EFFECT OF PATIENT-CONTROLLED ANALGESIA ON PLASMA CATECHOLAMINE, CORTISOL AND GLUCOSE CONCENTRATIONS AFTER CHOLECYSTECTOMY

I. W. MØLLER, K. DINESEN, S. SØNDERGÅRD, U. KNIGGE AND H. KEHLET

Postoperative pain constitutes one of the mechanisms involved in the endocrine-metabolic response to surgery [1].

Pain alleviation by extradural local anaesthetics reduces the stress response, especially during operations on the lower part of the body, while extradural opioids have only a minor effect, despite producing sufficient pain relief [1].

Patient-controlled analgesia (PCA) has been demonstrated to produce good pain relief [2, 3], but its effect on postoperative endocrine-metabolic changes remains unclear.

The purpose of this study was to investigate the influence of postoperative pain relief with PCA on postoperative changes in plasma catecholamine, cortisol and glucose concentrations.

PATIENTS AND METHODS

Sixteen otherwise healthy patients scheduled for elective cholecystectomy with subcostal incision were allocated randomly to postoperative pain treatment with either PCA (group I) or subcutaneous morphine on demand (group II) in a double-blind study. None of the patients was suffering from hormonal disease or receiving any medication. The study was approved by the Ethics Committee of Copenhagen municipal hospitals and written informed consent was obtained from each patient.

The patients were premedicated with oral diazepam 10 mg/70 kg 1–2 h before induction of anaesthesia. All operations began between 8 a.m. and 1 p.m. Anaesthesia was induced with thiopentone and intubation facilitated by suxamethonium 1–1.5 mg kg⁻¹. Anaesthesia was maintained with 0.5–1.5 % halothane and 67 % nitrous oxide in oxygen using a circle system. Muscle relaxation was achieved with intermittent doses of pancuronium, and incremental doses of fentanyl 0.05 mg were given i.v. not later than 45 min before the end of surgery.

In the recovery room all patients were given subcutaneous morphine 10 mg/70 kg. According to the randomization, group I (eight patients) received a continuous infusion of fentanyl 40.5
PATIENT-CONTROLLED ANALGESIA AND STRESS RESPONSE

µg/50 kg h⁻¹ plus boluses of 9 µg/50 kg controlled by the patient via a microprocessor-controlled infusion pump (Prominject, Pharmacia, Uppsala, Sweden). In addition, they received isotonic saline 0.5 ml s.c. on demand. Group II (eight patients) received isotonic saline via the infusion pump and subcutaneous morphine 10 mg/70 kg on demand in a volume equal to that for group I. Both groups received additional morphine 5 mg/70 kg s.c. on request, if pain relief was insufficient.

The patients received isotonic saline 10–15 ml kg⁻¹ h⁻¹ i.v. during the first 2 h and thereafter 1–2 ml kg⁻¹ h⁻¹. Intraoperative bleeding, which never exceeded 500 ml, was corrected by administration of isotonic saline 2.5 ml/ml of blood lost. None of the patients received blood transfusion or sympathomimetic agents.

Venous blood was obtained for measurement of cortisol, glucose, adrenaline and noradrenaline immediately before the first injection of morphine and again 2, 4, 6, 8, 10 and 12 h later.

Pain intensity was estimated using a 10-cm visual analogue scale (VAS) where 0 = no pain and 10 = unbearable pain.

Plasma cortisol concentrations were measured by a commercial radioimmunoassay (Kingo Diagnostics, Haslev, Denmark) and plasma glucose concentration by a routine glucose oxidase method. Plasma adrenaline and noradrenaline concentrations were measured by a radio-enzymatic technique [4]. Plasma was mixed with an equal volume of ice-cold perchloric acid 0.6 mol litre⁻¹ containing 0.1% EGTA and centrifuged. The supernatant was frozen at −20 °C until required for assay. The sensitivity of the assay was 10–20 pg ml⁻¹. The intra-assay coefficients of variations for noradrenaline and adrenaline were 6.8 and 4.3%, respectively, and the interassay coefficients of variation 14.8 and 12.3%, respectively. The plasma concentrations of noradrenaline and adrenaline in normal resting subjects were 305 ± 101 pg ml⁻¹ (mean ± SD) and 87 ± 20 pg ml⁻¹ (n = 15), respectively.

ECG and heart rate were displayed continuously on an oscilloscope and arterial pressure was monitored intermittently by sphygmomanometry.

Statistical analysis was performed using the Wilcoxon test for intragroup variation and the Mann-Whitney test for intergroup variation. P values less than 0.05 were regarded as significant.

RESULTS

Mean age was lower in group I (56 ± 4 yr v. 67 ± 4 yr, P < 0.05). Patient weight (group I 66 ± 4 kg, group II 74 ± 4 kg (mean ± SEM)) was similar in the two groups, as was duration of surgery (group I 86 ± 10 min, group II 89 ± 9 min). Mean arterial pressure was not significantly different between the two groups at any stage.

The amounts of fentanyl used during operation (group I 0.14 ± 0.09 mg, group II 0.10 ± 0.06 mg) were not statistically different. The amount of fentanyl used after operation in group I varied from 434 to 1231 µg (mean 819 µg) and only one patient asked for additional morphine (10 mg). In group II the mean dose of morphine received in this period was 13 mg (range 0–40 mg).

The mean pain intensity score was significantly

![FIG. 1. Pain intensity scores (arbitrary units) (mean ± SEM) after cholecystectomy in patients given PCA with fentanyl (O—O) (n = 8) or morphine on request (●—●) (n = 8). *P < 0.05.](image-url)
lower in group I (PCA) from 2 to 12 h after operation (fig. 1).

Plasma cortisol concentrations were identical at the start of analgesic treatment and increased after operation in both groups, but were significantly lower from 4 to 12 h after operation in group I compared with group II (fig. 2). Plasma glucose concentrations were similar in the two groups and remained unchanged throughout the study (fig. 2).

Plasma concentrations of adrenaline were similar and constant in both groups (fig. 3). Plasma noradrenaline concentrations were also constant throughout the study, but those in group I were significantly less than in group II 6 h after operation (fig. 3).

DISCUSSION
The release mechanisms involved in the endocrine metabolic response to surgery are predominantly afferent neurogenic stimuli, although various, mostly unknown humoral substances also contribute [1]. The role of specific pain stimuli in releasing various aspects of the stress response has not been clearly evaluated, but it is well documented that pain per se, either during acute experimental pain or in patients with chronic pain, leads to an endocrine metabolic response [1].

The effect of intraoperative systemic administration of opioids on the surgical stress response is well documented [5]. Thus high-dose intraoperative opioid anaesthesia inhibits the intra- and initial postoperative endocrine metabolic changes to abdominal surgery [6—8], but this attenuation does not extend into the later postoperative period from 4 to 9 h [9].

Studies on postoperative pain relief with single-dose injection of various opioids have shown either no effect or only slight attenuation of the stress response. Thus buprenorphine 0.3 mg i.m.
and i.v. produce only a slight reduction in plasma cortisol and glucose concentrations [10] and meptazinol 100 mg or morphine 15 mg i.m. failed to diminish the stress response [11].

The normal postoperative increase in oxygen consumption was either unaltered [12] or inhibited [13] following pain relief with small doses of morphine and pethidine, respectively. In contrast, a single dose of fentanyl 3.5 μg kg⁻¹ administered immediately after operation reduced systemic oxygen uptake and splanchnic release of glucose and 3-hydroxybutyrate [14, 15].

Patient controlled analgesia has been shown to be an effective technique for postoperative pain relief [2, 3, 16], and our results confirm this and have shown, in addition, that PCA with i.v. fentanyl has no major effect on the surgical stress response. Only the plasma cortisol response was affected, and the extent of attenuation was small. These results may not be unexpected, since the dose of morphine necessary to reduce the intraoperative stress response is approximately 2–4 mg kg⁻¹ and that for fentanyl is 30 μg kg⁻¹ [1].

Our results are also consistent with the observations during postoperative pain relief by administration of extradural opioids. Extradural or intrathecal morphine [17–20] or extradural diamorphine [21, 22] had no important effect on various endocrine-metabolic variables despite producing improved pain relief. Furthermore, extradural morphine 4 mg every 12 h for 72 h after abdominal surgery had no effect on urinary excretion of cortisol, adrenaline, noradrenaline and nitrogen, either on separate days or cumulatively over 4 days, neither did pain scores correlate with urinary excretion of stress hormones [23].
Thus all studies using either systemic or extradural administration of opioids in doses applicable to postoperative use in patients breathing spontaneously have demonstrated either no or only a slight effect on the surgical stress response. This is emphasized by the present study, where optimal pain alleviation using PCA with i.v. fentanyl also failed to reduce the stress response to any major extent following cholecystectomy.

REFERENCES


