EFFECTS OF THE EXTRADURAL ADMINISTRATION OF MORPHINE, OR BUPIVACAINE, ON THE ENDOCRINE RESPONSE TO UPPER ABDOMINAL SURGERY

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SUMMARY
The endocrine response, and the relief of pain, following the extradural administration of morphine or a local anaesthetic agent bupivacaine (0.5%) were studied for 24 h after abdominal surgery and compared with a control group given conventional i.v. morphine after operation. Samples were taken before and at 2, 4, 6, 12 and 24 h after skin incision. Pain relief in both extradural groups was significantly better when compared with the control group. In all three groups, the plasma concentration of cortisol was increased immediately after surgery. Thereafter, significantly lower values were seen in the extradural groups. Plasma adrenaline concentration was lower immediately after surgery only in the group given the extradural local anaesthetic. Plasma noradrenaline concentration remained unchanged after extradural local anaesthesia while an intermediate increase occurred after extradural morphine. Plasma noradrenaline concentration was significantly greater in the controls compared with both extradural groups. Our results indicate that extradural analgesia with a local anaesthetic drug can suppress the increases in the plasma concentrations of the catecholamines and cortisol after surgery. In contrast to extradural local anaesthetic extradural morphine cannot suppress the endocrine response immediately after surgery. However, later in the postoperative period, extradural morphine can suppress the endocrine response, thus indicating that postoperative pain is a factor involved in the stress response following surgery.

Surgical trauma and postoperative pain evoke an endocrine response characterized by an increased production of cortisol and catecholamines. The most prominent metabolic consequences of such hormonal alterations are hyperglycemia, increased lipolysis and protein catabolism. The endocrine response is thought to be mediated predominantly by afferent neurogenic stimuli, since it can be suppressed in lower abdominal surgery by an extradural block (with a local anaesthetic agent) extending from T4 to S5 (Engquist et al., 1977; Kehlet, Brandt and Rem, 1980). However, in upper abdominal surgery a similar blockade did not suppress the increase in plasma cortisol concentration, probably as a result of unblocked vagal afferents (Bromage, Shibata and Willoughby, 1971; Traynor et al., 1982). The effects of extradural analgesia on the endocrine response to upper abdominal surgery as opposed to lower abdominal surgery have received little attention (Traynor et al., 1982). Furthermore, there are only a few reports describing the effects of extradural analgesia on plasma catecholamine concentrations during abdominal surgery.

Since the discovery of opiate receptors in the spinal cord, several reports have demonstrated the beneficial effects of extradural morphine on postoperative pain (Bromage, Camporesi and Chestnut, 1980; Jörgensen, Andersen and Engquist, 1982; Schildt et al., 1982). There are, however, sparse and conflicting reports on the endocrine and metabolic effects of extradurally administered opiates and doubts have been expressed about the ability of extradural morphine to suppress the stress response induced by surgery (Christensen et al., 1982; Cowen et al., 1982; Jörgensen, Andersen and Engquist, 1982).

The present study, in patients undergoing upper abdominal surgery, was undertaken to compare the effects of extradural analgesia produced by a local anaesthetic drug, on the hormonal responses to surgery, with those produced by the extradural administration of morphine.

PATIENTS AND METHODS
Twenty-four otherwise healthy women admitted for cholecystectomy were investigated. The study was approved by the local Ethics Committee and informed consent was obtained from all patients. The patients were randomly allocated to one of the three groups, C (control), L (local anaesthetic) and M (extradural morphine).
(morphine). The groups were comparable ($P > 0.05$) with regard to age, weight, duration of surgery and blood loss (table I). All patients were in a postabsorptive state after an overnight fast and were premedicated with diazepam 10–15 mg rectally 1.5–2 h before surgery.

In groups L and M a catheter was introduced to the extradural space, via the T9/10 or T10/11 interspaces. Group L received 0.5% bupivacaine 7 ml through the catheter 1 h before surgery to produce segmental blockade from T4 to L3, evaluated by pin-prick. This level was maintained throughout the study by repeated doses of 0.25–0.375% bupivacaine 5–8 ml. In group M morphine 4mg dissolved in isotonic saline 7 ml was administered via the catheter 1 h before surgery and repeated doses of morphine 4mg were given every 10 h. In the latter group the correct position of the catheter was confirmed by a small dose of local anaesthetic after the study was completed.

In all groups anaesthesia was induced with thiopentone and fentanyl followed by intubation of the trachea after pancuronium had been given. Anaesthesia was maintained with nitrous oxide in oxygen (2:1) using a circle system with soda-lime absorption. Repeated doses of pancuronium, diazepam and fentanyl were given as required. The doses of fentanyl (mean±SEM) were $0.55±0.05$, $0.35±0.03$, $0.50±0.04$ mg in groups C, L and M, respectively. The difference between group C and group L was significant ($P > 0.05$). In the control group postoperative analgesia was achieved with morphine 2.5mg i.v., as required.

All operations started between 08.30 and 09.30 a.m. and the patients stayed in the postoperative ward for 24 h. All groups received physiological saline 500 ml i.v. before anaesthesia. During surgery physiological saline at a rate of 6 ml kg$^{-1}$h$^{-1}$ was infused and was continued after the operation at a rate of 1–2 ml kg$^{-1}$h$^{-1}$. Blood loss was replaced with Dextran 70 i.v. No other infusions were given.

Arterial blood samples were taken 1 h before surgery, before the extradural blockade and 2, 4, 6, 12 and 24 h after skin incision. Plasma catecholamine concentrations were determined by high pressure liquid chromatography with amperometric detection (Allenmark, Hedman and Söderberg, 1980). Plasma cortisol concentration was determined by radioimmunoassay (Farmer and Pierce, 1974). Pain was evaluated, in the postoperative period, by means of a visual analogue scale (VAS) with a scale from 0 to 10 (Scott and Huskinson, 1976) at the same times as the blood sampling.

Results are presented as mean values ± standard error of the mean (SEM). One- and two-way analysis of variance and Duncan’s new multiple range test were used (Winer, 1971). Pain scoring (VAS) was analysed statistically by using the Kruskal–Wallis test.

### RESULTS

The results are summarized in figures 1, 2 and 3. Before operation, there were no differences in the concentrations of plasma cortisol, adrenaline or noradrenaline between the three groups. All values were within the reference limits for our laboratory.

**Cortisol (fig. 1)**

The plasma cortisol concentration increased significantly 2 h after skin incision in all three groups.

![Figure 1](https://academic.oup.com/bja/article-abstract/56/3/233/503233/fig1.png)

**Fig. 1.** Plasma cortisol concentration (mean ± SEM) before and after cholecystectomy with general anaesthesia (GA) (●–●); GA + extradural local anaesthesia (▲ – ▲); GA + extradural morphine (■ – ■).
EXTRADURAL MORPHINE AND THE ENDOCRINE RESPONSE

(C and M, \( P < 0.01 \); L, \( P < 0.05 \)). In group C the plasma cortisol concentration continued to increase in the period after operation, with a peak value at the 4-h measurement and the increase was significant \( (P < 0.01) \) at 2, 4 and 6 h after skin incision when compared with the preoperative value. In the extradural groups there were no further increases in plasma cortisol concentration after the first postoperative value at 2 h, but the plasma cortisol concentration remained significantly greater than its preoperative value at 4 and 6 h \( (P < 0.05) \). The plasma cortisol concentration was significantly lower in group L compared with group C 2 h after skin incision \( (P < 0.05) \), whereas no difference was found between groups C and M. At 4 h after skin incision the plasma cortisol concentrations were significantly lower in both extradural groups, and there were no significant differences between the extradural groups.

Adrenaline (fig. 2)

The plasma adrenaline concentration increased markedly after surgery in group C, being significantly higher than the preoperative value at 2 h \( (P < 0.05) \) and 4 h \( (P < 0.01) \) after skin incision. In group L the increase in plasma adrenaline concentration was less pronounced and significant only at 2 h after skin incision \( (P < 0.05) \). In group M the plasma adrenaline concentrations were between those found in groups L and C throughout the study and significant increases were observed at 2 h and 4 h after skin incision \( (P < 0.01) \) (that is, compared with preoperative values). Two hours after skin incision there were differences \( (P < 0.05) \) between group L and groups C and M, but no other differences were observed between the groups.

Noradrenaline (fig. 2)

The plasma noradrenaline concentrations were increased \( (P < 0.05) \) 2 h and 4 h after skin incision in groups C and M, whereas in group L there was no increase when compared with preoperative values. Two hours after skin incision group L had significantly lower plasma concentrations than both groups C and M \( (P < 0.01) \). At 6, 12 and 24 h after the start of the operation plasma noradrenaline concentration was significantly lower in groups L and M when compared with group C, but no differences were observed between the L and M groups during this period.

Pain evaluation (fig. 3)

Pain relief was significantly more effective \( (P < 0.01) \) in the extradural groups (L and M) when
compared with group C at 2, 4, 6 and 12 h after skin incision, whereas no significant differences were found between groups L and M.

**DISCUSSION**

The influence of extradural analgesia on the hormonal response to lower abdominal surgery is well documented. In this form of trauma an extensive extradural blockade extending from S5 to T4 can suppress the increase in catecholamine and cortisol concentrations induced by surgery. However, a less extensive blockade is insufficient to suppress this response even if it gives good relief of pain. This is probably because of patent sympathetic pathways (Engquist et al., 1977; Kehlet, Brandt and Rem, 1980). In upper abdominal surgery not even an extensive extradural blockade can inhibit the increase in cortisol concentration, unblocked afferent vagal stimulation being the probable reason (Bromage, Shibata and Willoughby, 1971). However, Traynor and colleagues (1982) reported recently that thoracic extradural analgesia, even when combined with vagal blockade, failed to suppress the adrenocortical response to upper abdominal surgery although, as pointed out by the authors, retraction and dissection while identifying the vagal trunks may have caused autonomic afferent stimulation. Furthermore, it is difficult to assess the accuracy of vagal blockade.

Our results confirm that the extradural administration of a local anaesthetic agent did not inhibit the increase in plasma cortisol concentration observed immediately after upper abdominal operations, although the increase was significantly less pronounced than in the control group. However, the extradural administration of the local anaesthetic, and of morphine, could suppress the increase in plasma cortisol concentration in the period after operation. This finding is in contrast to that of Bromage, Shibata and Willoughby (1971). The differences between the two studies could be explained by the fact that patients undergoing both thoracic and different kinds of abdominal surgery were included in their study, whereas all the patients in the present study were undergoing cholecystectomy.

Our finding that upper abdominal surgery in unblocked patients produced an increase in plasma adrenaline and noradrenaline concentrations is in accordance with previous reports (Halter, Pflug and Porte, 1977; Brown et al., 1982). As described by these authors, we also found high concentrations of both plasma adrenaline and noradrenaline more than 2 h after the end of operation. This is in contrast to Engquist and colleagues (1980) who were unable to demonstrate an increase in plasma noradrenaline concentration during and after lower abdominal surgery under enflurane anaesthesia. The differences noted could perhaps be attributed to different techniques of anaesthesia, since patients receiving enflurane anaesthesia have been reported to have lower plasma noradrenaline concentrations during surgery than those receiving fentanyl anaesthesia (Brown et al., 1982).

The present study indicates that the extradural administration of a local anaesthetic can suppress the increase in the concentrations of adrenaline and noradrenaline in the period following abdominal surgery. The suppression of catecholamines has been reported previously during spinal anaesthesia for minor surgery in the lower part of the body (Pflug and Halter, 1981). However, in lower abdominal surgery with extradural analgesia an increase was seen in the plasma concentration of noradrenaline, although the plasma adrenaline concentration remained unchanged (Engquist et al., 1980). From this and other discrepancies between the different studies it is obvious that it is important to standardize the type of operation and the anaesthetic technique in investigations of the endocrine response to surgical trauma.

Extradural blockade with a local anaesthetic drug blocks nociceptive as well as other neurogenic pathways, including sympathetic stimuli. Since the discovery of opiate receptors in the substantia gelatinosa in the dorsal horn of the spinal cord, extradural and intradural opiates have been used for selective depression of nociceptive pathways. It is well documented that morphine given extradurally gives good relief of pain after surgery (Bromage, Camporesi and Chestnut, 1980; Jorgensen, Andersen and Engquist, 1982; Schildt et al., 1982). In the present study, pain relief in the extradural morphine group was significantly better than in the control group and was equal to that in patients receiving bupivacaine.

However, whether the improved pain relief influences the endocrine response to surgery also, has been unclear. Our results indicate that, immediately after surgery, extradural morphine fails to suppress the adrenocortical response to upper abdominal surgery. However, later in the period after operation the increase in cortisol concentration can be blocked by the extradural administration of morphine. During the whole investigation no differences were
found between the morphine and the local anaesthetic group in plasma cortisol concentrations. The finding that extradural opiates can block the increase in plasma cortisol concentration after operation is in accord with earlier reports (Christensen et al., 1982; Cowen et al., 1982).

To our knowledge there are no previous studies reporting the effect of extradural morphine on catecholamine concentrations after surgery. Although we did not find any significant differences in the plasma concentrations of adrenaline between the control group and the extradural morphine group, the values tended to be lower in the latter group throughout the study. However, the plasma noradrenaline concentration was significantly lower in the extradural morphine group, apart from the first two samples taken after operation. During this period there were no differences between the two extradural groups.

The difference between the groups in pain relief and endocrine response cannot be attributed to differences in the dose of fentanyl, since the control and extradural morphine groups received a similar dose.

The results of the present study indicate that extradural local anaesthetic, in contrast to extradural morphine, can suppress the increase in plasma catecholamines normally seen immediately after upper abdominal surgery. Further, our results indicate that the extradural administration of a local anaesthetic agent, and of morphine, can attenuate the endocrine response in the later postoperative period. This finding that extradural morphine can attenuate the stress response after surgery suggests that nociceptive stimulation is a factor involved in this endocrine response.

ACKNOWLEDGEMENTS

This investigation was supported by grants from Astra Research Foundation and the Swedish Medical Research Council (project No. 04139) and the County Council of Östergötland.

REFERENCES


EFFETS DE L’ADMINISTRATION PERIDURALE DE MORPHINE OU DE BUPIVACAINE SUR LES LES RESPONSES ENDOCRINES A LA CHIRURGIE ABDOMINALE SUS-MESOCOLIQUE

RESUME

Nous avons étudié la réponse endocrinienne et l’analgesie obtenues après administration peridurale de morphine ou d’un anesthésique local (0,5% bupivacaine) pendant les premières 24 h suivant des actes de chirurgie abdominale. Les résultats ont été
WIRKUNGEN EXTRADURALER VERABREICHUNG
VON MORPHIN ODER BUPIVACAIN AUF DIE
ENDOKRINE REAKTION AUF OBERE
ABDOMINALCHIRURGIE

ZUSAMMENFASSUNG

Bis 24 h nach einem abdominalchirurgischen Eingriff wurde die
diokraine Reaktion und die Schmerzlinderung nach extraduraler
Gabe von Morphin oder einem Lokalanästhetikum (0,5%iges Bupivacain) untersucht und mit einer Kontrollgruppe vergl-
lchen, bei der Morphin postoperativ intravenös verabreicht
wurde. Blutproben wurden 2, 4, 6, 12 und 24 h nach dem
Hautschnitt entnommen. Die Schmerzlinderung war in beiden
extraduralen Gruppen signifikant stärker als in der Kon-
trollgruppe. Bei allen drei Gruppen stieg die Plasma-
cortisolkonzentration unmittelbar nach der Operation an. Später zeigten sich
in den extraduralen Gruppen signifikant niedrigere Werte. Die Plas-
maadrenalkonzentration war in der Kontrollgruppe sig-
ifikant höher als in beiden extraduralen Gruppen. Unsere
Ergebnisse zeigen, daß durch extradurale Analgesie mit einem
Lokalanästhetikum der postoperative Anstieg der Plasma-
cortisolkonzentration von Katecholaminen und Cortison unterdrückt
werden kann. Extradurales Morphin kann im Vergleich dazu die
diokraine Reaktion unmittelbar postoperativ nicht sup-
primir, wohl aber in der späteren postoperativen Phase. Dies
zeigt, daß postoperative Schmerzen ein Faktor der Stressreak-
tion auf Operationen sind.

EFFECTOS DE LA ADMINISTRACION
EXTRADURAL DE MORFINA O DE
BUPIVACAINA SOBRE LA RESPUESTA
ENDOCRINA A LA CIRUGIA ABDOMINAL
SUPERIOR

SUMARIO

Se llevaron a cabo estudios de la respuesta endocrina y del alivio
del dolor después de la administración extradural de morfina o de
un agente anestésico local (bupivacaina al 0,5%) durante 24 h
después de una cirugía abdominal y se hizo una comparación con
un grupo de control a quien se administró morfina i.v. de manera
tradicional después de la operación. Se tomaron muestras antes y
a las 2, 4, 6, 12 y 24 h después de la incisión de la piel. El alivio del
dolor en ambos grupos con anestesia extradural fue bastante
mejor cuando se lo comparó con el grupo de control. En los tres
grupos, la concentración en el plasma del cortisol aumentó in-
mediatamente después de la operación. Sin embargo, se observa-
ron valores bastante más bajos en los grupos con anestesia
extradural. La concentración en el plasma de adrenalina, in-
mediatamente después de la cirugía, fue menor sólo en el grupo
que recibió anestésico extradural local. La concentración en el
plasma de noradrenalina permaneció sin cambio después de la
anestesia extradural local mientras que un aumento intermedio
ocurrió después de la morfina extradural. La concentración en el
plasma de noradrenalina fue bastante mayor en los controles en
comparación con ambos grupos con anestesia extradural. Neus-
tros resultados indican que la analgesia extradural con una sub-
stancia anestésica local puede suprimir los aumentos en las con-
centraciones en el plasma de catecolaminas y de cortisol después
de la cirugía. Al contrario de lo que ocurre con anestésico local
extradural, la morfina extradural no puede suprimir la respuesta
diokrina inmediatamente después de la cirugía. Sin embargo,
más tarde en el periodo postoperatorio, la morfina extradural
puede suprimir la respuesta endocrina, lo que indica que el dolor
postoperatorio constituye un factor involucrado en la respuesta de
tensión que sigue la cirugía.