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

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Moderate surgical trauma such as cholecystectomy or hysterectomy results in significant endocrine and metabolic responses (Stjernström, Jorfeldt and Wiklund, 1981; Christensen et al., 1982; Jørgensen, Andersen and Engqvist, 1982; Traynor et al., 1982). However, although extradural blockade with local anaesthetics can suppress most of the response associated with lower abdominal surgery (for review, see Kehlet, 1982), less is known as to the effects of extradural blockade on the stress response associated with upper abdominal surgery (Bromage, Shibata and Willoughby, 1971; Traynor et al., 1982; Asoh et al., 1983).

In a previous paper we discussed the endocrine effects of extradural local anaesthetics and extradural morphine after upper abdominal surgery (Rutberg et al., 1984a). The main finding was that extradural local anaesthetics almost completely abolished the catecholamine response, whereas extradural morphine did not suppress the increase in plasma adrenaline concentration and suppressed only partly the increase in plasma noradrenaline concentrations. Although the extradural administration of local anaesthetics or morphine did not suppress the cortisol release immediately after surgery, subsequent postoperative values were lower in both of these groups when compared with a control group. Furthermore, the pain relief in both extradural groups was significantly better than in the control group (morphine i.v.).

The metabolic implications of suppression of the hormonal response by extradural morphine remain unclear. There are disparate results concerning postoperative concentrations of glucose, the only metabolite studied previously in connection with extradural morphine (Christensen et al., 1982; Cowen et al., 1982; Jørgensen, Andersen and Engqvist, 1982).

The present study was undertaken to evaluate the metabolic consequences of suppression of the endocrine response by extradural morphine and extradural local anaesthetics.

PATIENTS AND METHODS

The study included 24 otherwise healthy women undergoing elective cholecystectomy. The details of the patients have been described previously (Rutberg et al., 1984a). The investigation was approved...
by the local Ethics Committee and informed consent was obtained from each patient. They were randomly allocated to one of the groups: C (control), L (local anaesthetic) and M (morphine). The groups were comparable with regard to age (43.0 ± 4.2, 45.5 ± 4.1, 40.1 ± 3.4 yr (mean ± SEM), weight 73.6 ± 4.5, 66.4 ± 4.8, 75.0 ± 3.8 kg), duration of surgery (70 ± 6, 73 ± 10, 72 ± 3 min) and estimated blood loss (234 ± 50, 228 ± 52, 233 ± 53 ml), respectively.

The 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. All operations started between 08.30-09.30 a.m. and the patients remained in the postoperative ward for 24 h. Before the induction of anaesthesia, physiological saline 500 ml was given i.v. This infusion was continued during surgery at a rate of 6 ml kg⁻¹ h⁻¹, and in the period after operation at a rate of 1-2 ml kg⁻¹ h⁻¹. Blood loss was replaced with Dextran 70. No other i.v. infusions were given during the investigation.

One hour before surgery an extradural catheter was placed (T9–10 or T10–11 spaces) in groups L and M. In group L, 0.5% bupivacaine 7 ml was given to produce a segmental blockade from T4 to L3 as evaluated by pin-prick. Throughout the study this level of blockade was maintained by repeated doses of 0.25% or 0.375% bupivacaine 5-8 ml. In group M, morphine 4 mg dissolved in isotonic saline 7 ml was given extradurally. Repeated doses of morphine 4 mg were then given every 10 h. After the study the correct position of the catheter in group M was confirmed by a small dose of local anaesthetic.

In all groups general anaesthesia was induced with thiopentone and fentanyl. Endotracheal intubation was facilitated with pancuronium, and anaesthesia was maintained with nitrous oxide in oxygen (3:1.5 litre min⁻¹) using a circle system with soda-lime absorption. Repeated doses of fentanyl, pancuronium and diazepam were given. 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 dose in group L was significantly (P < 0.05) smaller than in groups C and M. The control group received morphine 2–5 mg i.v. as required to provide analgesia after operation.

Arterial blood samples for assay of metabolites were immediately precipitated with ice-cold perchloric acid. After centrifugation, the protein-free extract was deep-frozen (−80 °C) pending analysis. The analyses were performed by microfluorimetry: d-glucose by modification for fluorimetry of the hexokinase method described by Schmidt (1961) and Barthelmai and Czek (1962) and lactate, glycerol, 3-hydroxybutyrate and alanine as described previously (Jorfeldt and Juhlin-Dannfeldt, 1977). Free fatty acids (FFA) were analysed according to Ho (1970). Oxygen consumption was measured 1 h before surgery and at 4, 6, 12 and 24 h after skin incision. The expired air was collected in a Douglas bag and then analysed using a mass spectrometer (the coefficient of variation of a single determination was 3.3%).

Statistical methods and presentation of data
One- and two-way analysis of variance and Duncan's new multiple range test were used (Winer, 1971). The term "significant" implies statistically significant. Tests were made at the 1% and 5% level. Data are presented as mean values ± standard error of the mean (SEM).

RESULTS
Glucose concentration (fig. 1)
The arterial concentration of glucose increased in all groups during surgery (P < 0.01). This increase was about 50% in groups C and M, but only 14% in group L. In group C blood glucose concentration remained increased at 2, 4, 6 and 12 h after skin incision (P < 0.01). In group M the arterial glucose concentrations were increased at 2, 4, 6 and 12 h (P < 0.05) whereas the only increase in group L was at 2 h. At 24 h the arterial glucose concentration in group L was lower than before the operation (P < 0.05). Group L demonstrated lower values than groups M and C at 2 h (P < 0.05). Group M and C did not differ.

Insulin concentration (fig. 1)
There were no significant differences in serum insulin concentrations between the three groups, although there was a significant increase in group M at 2 h (P < 0.01).

Lactate concentration (fig. 2)
The arterial concentration of lactate showed a pattern of reaction very similar to that of glucose. Thus, the lactate concentration had increased significantly in all three groups 2 h after skin incision (groups C
and L, $P < 0.05$; group M, $P < 0.01$). Thereafter, concentrations decreased and became similar to the values observed before operation. The arterial lactate concentrations in group L were consistently lower than those in groups M and C, but no significant differences occurred.

### Alanine concentration (fig. 2)

The arterial concentration of alanine decreased in all groups to about 70% of its value before operation. The decrease was significant by 2 h in groups C and L, ($P < 0.05$) and for the remaining period in all groups ($P < 0.01$). No significant differences were observed between the three groups.

### FFA concentration (fig. 3)

The arterial concentration of FFA increased ($P < 0.01$) in group C at 4 and 6 h after skin incision, and in group M at 4 ($P < 0.05$), 6 ($P < 0.01$) and at 24 h ($P < 0.05$) after skin incision. In group L, a decrease was seen at 2 h ($P < 0.05$). At 2 and 4 h significantly ($P < 0.01$) smaller values were seen in group L than in groups M and group C. At 4 h the value in group M was smaller ($P < 0.05$) than that obtained in group C.

### Glycerol concentration (fig. 3)

The arterial concentration of glycerol was increased in all groups, but significant ($P < 0.05$) only at 4 h in group C. No significant differences were seen between the three groups, although consistently smaller values were seen in group L when compared with the other groups.

### 3-Hydroxybutyrate concentration (fig. 3)

The arterial concentration of 3-hydroxybutyrate increased almost continuously in all groups and reached a value about four to five times the preoperative concentration. The increase was significant ($P < 0.01$) at 4, 6, 12 and 24 h in group C, at 6, 12 and 24 h in group M and at 12 and 24 h in
group L. The only difference between groups was seen at 4 h, when groups L and M had smaller ($P < 0.01$) values than group C.

![Plots of FFA, glycerol, and 3-hydroxybutyrate concentrations over time](image)

**FIG. 3.** Plasma FFA, blood glycerol and 3-hydroxybutyrate concentrations (mean ± SEM) before and after cholecystectomy with general anaesthesia (GA) ( ), GA + extradural local anaesthetics ( ), and GA + extradural morphine ( ).

**Oxygen uptake (fig. 4)**

Oxygen uptake in group C was increased at 12 and 24 h ($P < 0.01$), and in group L at 6 and 24 h ($P < 0.05$). In group M, as a result of technical problems, only four observations were obtained before the operation. No differences were obtained between the three groups.

![Plot of oxygen uptake over time](image)

**FIG. 4.** Oxygen uptake (mean ± SEM) before and after cholecystectomy with general anaesthesia (GA) ( ), GA + extradural local anaesthetics ( ) and GA + extradural morphine ( ).

**DISCUSSION**

The increase in oxygen uptake by about 20% in the present study was slightly higher than that noted by Kinney (1983), but is in accord with the results of other workers after elective surgery (Renck, 1969; Wiklund, 1975; Rutberg et al., 1984b). Pain and relief of pain have been considered to be important factors influencing oxygen uptake in the period after operation (Wiklund, 1975). Although, in the present study, pain relief in both extradural groups was significantly better than in the control group, and the catecholamine concentrations were significantly depressed in the extradural local anaesthetic group, no difference in systemic oxygen uptake was obtained between the three groups. Thus, our results indicate that, in moderate surgical trauma, other factors than pain and catecholamines are involved in the increase in energy expenditure. Such factors could be other hormones or pyrogens.

In the following sections we will discuss first the metabolic response to trauma and the modification of this stress response by local anaesthetics, and then the effects of extradural morphine.

Adrenaline, cortisol and glucagon act synergistically to stimulate hepatic glucose output and counteract the suppressant role of insulin on hepatic glucose production (Gelfand, De Fronzo and Gusberg, 1983). These effects increase the blood glucose concentration and this is often used as a indicator of surgical stress. The magnitude of the hyperglycaemia
is proportional to the severity of the trauma (Clarke, 1970; Stoner et al., 1979; Traynor and Hall, 1981) and there is a continuous increase during surgery and immediately afterwards (Stjernström, Jorfeldt andWiklund, 1981). A maximal increase of 50% in the control group was noted in this study compared with a 14% increase in the extradural local anaesthetic group. This influence on blood glucose concentration by extradural local anaesthetics is of about the same magnitude as that described previously in the early period after operation (Bromage, Shibata and Willoughby, 1971), is slightly greater than that observed in the late peroperative period (Traynor et al., 1982), and is probably the result of adrenocortical and sympathoadrenergic suppression. In spite of considerably higher blood glucose concentrations following surgery in the control group, the serum insulin concentrations were similar. It is known that trauma decreases the insulin response to hyperglycaemia, probably as a result of α-adrenergic inhibition of β-cell function caused by the release of catecholamines (Halter and Pflug, 1980). Since the blood glucose concentration in the extradural local anaesthetic group was only slightly increased it was not possible, from our data, to evaluate whether the blockade and catecholamine concentrations influenced the insulin–glucose relationship. To clarify this point it would be necessary to study the insulin response to an infusion of glucose (Halter and Pflug, 1980).

Catecholamines, in particular, but also cortisol stimulate lipolysis and oppose the lipogenesis controlled by insulin. Although there are reports that indicate that these catabolic hormones are increased in the plasma after surgery, there is less consensus as to the influence of surgical trauma on fat metabolism (Hall et al., 1978; Kehlet et al., 1979; Stjernström, Jorfeldt andWiklund, 1981; Traynor et al., 1982; Asoh et al., 1983). This might result from different anaesthetic techniques and surgical procedures, as well as from varying times of sampling in relation to the operation. Although we found marked increase in both plasma FFA and blood glycerol concentrations in the control group, there was no significant change until 4 h after skin incision—that is more than 2 h after the end of surgery. At this time plasma cortisol and plasma catecholamine concentrations were still greater than normal (Rutberg et al., 1984a). It would be expected that there would be a decrease in lipolysis in the extradural local anaesthetic group because of the decrease in sympathoadrenergic stimulation. Certainly, in the present study plasma FFA concentration was significantly lower and blood glycerol concentration consistently but not significantly lower. This accords with the findings of Kehlet and colleagues (1979) and Asoh and co-workers (1983), but is in contrast to those of Traynor and colleagues (1982).

The results of the present study indicate that the suppressant effect of extradural local anaesthetics on the endocrine response after operation is accompanied by metabolic changes. The partial suppression of the endocrine response induced by extradural morphine was, however, only to a minor degree reflected by a decrease in the metabolic response to the trauma of cholecystectomy. Extradural morphine was unable to suppress significantly the postoperative increase in blood glucose concentration and this accords with the findings of Jørgensen, Andersen and Engqvist (1982). However, it is in contrast to those of Christensen and colleagues (1982), and Cowen and associates (1982), although Cowen and co-workers (1982) used extradural local anaesthetics during surgery and, furthermore, they used extradural diamorphine to provide pain relief after operation. Christensen and colleagues (1982), used morphine 4 mg before operation (as in this study), but at the end of surgery they gave another 4 mg. These differences in procedures might explain the discrepancy between our results and theirs. However, even though a higher dose of extradural morphine may suppress the hyperglycaemic response after surgery, its clinical value is debatable, since the risk of respiratory depression increases with increasing doses of extradural morphine (Rawal andWattwil, 1984).

The increases in blood or plasma concentrations of glucose, lactate, FFA and glycerol after trauma were suppressed considerably more by extradural local anaesthetics than by extradural morphine. This finding might be explained by the inability of extradural morphine to suppress adrenaline (Rutberg et al., 1984a) which, in this stress situation, is considered to be the prime active metabolic hormone. Furthermore, not only adrenaline but also direct activation of sympathetic nerves to the liver causes hepatic release of glucose (Järhult et al., 1979). These efferent sympathetic nerves to the liver can be blocked by extradural local anaesthetics (Bromage, Shibata and Willoughby, 1971). Extradural opiates, however, are not considered to have any sympathetic blocking effects (Bromage, Camporesi and Leslie, 1980).

Another plausible explanation for the lesser effect of extradural morphine on the metabolic response might be that the metabolic response to trauma,
once released, leads to persistent changes, even if afferent stimuli from the injured area are blocked later (Møller et al., 1982). It is well known that it is not possible to achieve surgical anaesthesia with extradural morphine. Therefore, it is possible that the hormonal release initiated by surgery evokes metabolic changes that persist despite the partial postoperative hormonal suppression by extradural morphine.

In conclusion, cholecystectomy induces significant increase in the concentrations of the catecholamines, cortisol, glucose, lactate, FFA, glycerol and 3-hydroxybutyrate. With the exception of 3-hydroxybutyrate, these concentrations increase to a peak in the early period after operation and then decrease rapidly. Extradural local anaesthetics can suppress considerably the catecholamine response and the increases in glucose, lactate, FFA and glycerol concentrations. Although extradural morphine provides pain relief comparable to that of extradural local anaesthetics, morphine is less efficient in decreasing the endocrine response to surgery, and has only a very minor influence on the metabolic response.

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REFERENCES