HORMONAL RESPONSES TO HIGH-DOSE FENTANYL ANAESTHESIA
A study in patients undergoing cardiac surgery

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SUMMARY
The hormonal responses to anaesthesia and cardiac surgery were studied in 20 patients. Ten patients were anaesthetized with fentanyl 60 μg kg⁻¹ and nitrous oxide in oxygen and 10 with etomidate 0.3 mg kg⁻¹ and nitrous oxide in oxygen plus halothane. There were no significant changes in cortisol, growth hormone or insulin concentrations in response to surgery in either group, although cortisol concentrations decreased during cardiopulmonary bypass. Both groups showed increases in prolactin concentrations. Patients anaesthetized with etomidate and halothane showed a significant increase in adrenaline and glucose concentrations not seen in the fentanyl group. Cardiopulmonary bypass was associated with marked increases in catecholamines in both groups.

Fentanyl 50–100 μg kg⁻¹ has been shown to produce adequate anaesthesia with minimal changes in cardiovascular dynamics in patients undergoing cardiac surgery (Stanley and Webster, 1978) and, when used as a supplement (50 μg kg⁻¹) to thiopentone, nitrous oxide and oxygen, will decrease the metabolic and hormonal responses to gynaecological surgery (Hall et al., 1978). Although the effects of surgery on the antidiuretic hormone are suppressed by fentanyl, those of patients with severe coronary artery disease undergoing surgery. We have studied the hormonal and metabolic responses to fentanyl 60 μg kg⁻¹ used as an anaesthetic for cardiac surgery and compared them with an anaesthetic technique not using narcotic analgesics.

PATIENTS AND METHODS
Twenty patients undergoing cardiac surgery involving cardiopulmonary bypass were studied.

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>Valves</th>
<th>Coronary + CA</th>
<th>Aneurysm + CA</th>
</tr>
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<tbody>
<tr>
<td>Fentanyl group</td>
<td>1</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Etomidate/halothane group</td>
<td>1</td>
<td>7</td>
<td>2</td>
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Those patients scheduled for coronary artery grafts were all receiving beta-blocking drugs and nitrates for the control of angina pectoris and those undergoing valve replacements were receiving digoxin and diuretics to control congestive cardiac failure. All medication, except nitrates, was discontinued the evening before surgery. Details of the patients and type of operation are shown in Table I.

All patients were premedicated with lorazepam 4 mg orally 1.5 h before the scheduled time of operation. In the operating theatre, two peripheral infusions, a radial artery cannula and a wide-bore central venous catheter (via external jugular vein) were inserted under local anaesthesia. E.g. electrodes were applied.
The patients were randomly divided into two groups of 10 patients each. In the first (fentanyl) group, anaesthesia was induced with fentanyl 60 \( \mu g \) kg\(^{-1} \) i.v. over a 2-min period and continued with 50% nitrous oxide in oxygen. In the second (halothane) group, anaesthesia was induced with etomidate 0.3 \( mg \) kg\(^{-1} \) and continued with 50% nitrous oxide in oxygen and halothane as required. Both groups received pancuronium 8 mg to produce neuromuscular blockade. Respiration was assisted and then controlled manually using a face-mask. Five minutes after induction of anaesthesia, the trachea was intubated and thermocouple probes inserted into the oesophagus, nasopharynx and triceps muscle to monitor body temperature. A nasogastric tube was inserted and the bladder catheterized. During anaesthesia, ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 4.5–5%. An arterial blood sample was taken within 30 min of induction for blood-gas analysis and served as an assessment of the adequacy of ventilation.

Cardiopulmonary bypass was conducted using a Polystan Rygg–Kyvsgaard 5000 bubble oxygenator with moderate hypothermia (24 °C) and haemodilution to a haematocrit of 20–25%. Pump flow was maintained at 55 ml kg\(^{-1} \) min\(^{-1} \). The carbon dioxide concentration in the expiratory vent of the oxygenator was kept at a constant 6%, corresponding to \( Pa_{CO_2} \) 6 kPa.

In the fentanyl group, fentanyl 1 mg was added to the pump prime immediately before the start of bypass. In the halothane group, 0.5% halothane was added to the oxygenator throughout the period of bypass. Venous blood samples were withdrawn from the central venous catheter. Sampling times are shown in table II. From each blood sample a 5-ml aliquot of blood (for adrenaline, noradrenaline and dopamine assay) was added to a tube containing glutathione and EGTA (ethylene-glycol-bis (\( \beta \)-aminoethyl)-N,N' tetraacetic acid) and the tube placed in an ice-water bath. The sample was immediately centrifuged using ice-filled centrifuge cups and the plasma placed in a screw-topped plastic container which was frozen to \(-26^\circ C\) and stored until assayed. Ten millilitre of blood was injected into a lithium–heparin tube (for measurement of the concentrations of insulin, growth hormone cortisol and prolactin), centrifuged and the plasma stored at \(-26^\circ C\). In the fentanyl group 10 ml of blood was taken into a lithium–heparin tube before bypass and 15 min on bypass for the estimation of plasma fentanyl concentration. Two millilitre of blood was added to a tube containing potassium oxalate and sodium fluoride and immediately analysed for blood glucose concentration.

All assays were carried out in duplicate. Glucose was measured with an IL 919 blood glucose analyser (Instrumentation Laboratories) using a modification of the glucose oxidase/peroxidase method (Trinder, 1969). Insulin, growth hormone, cortisol and prolactin concentrations were measured by standard radioimmunoassay techniques (Peake, 1974; Starr and Rubenstein, 1974; Assies, Schellekens and Touber, 1978; Thijssen, van den Berg and Adlercreutz, 1980). The concentrations of the catecholamines were estimated by radio enzyme assay using a modification of the method described by Peuler and Johnson (1977). Plasma fentanyl concentration was measured by radioimmunoassay (Michiels, Hendriks and Heykants, 1977). Data are presented as mean values ± SEM. Statistical analysis was carried out using analysis of variance. A modified \( t \) test was used to identify significant differences from control values using critical values for \( P \) calculated according to the method of Bonferroni (Wallenstein, Zucker and Fleiss, 1980). The plasma fentanyl concentrations were compared using a paired \( t \) test.

### RESULTS

#### Control values

All control values were within the normal laboratory range except for three patients. One patient had an insulin concentration of 30 \( mu. \) litre\(^{-1} \) (normal range 5–25 \( mu. \) litre\(^{-1} \)) which decreased to 16 \( mu. \) litre\(^{-1} \) immediately after induction and did not increase beyond 18 \( mu. \) litre\(^{-1} \). Two patients in the fentanyl group had cortisol concen-
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Concentrations of 0.68 and 0.69 μmol litre⁻¹ (normal range 0.16–0.65 μmol litre⁻¹), both of which were within the normal range by the time of incision.

Glucose (fig. 1)

In the fentanyl group, there were no significant changes in blood glucose concentration at any time. In the patients anaesthetized with etomidate and halothane, there was a highly significant change in blood glucose concentration ($F = 6.373; P < 0.005$). Compared with control values, the differences were highly significant at samples 6, 7 and 8 ($P < 0.005$).

Insulin (fig. 2)

The changes in blood glucose concentration were not reflected by insulin suppression. In the period before bypass the insulin concentrations were not significantly different from control values. No insulin results are available from the period during cardiopulmonary bypass since the assay showed "negative" insulin concentrations. These result from some interference with the assay method, possibly by "Haemaccel", which was used in the prime. This phenomenon is being further investigated.

Cortisol (fig. 3)

Cortisol concentrations decreased after induction in both groups although the difference was only significant ($P < 0.01$) at 15 min on bypass in the fentanyl group and was significant ($P < 0.01$) for both samples on bypass in the halothane group. These significant reductions may have been caused by haemodilution.

Growth hormone (fig. 4)

There were no significant variations in growth hormone concentrations in either group at any time. No insulin results are available from the period during cardiopulmonary bypass since the assay showed "negative" insulin concentrations.
time in the period of the study. The values in the fentanyl group were smaller throughout, but the control value was also lower than in the halothane group.

**Prolactin (fig. 5)**

Prolactin concentrations increased in both groups, to three times control in the halothane group and five times in the fentanyl group. The concentrations decreased markedly on cardiopulmonary bypass, probably as a result of haemodilution.

![Graph of Prolactin concentrations](image)

Fig. 5. Change in plasma prolactin concentration (μg litre\(^{-1}\)) (mean±SEM). Sample times as in table II. Fentanyl = •; halothane = O; *P<0.05.

**Catecholamines before bypass (figs 6, 7, 8)**

Induction of anaesthesia with fentanyl was associated with a decrease in plasma catecholamine concentrations, although this did not reach significance. In the halothane group, the adrenaline concentrations increased, but became significant only just before bypass in sample 6 (P<0.005).

![Graph of Adrenaline concentrations](image)

Fig. 6. Change in plasma adrenaline concentration (pg ml\(^{-1}\)) in the period before cardiopulmonary bypass (mean±SEM). Sample times as in table II. Fentanyl = •; halothane = O; *P<0.05.

Noradrenaline concentrations in this group varied widely. In the period before bypass there were no significant changes in dopamine concentrations, although the trend was for the halothane group to be greater.

**Catecholamines during cardiopulmonary bypass (fig. 9)**

Cardiopulmonary bypass was associated with marked increases in plasma catecholamine concentrations. In the fentanyl group these were highly significant (P<0.001) for adrenaline, noradrenaline and dopamine at 1 h on bypass. In the patients anaesthetized with halothane there was a highly significant increase (P<0.005) in adrenaline in both samples during bypass.

![Graph of Catecholamines during bypass](image)
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Noradrenaline was significantly increased \((P<0.001)\) at 1 h on bypass but not at 15 min. Dopamine was significantly increased \((P<0.05)\) at 15 min on bypass but not at 1 h.

**Fentanyl**

The mean plasma fentanyl concentration before cardiopulmonary bypass was 20.6 \((\pm 1.53)\) ng.ml\(^{-1}\) and at 15 min on bypass was 16.2 \((\pm 0.70)\) ng.ml\(^{-1}\), a significant decrease \((P<0.005)\).

**DISCUSSION**

The neuro-endocrine response is part of the human physiological response to stress (Cannon, 1929). However, this physiological response may have adverse effects on a patient undergoing surgery by increasing the work of the heart and the catabolism of protein (Savege, 1978).

It is possible to modify the neuro-endocrine response to surgical stress by interrupting the afferent pathways by local anaesthetic techniques (Newsome and Rose, 1971). Large doses of morphine have been shown to modify the response to surgery: morphine 1–4 mg kg\(^{-1}\) will obtund the increases in plasma cortisol and growth hormone concentrations seen during surgery (George et al., 1974). However, an anti-diuretic hormone response remained during morphine anaesthesia (Philbin et al., 1976). Morphine also produced significant increases in plasma adrenaline and noradrenaline concentrations which correlate with increases in arterial pressure and heart rate (Hasbrouk, 1970). Therefore, morphine anaesthesia modifies, but does not abolish, the endocrine response to surgery.

We have shown that fentanyl 50–70 \(\mu g\).kg\(^{-1}\) produces deep surgical anaesthesia (Sebel et al., 1980). Stanley and colleagues have shown in various studies that anaesthesia with fentanyl 50 \(\mu g\).kg\(^{-1}\) was an improvement on morphine, producing a high degree of cardiovascular stability (Stanley and Webster, 1978; Lunn et al., 1979; Stanley, Philbin and Coggins, 1979). Hall and co-workers (1978) showed that fentanyl 50 \(\mu g\).kg\(^{-1}\), compared with halothane as a supplement to anaesthesia, significantly decreased the metabolic and endocrine responses to surgery in young healthy women undergoing tubal surgery. They found that fentanyl abolished the hyperglycaemic response to surgery seen during halothane anaesthesia and the findings of our study are in agreement with this observation. However, we were unable to demonstrate the difference between cortisol and growth hormone responses seen in that study. The patients who received halothane in Hall’s study showed a marked increase in both plasma growth hormone and cortisol concentrations, whereas the patients who received fentanyl showed no change. We were unable to demonstrate any significant change in growth hormone concentrations in either group. In both our groups, the concentration of cortisol decreased.
significantly although the decrease was more marked in the fentanyl group. The decrease in cortisol seen in both groups during cardio-pulmonary bypass may have been a result of haemodilution. The explanation for the difference in response is probably not related to surgical stress, cardiac surgery being more “stressful” than tubal surgery. It is more likely to be a result of differences in patient groups or premedication. Our patients were older, with pre-existing cardiac disease and were all taking medication including beta-blocking drugs, which may affect endocrine responses.

Although beta-blocking drugs were discontinued on the evening before surgery, in both groups of patients sufficient residual beta blockade may have existed to affect glucose and fat metabolism. No attempt was made during the study to assess the degree of residual blockade that existed on the morning of surgery, although it is likely to have been comparable in the two groups. Because of the problem of residual beta blockade, it is impossible to extrapolate the results of this study to other groups of patients not taking beta blockers. This does not limit the validity of the results with respect to patients undergoing coronary artery surgery, as a very high proportion of these patients will be taking beta blockers. Stanley and others (1980) have reported marked reductions in cortisol concentrations in response to fentanyl anaesthesia. Their patients were not taking beta blockers.

Their patients were older, with pre-existing cardiac disease and were all taking medication including beta-blocking drugs, which may affect endocrine responses.

Prolactin concentration increases fivefold during anaesthesia and surgery, although its significance as part of the stress response is uncertain (Noel et al., 1972). The increase in prolactin concentration may alter the myocardial response to catecholamines and cause tachycardia and arrhythmias (Manku, Nassar and Horrobin, 1973). In our series both groups of patients showed a significant increase in prolactin concentration in the period before bypass period. Prolactin was the only hormone that increased significantly during that period in the fentanyl group. Opiates are known to have a direct stimulating effect on prolactin secretion (Clemens and Shaar, 1980), which may explain the changes seen in this group.

Van der Vusse and others (1979) have shown that fentanyl decreases the energy demand of artificially-induced ischaemic myocardium in dogs and suggested that this is the result of the negative chronotropic effect of fentanyl. We suggest that a decrease in catecholamine secretion may be responsible also. In our study the decrease in catecholamine concentrations did not reach significance, but Stanley and others (1980) found highly significant reductions in both adrenaline and noradrenaline concentrations. Therefore, fentanyl may be beneficial in decreasing myocardial work and thus oxygen requirement. This is important in patients with severe coronary artery disease in whom coronary blood flow is limited. Stanley and co-workers (1980) showed that cardiopulmonary bypass was associated with marked increases in catecholamine concentrations. Following a bolus injection of fentanyl 60 μg kg⁻¹ the plasma fentanyl concentration decreases by about 50% at the start of cardiopulmonary bypass (Bovill and Sebel, 1980). Despite maintaining plasma fentanyl concentrations close to prebypass values (20.6 (± 1.53) ng ml⁻¹ compared with 16.2 (± 0.70) ng ml⁻¹), we were unable to eliminate the changes in the concentrations of the catecholamines during cardiopulmonary bypass.

Cardiopulmonary bypass, with non-pulsatile flow, haemodilution and hypothermia is an extremely non-physiological state. Whilst we suspect that it may be possible to modify the endocrine responses to this situation by achieving sufficiently high plasma concentrations of fentanyl, it is likely that this would result in unacceptable respiratory depression following operation.

No attempt has been made to continue the study after cardiopulmonary bypass since there are many uncontrollable factors during this period. Such a study, of the longer term effects of “high-dose” fentanyl anaesthesia, would be more appropriate in non-cardiac major surgery. Therefore, we conclude that anaesthesia with fentanyl 60 μg kg⁻¹ causes a significant decrease in the concentrations of the circulating catecholamines and abolition of hyperglycaemic response to surgery in the period before bypass. This is not maintained during cardiopulmonary bypass.
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HORMONALE REAKTIONEN AUF NARKOSE MIT Hohen Dosen von Fentanyl
Eine Studie an Patienten, die sich Herzoperationen unterziehen

ZUSAMMENFASSUNG

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RESPUESTAS HORMONALES A LA ANALGESIA POR FENTANILo EN DOSIS ALTAS
Un estudio con pacientes sometidos a cirujia cardiaca

SUMARIO
Se estudiaron en 20 pacientes las respuestas hormonales a la anestesia y cirujia. Diez de los pacientes fueron anestesiados con 60μg kg⁻¹ de fentanilo y oxido nitroso en oxigeno y 10con 0,3 mg kg⁻¹ de etomidato y oxido nitroso en oxigeno más halotano. No hubo cambios significativos en las concentraciones de cortisol, crecimiento hormonal o de insulina, como respuesta a operaciones quirurjicas en cualquiera de los grupos, aunque las concentraciones de cortisol disminuyeron durante el desvio cardiovascular. Ambos grupos mostraron un incremento en las concentraciones de prolactina. Los pacientes anestesiados con etomidato y halotano, mostraron un incremento significativo en las concentraciones de adrenalin y de glucosa que no se presentaron en el grupo de fentanilo. El desvio cardiovascular se asoció; en ambos grupos, con un marcado incremento de catecolaminas.