EFFECT OF EXTRADURAL ANALGESIA ON GLUCOSE METABOLISM AND GLUCONEOGENESIS

Studies in Association with Upper Abdominal Surgery

J. LUND, H. STJERNSTRÖM, L. JORFELDT AND L. WIKLUND

During lower abdominal surgery, extradural analgesia suppresses the metabolic response to surgery (Kehlet, 1982). During upper abdominal surgery extradural analgesia decreases the endocrine and metabolic changes (Rutberg et al., 1984; Hakansson et al., 1985) but is only fully effective when combined with splanchnic blockade (Tsuji et al., 1983). One consistent effect of extradural analgesia in relation to major abdominal surgery is the suppression of the increase in blood glucose concentration observed during the surgical procedure (Bromage, Shibata and Willoughby, 1971; Kossman et al., 1982; Seeling et al., 1982; Traynor et al., 1982; Asoh et al., 1983). The mechanism behind this decrease in blood glucose concentration may be a decrease in the splanchnic release of glucose, an increase in the peripheral uptake of glucose or a combination of both. If the lower glucose concentration is the result of a decrease in the hepatic release of glucose, there should be less need for an augmented splanchnic uptake of gluconeogenic substrates in this situation and, hence, nitrogen balance might be improved.

In previous studies we have found that the infusion of glucose at a constant rate (1 mmol min⁻¹) suppresses the splanchnic release of glucose (Stjernström, Jorfeldt and Wiklund, 1981a), but could not prevent the increased release of amino acids from the periphery (Lund et al., 1986). The aim of the present study was to investigate the splanchnic exchange of glucose and gluconeogenic substrates in patients given both thoracic extradural analgesia and an infusion of glucose during upper abdominal surgery.

SUMMARY
Concentrations of glucose and gluconeogenic substrates across the splanchnic circulation were studied in 20 patients undergoing cholecystectomy with general anaesthesia. In 10 patients, general anaesthesia was administered alone, and in 10 general anaesthesia was combined with thoracic extradural analgesia. All patients received a constant i.v. infusion of glucose. Blood glucose concentration increased markedly in the general anaesthesia group in contrast to a moderate and shortlived increase in the patients given extradural analgesia, in whom the splanchnic release of glucose tended to be lower. The splanchnic uptake of glycerol was lower in the patients given extradural analgesia, while the uptake of lactate and the increase in alanine uptake was similar in both groups. Plasma catecholamine and serum cortisol concentrations were higher in the group receiving general anaesthesia alone, while serum growth hormone concentration was higher after surgery in the extradural group. The addition of extradural blockade to general anaesthesia suppresses the increase in blood glucose concentration—and this may be related to a reduced splanchnic release of glucose combined with an increased peripheral uptake.

PATIENTS AND METHODS
Twenty patients undergoing elective cholecystectomy participated in the study. Informed consent and the approval of the Ethics Committee were obtained. All patients were healthy (except for their gallbladder disease) and in good nutritional condition. Throughout the study all received an i.v. infusion of glucose to a cubital vein at a constant rate of 1.1 mmol min⁻¹, the infusion...
beginning 30 min before the first measurements were obtained. Ten of the patients were given general anaesthesia combined with thoracic extradural analgesia (TE), while the other 10 patients, who served as a control group, received general anaesthesia only (GA). Data of the patients are given in Table I.

Measurements of splanchnic blood flow and of the arterio-hepatic venous differences for glucose, lactate, glycerol and alanine, of the venous concentrations of insulin, cortisol and growth hormone, and of the arterial concentrations of catecholamines were obtained at intervals (Table II).

**Anaesthesia**

After an overnight fast all patients received diazepam 10–15 mg by mouth and atropine 0.5 mg i.m. as premedication. In 10 patients, an extradural catheter was inserted (T6–7). Bupivacaine 0.5% plain was injected and pin-prick anaesthesia from T3 to L1–2 confirmed before general anaesthesia was induced. Regular additional doses of 0.5% bupivacaine plain were given every 60 min throughout the investigation. After general anaesthesia had been terminated, the extent of extradural anaesthesia was confirmed by pin-prick. In all patients, general anaesthesia was induced with thiopentone 5–7 mg kg⁻¹, droperidol 2.5–5 mg and fentanyl 0.1–0.2 mg, and was maintained with 70% nitrous oxide in oxygen and incremental doses of fentanyl i.v. Ventilation of the lungs was controlled by an Engström ECS 2000 ventilator. Ventilatory volumes were adjusted according to the Engström, Herzog and Norlander nomogram (Engström and Herzog, 1959). Pancuronium (0.1 mg kg⁻¹ initially) was administered to provide neuromuscular blockade.

**Fluid therapy**

Blood loss was calculated from the weight of the swabs, the volumes of blood withdrawn and the volume of blood in the suction jar. During the operation, dextran 70 was infused to replace blood lost. In addition to the constant infusion of glucose given to all patients, the extradural patients received approximately 500 ml of physiological saline to prevent undue hypotension. No vaso-pressors were given.

**Catheterization procedure**

A 2.0-mm Teflon catheter was introduced by percutaneous puncture of a cubital vein and its tip was advanced under fluoroscopic control to lie in a right-sided hepatic vein. A 1.0-mm catheter was inserted to a radial artery. The catheters were kept patent with physiological saline. Heparin was not used.

**Investigations**

Estimated splanchnic blood flow (ESBF) was determined according to the method of Caesar and others (1961) which is a modification of the original technique described by Bradley and colleagues (1945). Blood samples for assay of energy metabolites were taken in triplicate from the radial artery and the hepatic vein simultaneously and were deproteinized with ice-cold perchloric acid 3 mol litre⁻¹. The protein-free extract was frozen (−80°C) until analysis. The assays were performed by microfluorimetry: D-glucose by a modification of the hexokinase method described by Schmidt (1961) and Barthelmaj and Czok (1962); lactate, glycerol and alanine as described by Jorfeldt and Juhlin-Dannfelt (1977). Catecholamines in plasma were analysed by HPLC (Hallmann et al., 1978). Insulin, cortisol and growth hormone were analysed by radioimmunoassay.

**Statistical methods and presentation of data**

Blood flow and other data are given in relation to a body surface area of 1.73 m². The two-sample t test for unpaired data was used for analysis of differences between the two groups.
RESULTS

The two groups were similar with respect to age, body weight and body surface area (table I).

Hormone concentrations

Serum cortisol concentrations showed a rapid response to surgical stimulation, increasing by 300 nmol litre\(^{-1}\) in both groups (fig. 1). The concentration of adrenaline tended to increase more in the non-extradural group and the difference increased after the termination of anaesthesia (fig. 2).

There were no changes in plasma noradrenaline concentrations in the extradural group, in contrast to the GA group in whom the increase followed a pattern similar to that of adrenaline (fig. 3).

Insulin concentration increased in both groups, to reach a maximal value immediately after surgery, after which it tended to decrease (fig. 4).

Growth hormone increased similarly in both groups during surgery, but continued to increase and reached a significantly higher value in the early postoperative period in the extradural group (fig. 5).

![Fig. 1. Serum cortisol. O = Patients (n = 10) given general anaesthesia; • = patients (n = 10) given general anaesthesia + thoracic extradural analgesia. Mean ± SEM. Statistically significant differences between the groups: *P < 0.05.](image1)

![Fig. 2. Plasma adrenaline. O = Patients (n = 10) given general anaesthesia; • = patients (n = 10) given general anaesthesia + thoracic extradural analgesia. Mean ± SEM. Statistically significant differences between the groups: *P < 0.05.](image2)

![Fig. 3. Plasma noradrenaline. O = Patients (n = 10) given general anaesthesia; • = patients (n = 10) given general anaesthesia + thoracic extradural analgesia. Mean ± SEM. Statistically significant differences between the groups: *P < 0.05.](image3)
Metabolite concentrations (table III)

In the general anaesthesia group, the blood glucose concentration increased significantly during surgery and reached a maximal value in the early postoperative period, being unchanged 45 min later. The rate of increase was approximately 1.3 mmol litre⁻¹ h⁻¹. In the extradural group, the blood glucose concentration before surgery was approximately 1.3 mmol litre⁻¹ lower than the corresponding value in the other group. During surgery a small increase was found, but this returned to normal after surgery. The differences in blood sugar concentrations between the groups were significant at all measurement times.

Splanchnic glucose release was very low and statistically insignificant before surgery. During and immediately after surgery, the splanchnic release of glucose was, on average 0.15 mmol min⁻¹ greater in the general anaesthesia group, although this difference did not reach statistical significance.

Arterial concentrations of lactate before the onset of surgery were within normal limits and were similar in both groups. They increased by 70% in the general anaesthesia group, reached their greatest value during surgery and remained increased in the late postoperative period. In contrast, no significant change was found in the patients given extradural analgesia. The splanchnic uptake of lactate followed the same pattern in both groups. It increased during surgery, while the greatest uptake was found in the period immediately after operation. In the late postoperative period the uptake returned to its preoperative value.

The arterial concentrations of glycerol were significantly higher in the general anaesthesia group even before surgery. Values were essentially stable throughout the whole period of investigation in both groups—that is, arterial concentrations were consistently greater in the general anaesthesia group. The differences in arterial values were reflected in the splanchnic uptake of glycerol, which was significantly higher in the GA group.

The arterial concentrations of alanine did not differ significantly between the groups. In both
groups the highest values were recorded in the period immediately after operation. Throughout the investigation the arterial concentrations of alanine tended to be higher in the patients receiving the thoracic extradural. There were no differences between the groups concerning the splanchnic uptake of alanine which, after surgery, was 0.1 mmol min\(^{-1}\) greater than before surgery in both groups.

**DISCUSSION**

In patients undergoing upper abdominal surgery, and receiving an infusion of physiological saline only, we noted that the hyperglycaemic response to surgery was attributable to a slightly increased splanchnic release of glucose (1.1 mmol min\(^{-1}\)) in combination with a reduced peripheral uptake (Stjernström, Jorfeldt and Wiklund, 1981b). The intraoperative infusion of glucose at the same rate as the endogenous net splanchnic glucose production suppressed the splanchnic glucose release and resulted in a higher blood glucose concentration compared with patients given saline only. Intravenous glucose tolerance tests performed under general anaesthesia show a diabetes-like response in contrast to the normal response seen during lower abdominal surgery under extradural analgesia (Houghton et al., 1978).

It has been suggested that a more cephalad neural blockade, as in the present extradural group, could lead to an impaired glucose tolerance because of an inhibition of the pancreatic beta cell function. In the present study, patients given an infusion of glucose before and during cholecystectomy performed under general anaesthesia combined with thoracic extradural analgesia showed a small initial increase in blood glucose concentration which then tended to decrease during surgery and in the early postoperative period. The increase in arterial blood glucose concentration during surgery was less than half that of the control group.
receiving general anaesthesia alone. This would not indicate an impaired glucose tolerance in the patients given extradural blockade.

Local anaesthetic agents are known to influence splanchnic metabolism. The i.v. infusion of bupivacaine plain to healthy volunteers (resulting in blood concentration of the local anaesthetic four to five times higher than that obtained by extradural administration) demonstrated small effects on the blood glucose concentration and splanchnic glucose release (Wiklund and Jorfeldt, 1981). These effects were, however, opposite to the effects of bupivacaine given extradurally in the present study. Thus the ability to suppress the hyperglycaemic response to surgery seems to be the result of neural blockade.

The attenuated increase in arterial glucose concentration in the extradural group indicates a reduced production or an augmented peripheral uptake of glucose or a combination of both mechanisms. In the present study, no statistically significant difference in net splanchnic glucose production was found between the groups, but the extradural group tended to have a lower production before, during and immediately after the operation. Even small discrepancies between glucose production and uptake may, however, give rise to substantial increases or decreases in the arterial glucose concentration (Stjernström, Jorfeldt and Wiklund, 1981c). Thus the influence of thoracic extradural analgesia on the arterial concentration of glucose may be partly explained by a slight decrease in net splanchnic glucose production. The increase in blood glucose during surgery was about 22 μmol litre⁻¹ min⁻¹ in the control group and about 10 μmol litre⁻¹ min⁻¹ in the extradural group. Assuming a distribution volume for glucose corresponding to 25 % of the body weight, the diversion of glucose to this compartment during surgery would be 0.46 mmol min⁻¹ in the control group and 0.19 mmol min⁻¹ in the extradural group. During the same period the total supply of exogenous and endogenous glucose in the two groups averaged 1.30 mmol min⁻¹ and 1.19 mmol min⁻¹, respectively. Hence the calculated peripheral uptake of glucose would be 0.84 mmol min⁻¹ in the control group and 1.0 mmol min⁻¹ in the extradural group. This suggests that the neural blockade may also facilitate the peripheral uptake of glucose, in spite of lower arterial glucose and plasma insulin concentrations in the extradural group. The arterial concentration as well as the splanchnic uptake of glycerol was lower during extradural analgesia, indicating that the lipolytic response to surgery was suppressed by regional anaesthesia—a result which is in accord with other studies during upper abdominal surgery (Asah et al., 1983). A decrease in lipolytic activity may enhance peripheral glucose uptake, as muscular tissue otherwise prefers FFA and ketones (Newsholme, 1976). The increased lipolysis seen in the patients without regional blockade may be associated with greater sympathetic activity and increases in plasma catecholamine concentrations.

The increase in growth hormone normally seen during surgery is reported to be inhibited by neural blockade (Kehlet, 1982). In this study, growth hormone increased in both groups, but the increase was significantly greater at the end of surgery in the group with a thoracic extradural blockade. This finding, contrary to what was expected, may be related to the higher blood glucose concentrations in the patients receiving general anaesthesia only, as the secretion of growth hormone is normally suppressed by the infusion of glucose (Williams, 1968).

There was no increase in blood lactate concentration during surgery in the extradural group. This was not because of an increased splanchnic uptake of lactate in the extradural group, as the splanchnic lactate uptake tended to increase by the same extent in both groups. To a certain extent, the small increase in blood lactate concentration may be attributed to modest hyperventilation during anaesthesia. However, there were no differences between the groups in that respect, since Pco₂ and pH did not differ. Thus it seems that the suppression of sympathetic activity in the extradural group may have resulted in an inhibition of the muscular glycogenolytic response which otherwise leads to an increased peripheral release of lactate in this situation (Stjernström, Jorfeldt and Wiklund, 1981c).

An important question is whether regional analgesia can reduce protein losses associated with surgery. From studies of nitrogen balance after lower abdominal surgery, it has been claimed that extradural analgesia improves nitrogen balance (Brandt et al., 1978). However, nitrogen balance seems not to be affected by extradural analgesia during more extensive surgery (Seeling et al., 1982). This is in accord with the results of the present study where the splanchnic
uptake of alanine increased by 0.1 mmol min\(^{-1}\) in both groups and was unaffected by the provision of regional analgesia.

The splanchnic uptake of the gluconeogenic substrates lactate, alanine and glycerol did not correlate with the splanchnic glucose turnover as there was a significant uptake of the gluconeogenic substrates even when glucose was taken up. In the late postoperative period, the uptake of lactate returned to the preoperative value, while the splanchnic alanine uptake reached its highest values in both groups in this period. It is not possible in this study to draw any conclusions as to whether alanine is converted to glucose or stored as glycogen in this situation. However, there is a possibility that alanine might also be used in the synthesis of proteins, for example acute-phase proteins. In that case the splanchnic uptake of alanine and other amino acids from the periphery may be beneficial for patients if these substrates are not available from other sources.

ACKNOWLEDGEMENTS

Financial support was given by the Swedish Medical Research Council (Project No. 06579—Lars Wiklund; Project No. K84-17P-6353—Hans Stjernstrom; Project No. 04139—Lennart Jorfeldt).

REFERENCES


