HIGH- AND LOW-DOSE FENTANYL ANAESTHESIA: HORMONAL AND METABOLIC RESPONSES DURING CHOLECYSTECTOMY

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Trauma triggers a hormonal–metabolic response, cardiovascular stimulation [1] and augmented breakdown of muscle protein [2]. The degree of stress may be evaluated by measuring hormonal and metabolic responses [3—9]. It has been documented that the hormonal changes may have profound effects on metabolic homeostasis, circulatory haemodynamics, immune competence, renal homeostasis and gastrointestinal physiology in addition to behavioural effects on patients undergoing surgery (8). However, it is still not clear if it is beneficial to attenuate these stress responses in patients undergoing surgery [10].

High-dose fentanyl anaesthesia (HFA) has been shown to reduce substantially the hormonal and metabolic responses to open heart surgery before cardiopulmonary bypass [11–13]. In a few studies on abdominal surgery, suppression of cortisol and glucose responses were observed during HFA [3, 14, 15], but more complete information on hormonal–metabolic changes is lacking.

In a preceding study [16] we described large differences in circulatory and catecholamine responses during standardized abdominal surgery undertaken with HFA and a balanced neuroleptanalgesic technique (BLA). The aim of the present study was to elucidate further the hormonal and metabolic events occurring in the same category of patient. In order to achieve this we have measured a large number of hormones and metabolites at defined points during anaesthesia and surgery.

PATIENTS AND METHODS

The study was approved by the Ethics Committee of the Karolinska Institute and informed consent was obtained from each patient. Twelve patients were studied during cholecystectomy (table I). The patients were not receiving any medication and their preoperative haemoglobin, creatinine and electrolyte values were within normal limits.
No patient had a history of cardiovascular disease and preoperative ECG and physical examinations were normal. They were allocated randomly to two groups of six, one receiving high-dose fentanyl anaesthesia (HFA) and the other balanced fentanyl anaesthesia (BLA).

### Anaesthesia

All patients were given morphine 0.15 mg kg\(^{-1}\) i.m. 1 h before surgery and atropine 0.5 mg and diazepam 0.1 mg kg\(^{-1}\) i.v. immediately before induction of anaesthesia. In the HFA group fentanyl was given as a loading dose of 100 µg kg\(^{-1}\) over 1–2 min. In the BLA group anaesthesia was induced with thiopentone 4–5 mg kg\(^{-1}\) and fentanyl 5 µg kg\(^{-1}\) and maintained with a continuous infusion of fentanyl 3 µg kg\(^{-1}\) h\(^{-1}\). In both groups, neuromuscular blockade was obtained with pancuronium 0.1 mg kg\(^{-1}\).

After tracheal intubation, the patient’s lungs were ventilated using a Siemens—Elema Servo-ventilator 900 B with 67 % nitrous oxide in oxygen and normocapnia maintained as assessed by repeated blood-gas analysis.

### Procedure

Lactated Ringer’s solution was infused i.v. at a rate of 200 ml h\(^{-1}\) through a peripheral i.v. cannula. The left radial artery was cannulated using a 20-gauge Teflon catheter and systemic arterial pressure measured using a pressure transducer (Bentley) and a Kontron 128A monitor. Heart rate was obtained from the ECG.

Arterial blood samples for determination of glucose, glycerol, FFA, beta-hydroxy-butyrate, insulin, c-peptide, glucagon, HGH, cortisol and adrenaline concentrations were obtained: (1) before induction of anaesthesia, at least 15 min after completion of catheterization; (2) after induction of anaesthesia; (3) immediately before skin incision after 15–30 min of anaesthesia; (4) at the start of surgery; (5) during surgical exploration of the gall bladder; (6) after 10 min without surgical stimulation; (7) 5 min after surgery had been resumed. Systemic arterial pressure and heart rate were also recorded at these times.

All blood loss was replaced with twice the volume of lactated Ringer’s solution. No patient lost more than 500 ml of blood (including sampling loss).

Blood glucose concentration was determined by a glucose oxidase method. Blood samples for catecholamines, glycerol, beta-hydroxy-butyrate, FFA, HGH, insulin and c-peptide were chilled in heparinized tubes, centrifuged and stored at -70 °C until analysis. Glycerol and beta-hydroxy-butyrate were determined enzymatically and FFA by a radiochemical assay [17-19].

Human growth hormone, insulin and c-peptide were measured by radioimmunoassay methods [20-23]. The catecholamines were separated by high performance liquid chromatography and quantified by electrochemical detection [24]. Serum for cortisol analysis was frozen for later determination by radioimmunoassay [25]. For glucagon analysis, 2 ml of blood was pipetted immediately into tubes with EDTA and aprotinin 0.1 ml (Trasylol, Bayer). After centrifugation, plasma was frozen until analysis by radioimmunoassay [26, 27].

The coefficients of variation for the various assays are listed in table II.

### Statistics

Differences within and between the two groups of patients were subjected to analysis of variance according to the method described by Kirk [28]. The variances of the measurements were found to vary with their values, and thus the logarithms of the values were used in analysis. Sampling times (1), (5), (6) and (7) were compared within and between the groups. These points were chosen as
(1) represents the initial level, and (5), (6) and (7) values during surgery.

RESULTS

Unless otherwise stated, the succeeding data are the averages in each group at different sampling times.

Adrenaline (fig. 1)

Induction of anaesthesia was associated with a reduction in plasma adrenaline concentrations in both groups. In the HFA group, the concentrations decreased significantly after induction of anaesthesia ($P < 0.01$) and remained low during surgery. In the BLA group the initial decline was

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**Fig. 1.** Plasma concentrations of adrenaline (nmol litre$^{-1}$) at the sampling times defined in the text. Bars represent SEM. □ = BLA; ● = HFA.

**Fig. 2.** Plasma concentrations of cortisol (nmol litre$^{-1}$) at the sampling times defined in the text. Bars represent SEM. □ = BLA; ● = HFA.
not significant, but the mean concentration increased sharply after skin incision. During the pause in the operation (sample time (6)) it declined, and increased again during active surgery. The difference between the two groups was significant for sample times (5) and (7) ($P < 0.001$).

Cortisol (fig. 2)

Plasma cortisol concentration decreased after induction of anaesthesia. Onset of surgery was associated with a significant increase ($P < 0.01$) in the BLA group, but not in the HFA group. The difference between the two groups was significant at sample times (6) and (7) ($P < 0.001$).

Glucose (fig. 3)

After an initial increase in the HFA group, blood glucose concentrations declined in both groups. The reduction in the BLA group between sample times (1) and (5) was significant ($P < 0.05$). During surgery, the concentration increased significantly ($P < 0.01$) from (5) to (7) in

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**FIG. 3.** Plasma concentrations of glucose (mmol litre$^{-1}$) at the sampling times defined in the text. Bars represent SEM. □ = BLA; • = HFA.

**FIG. 4.** Plasma concentrations of free fatty acids (FFA) (mmol litre$^{-1}$) at the sampling times defined in the text. Bars represent SEM. □ = BLA; • = HFA.
HORMONAL AND METABOLIC RESPONSES TO FENTANYL

the BLA group. There were no significant differences between the two groups.

**FFA (fig. 4)**

The concentrations of FFA declined significantly \( (P < 0.01) \) between sample times (1) and (5) for both groups. The subsequent increase during surgery was significant \( (P < 0.01) \) between (5) and (6) for both groups. There were no significant differences between groups.

**Beta-hydroxy-butyrate (fig. 5)**

In both groups the beta-hydroxy-butyrate concentrations decreased significantly \( (P < 0.01) \) between sample times (1) and (5). After onset of operation the concentrations increased signifi-

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**Fig. 5.** Plasma concentrations of beta-hydroxy-butyrate \( (\beta\text{-OH-Butyrate}) \) \( (\text{mmol litre}^{-1}) \) at the sampling times defined in the text. Bars represent SEM. □ = BLA; ● = HFA.

**Fig. 6.** Plasma concentrations of human growth hormone \( (\text{HGH}) \) \( (\mu \text{g litre}^{-1}) \) at the sampling points defined in the text. Bars represent SEM. □ = BLA; ● = HFA.
BRITISH JOURNAL OF ANAESTHESIA

DISCUSSION

In recent years there has been considerable increase in understanding of the metabolic pathways of importance to the anaesthetist [6–8, 10, 29–31]. As yet there is no anaesthetic technique which effectively inhibits the stress response associated with upper abdominal surgery. Although HFA greatly attenuates this stress response, it is not generally applicable as the postoperative respiratory depression produced requires intensive care resources.

Kehlet [6] has shown that the stress response to lower abdominal surgery may be blocked by extradural anaesthesia and Shirasaka [32] has shown that splanchnic nerve block in one group of patients undergoing upper abdominal surgery produced approximately the same attenuation of the hormonal response as did high extradural block in a second group. However, there was a marked increase in cortisol, glucose and FFA from preoperative to intraoperative values in both groups.

Lacoumenta and his colleagues [33] attempted to establish whether or not high inspired concentrations of volatile anaesthetics inhibited the hormonal–metabolic response to the same degree as fentanyl. They found no difference between halothane anaesthesia at MAC 1.2 or 2.1 and fentanyl anaesthesia. Another study by Lacoumenta’s group [34] showed that sufentanil caused reduction in the hormonal–metabolic response approximately equivalent to that with high-dose fentanyl. In this study, there was also no difference between a sufentanil dose of 10 and 20 μg kg⁻¹.

Anand and his colleagues [35, 36] studied premature babies undergoing thoracic surgery. One group received only nitrous oxide, and the other group fentanyl in addition. The latter group showed an attenuated hormonal–metabolic response and a lower frequency of postoperative complications.

In our study we used a high dose of fentanyl, in combination with diazepam and nitrous oxide as there is one report of patient awareness during this type of anaesthesia without diazepam [37]. Nonetheless, some patients promptly opened their eyes directly after surgery and following administration of neostigmine and atropine. However, none of our patients reported awareness during anaesthesia, and there were no complications in connection with the study.
HORMONAL AND METABOLIC RESPONSES TO FENTANYL

581

The hormonal and metabolic changes during surgery in the BLA-group are similar to those occurring during stress. With most general anaesthetic techniques major surgery induces a comparable response [3, 6, 7]. In a previous study we reported that the release ofnoradrenaline and, even more that of adrenaline, in response to surgery was inhibited by HFA, and was associated with reduced arterial pressure and rate-pressure product compared with BLA [16]. In the present study almost all hormones displayed a tendency towards greater variation during anaesthesia and surgery in the BLA than the HFA group.

Glycerol, FFA and beta-hydroxy-butyrate were increased initially, probably because of preoperative starvation (12 h). In contrast to FFA and beta-hydroxy-butyrate, glycerol did not vary during anaesthesia and surgery. This is somewhat surprising, but may result from a faster turnover rate to glucose from glycerol than FFA. It is also surprising that there was a significant increase for HGH in the BLA group, even though the patients were given atropine before surgery. As atropine attenuates release of HGH there may have been an even higher concentration of this catabolic hormone with a different premedication [34].

We conclude that HFA suppresses the hormonal and metabolic responses to surgical trauma, and subsequently lessens the catabolic effects of the anaesthetic regimen.

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