urinary excretion of cortisol, catecholamines and nitrogen. Previous investigations have demonstrated that extradural analgesia with local anaesthetics prevented a predominant part of the endocrine-metabolic response to lower (gynaecological) abdominal surgery and procedures on the lower extremities and, concomitantly, these patients were pain free (Kehlet, 1982). However, the existence of a disparity between the relief of pain after operation and modification of the stress response has been suggested in studies where the hyperglycaemic and adrenocortical responses to abdominal hysterectomy were only prevented if sensory analgesia extended to T4 despite adequacy of pain relief in patients with a sensory block to T8 and T10 (Engquist et al., 1977). Similarly, in studies using extradural morphine alone to relieve pain following hysterectomy (Christensen et al., 1982; Cowen et al., 1982; Jorgensen, Andersen and Engquist, 1982), the adrenocortical and hyperglycaemic responses to surgery were only suppressed partially, despite adequate pain relief, indicating that neurogenic pathways other than opiate-receptor dependent nociceptive pathways may be important in mediating the trauma response.

It might be argued that our method of pain assessment consisted of an overall estimation performed retrospectively each day, thereby increasing the risk of overlooking periods with more or less pain. However, the validity of the overall, retrospective assessment has been shown in studies with concomitant, repeated pain score assessments during the study (Rigamonti et al., 1983).

In the present study we used a combination of a local anaesthetic agent and morphine extradurally to obtain more complete afferent blockade. It may be argued that a more pronounced metabolic effect of the extradural regimen could have been overlooked.
since the randomization between groups was less than ideal in that the patients in the extradural group tended to be slightly younger, taller, heavier and most were male. Such patients have been considered to show a more pronounced catabolic response to trauma, although data on this point are not available. Nevertheless, the excretion of cortisol and catecholamines was increased markedly above upper normal limits in both groups and a major modifying effect of the extradural regimen on the stress response is unlikely, despite the slight skewness in the composition of patients.

Previous investigations have also been unsuccessful in preventing the response to major abdominal surgery by extradural analgesia with local anaesthetics (Bromage, Shibata and Willoughby, 1971; Menzies Gow and Cochrane, 1979; Traynor et al., 1982; Seeling et al., 1982; Kossman et al., 1982; Tsuji, Asoh et al., 1983), but this may be explained by the inclusion of abdomino-thoracic procedures in some studies (Bromage, Shibata and Willoughby, 1971; Seeling et al., 1982) or by inadequate afferent blockade when the operation extended to the pelvis (Kossman et al., 1982). However, in the remaining studies (Menzies Gow and Cochrane, 1979; Traynor et al., 1982; Tsuji, Asoh et al., 1983) the neurogenic blockade used would have been expected to provide an adequate afferent blockade from the surgical area and, at present, we have no good explanation as to why this does not lead to the decrease in postoperative catabolism observed during surgery on the lower part of the body (Kehlet, 1982). It has been suggested that this discrepancy may be attributable to unblocked afferent vagal pathways, but infiltration of the vagus nerve with local anaesthetics immediately after opening the abdomen (Traynor et al., 1982) or an initial surgical vagotomy (Tsuji, Asoh et al., 1983) failed to potentiate the effect of extradural analgesia on the stress response. In addition, experimental studies in dogs with vagotomy, ventrolateral cordotomy or combined vagotomy plus cordotomy failed to demonstrate that the vagal afferent pathway was important for the ADH response to surgery (Ukal, Moran and Zimmermann, 1968). Therefore, the lack of a major modifying effect of extradural analgesia on the response to major abdominal surgery may be simply the result of inadequate afferent blockade compared with the strength of the stimulus from the procedure. This is supported by the fact that, although the relief of pain produced by our extradural regimen was acceptable clinically, it did not result in the total alleviation of the pain. That afferent blockade may be insufficient following a conventional extradural analgesia during major abdominal surgery was confirmed recently by the demonstration of a more pronounced inhibition of the stress response when splanchnic blockade with local anaesthetics was provided with extradural analgesia (Tsuji, Shirasaka et al., 1983). This indicates that afferent sympathetic pathways from the abdomen are important in initiating the stress response. Furthermore, the finding of differential sensitivity of A and C nerve fibres to various local anaesthetic agents may be an additional explanation of the subtotal afferent blockade—certain afferent pathways may remain relatively unblocked compared with more complete blockade of the pain conducting pathways. However, at present the data are conflicting (Cusick, Myklebust and Abram, 1980; Gissen, Covino and Gregus, 1980; Raj et al., 1982), probably because of differences in experimental models, and no definite conclusion can be drawn with regard to the degree of afferent neurogenic blockade produced by the various local anaesthetic agents in the clinical situation. Finally, we are ignorant of the relative importance of neurogenic stimuli v. humoral factors originating from the wound in mediating the response, although some data appear to suggest that a circulating peptide may potentiate post-traumatic proteolysis (Clowes et al., 1983).

Although our results failed to demonstrate any major influence of the extradural analgesic regimen on the endocrine response to surgery, the finding of an unaltered overall nitrogen excretion does not exclude an effect on protein metabolism. Thus, urinary nitrogen excretion represents a crude expression of protein synthesis v. degradation from multiple sources, thereby excluding interpretation on possible alterations in protein metabolism in selective tissues such as muscle, gut, skin etc. (Rennie and Harrison, 1984). However, the finding of a lack of influence on both the endocrine response and nitrogen excretion argues against any important effect on the catabolic response to surgery.

In conclusion, our results indicate that the provision of adequate pain relief following major abdominal surgery using an extradural analgesic regimen consisting of a local anaesthetic plus morphine does not lead to an associated decrease in the catabolic response to surgery. Possibilities of mitigating the stress response to major trauma are still limited and await an improved understanding of the physiology and the substrates involved in the transmission of nociceptive information (Yaksh and Hammond, 1982).
ACKNOWLEDGEMENTS

This study was supported by a grant from Astra Läkemedel, Södertälje, Sweden and KabiVitrum A/S, Copenhagen.

The cortisol determinations were kindly performed by Dr Sixtus Thorsen, Department of Clinical Chemistry, Hvidovre Hospital, Copenhagen.

REFERENCES


