HIGH- AND LOW-DOSE FENTANYL ANAESTHESIA: CIRCULATORY AND PLASMA CATECHOLAMINE RESPONSES DURING CHOLECYSTECTOMY

C. KLINGSTEDT, K. GIESECKE, B. HAMBERGER AND P.-O. JÄRNBÉRG

High-dose (50–150 μg kg⁻¹) fentanyl anaesthesia is used widely in open-heart surgery (Stanley and Webster, 1978; Lunn et al., 1979) since it provides acceptable cardiovascular stability during anaesthesia and surgery (Stanley, Philbin and Coggins, 1979; Lappas et al., 1980). It has also been shown that this regimen decreases the usual neuroendocrine stress response associated with sternotomy (Stanley et al., 1980; Sebel et al., 1981)—although differences of opinion exist (Walsh et al., 1981; Zuric et al., 1982).

Plasma catecholamine concentrations have been measured during surgery by several groups, both during high-dose fentanyl anaesthesia (Stanley, Philbin and Coggins, 1979; Lappas et al., 1980; Sebel et al., 1981; Zuric et al., 1982) and during a standard neurolept anaesthesia using fentanyl 10 μg kg⁻¹ (Tammisto et al., 1973; Balogh et al., 1979; Hamberger and Järnberg, 1983). Fentanyl 50–75 μg kg⁻¹ has been shown to reduce the metabolic and hormonal changes occurring during abdominal surgery (Hall et al., 1978; Cooper et al., 1981; Haxholdt, Kehlet and Dyrberg, 1981). However, data on the stress response and plasma catecholamine concentrations when using fentanyl in doses of 100 μg kg⁻¹ or more are lacking.

The purpose of this study was to compare the cardiovascular and neuroendocrine effects of high-dose (100 μg/kg body weight) fentanyl anaesthesia with those of a balanced type of fentanyl anaesthesia (5 μg kg⁻¹) during upper abdominal surgery. High-dose fentanyl anaesthesia prevented the increase in catecholamine concentrations and attenuated the circulatory response to surgical stress seen in the group anaesthetized with the balanced technique of anaesthesia.

PATIENTS AND METHODS

Patients

Twelve patients, scheduled for routine cholecystectomy, were studied. They were randomly divided into two groups. Six patients received high-dose fentanyl (group 1); the remainder (group 2) received the balanced technique of fentanyl anaesthesia. All were healthy, except for their gallbladder disease. Preoperative ECG recordings and chest x-rays were normal. The patients were not on any continuous medication. The characteristics of the patients are summarized in table I.

The study was approved by the Ethical Committee of the Karolinska Institute, and informed consent was obtained from each patient.

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TABLE I. Patient characteristics (mean ± SEM). Group 1 received high-dose fentanyl anaesthesia; group 2 a balanced anaesthetic technique. * Time from start of anaesthesia to end of operation

<table>
<thead>
<tr>
<th>No.</th>
<th>Male/ Female</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Anaesthetic time (min)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>6</td>
<td>1/5</td>
<td>47.3 ± 4.1</td>
<td>58.5 ± 3.4</td>
</tr>
<tr>
<td>Group 2</td>
<td>6</td>
<td>2/4</td>
<td>39.3 ± 4.7</td>
<td>68.0 ± 4.2</td>
</tr>
</tbody>
</table>

TABLE II. Sampling times for plasma catecholamines

(1) Before induction of anaesthesia, at least 15 min after completion of catheterization.
(2) 1 min after tracheal intubation.
(3) Immediately before skin incision after 15–30 min of anaesthesia.
(4) 1 min after skin incision.
(5) During surgical exploration of the gallbladder.
(6) After 10 min intermission of surgery.
(7) 5 min after the operation had been resumed.

No complications attributable to the study occurred.

Anaesthesia

The patients were premedicated with morphine 0.15 mg kg⁻¹ given i.m. approximately 1 h before the induction of anaesthesia. All patients received atropine 0.5 mg and diazepam 0.1 mg kg⁻¹ i.v. immediately before induction.

In group 1, anaesthesia was induced with fentanyl 100 µg kg⁻¹, given as a bolus over 2 min; no further fentanyl was given to this group. The induction of anaesthesia in group 2 consisted of i.v. thiopentone 4–5 mg kg⁻¹ and fentanyl 5 µg kg⁻¹, followed by a continuous infusion of fentanyl 3 µg kg⁻¹ h⁻¹.

Neuromuscular blockade was obtained in all patients with pancuronium 0.1 mg kg⁻¹. The lungs of all patients were mechanically ventilated with nitrous oxide in oxygen (2:1), to normocapnia—as confirmed by blood-gas analyses (ABL-2).

Arterial samples were drawn into heparinized tubes, stored on ice, and centrifuged within 1 h. The plasma was frozen and stored at −70 °C until analysis. One millilitre of plasma was then used for the assay. The catecholamines were separated by high pressure liquid chromatography and quantified by electrochemical detection (Hallman et al., 1978). The sensitivity of the method was ±0.1 nmol litre⁻¹. Total sampling blood loss was less than 150 ml, including blood sampling for other chemical analyses.

Procedure

A peripheral vein was cannulated and an infusion of lactated Ringer’s solution commenced at 200 ml h⁻¹. The left radial artery was cannulated (20-gauge Teflon catheter) to permit measurement of arterial pressure (Kontron 128A monitor with a pressure transducer (Bentley)). Mean arterial pressure was obtained by electronic damping of the pressure signal. Heart rate was determined from the ECG.

Arterial samples for the measurement of catecholamine concentration were drawn as detailed in table II. Systolic arterial pressure (SAP) and heart rate (HR) were registered at these times. Blood lost was replaced with twice its volume of lactated Ringer’s solution. No patient lost more than 500 ml of blood (including sampling).

Statistics

Statistical analyses consisted of calculations of mean value, standard deviation, and standard error of the mean (SEM). Student’s t test for paired and unpaired data, with pooled estimates of variance, was used to compare data within and between the two groups, respectively. P < 0.05 was considered to indicate a significant difference.

RESULTS

Unless otherwise stated the values given below are the averages in each group for the different sampling points.

Plasma adrenaline concentration (table III)

Adrenaline concentrations were similar in both groups initially (0.5 nmol litre⁻¹ in group 2 and 0.3 nmol litre⁻¹ in group 1). In both groups, these concentrations decreased significantly to <0.1 nmol litre⁻¹ after the induction of anaesthesia. In group 1 this value persisted throughout the entire operation.

In group 2 the adrenaline concentration increased significantly during periods associated with the surgical exploration of the gallbladder: concentrations of 1.4, 0.6 and 0.9 nmol litre⁻¹ were found during surgery, after 10 min of interruption, and when surgery was resumed; all were significantly greater than those recorded in
heart rate decreased significantly in both groups, whereafter no significant differences were noted within or between the groups.

Initially, systolic arterial pressure was 141 mm Hg and 136 mm Hg in groups 1 and 2, respectively. Significant changes occurred after induction, with decreases to 95 and 104 mm Hg and increases (during surgery) to maximum values of 118 and 139 mm Hg, respectively. Systolic arterial pressures and rate—pressure product were significantly higher in group 2 during the two periods of active surgery (sampling points 5 and 7).

**Blood-gas tensions**

Arterial \( \text{PCO}_2 \) and \( \text{PO}_2 \) during anaesthesia were, respectively, 4.5 kPa and 20.0 kPa in group 1 and 4.7 kPa and 18.6 kPa in group 2.

**DISCUSSION**

Stress and anxiety are potent activators of the sympathoadrenal system. Adrenaline is released from the adrenal gland, and its plasma concentration can be regarded as an indicator of the degree of anxiety experienced. Noradrenaline in plasma comes mainly from the overflow of noradrenaline from sympathetic nerve terminals (Cryer, 1976). The initial adrenaline and noradrenaline concentrations in the two groups were similar to those reported in non-stressed, healthy individuals (Bühler et al., 1978), indicating that the patients were calm and free of anxiety.

During the induction of anaesthesia catecholamine concentrations and SAP either decreased or remained constant in both groups. There were no

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**TABLE III. Plasma adrenaline and noradrenaline concentrations (mean ± SEM). Significant differences: * From (1) group 1 (P < 0.05); † from (1) group 2 (P < 0.05); ** from (4) group 1 (P < 0.01); ‡ from (4) group 2 (P < 0.01); § from (4) group 1 (P < 0.05); ¶ from (4) group 2 (P < 0.05); †† between groups 1 and 2 (P < 0.05)**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Adrenaline</th>
<th>Noradrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 2</td>
<td>Group 1</td>
</tr>
<tr>
<td>(1)</td>
<td>0.5±0.3</td>
<td>0.3±0.1</td>
</tr>
<tr>
<td>(2)</td>
<td>&lt;0.1†</td>
<td>&lt;0.1*</td>
</tr>
<tr>
<td>(3)</td>
<td>&lt;0.1†</td>
<td>&lt;0.1*</td>
</tr>
<tr>
<td>(4)</td>
<td>&lt;0.1†</td>
<td>&lt;0.1*</td>
</tr>
<tr>
<td>(5)</td>
<td>1.4±0.6§</td>
<td>&lt;0.1*§</td>
</tr>
<tr>
<td>(6)</td>
<td>0.6±0.2§</td>
<td>&lt;0.1*§</td>
</tr>
<tr>
<td>(7)</td>
<td>0.9±0.4§</td>
<td>&lt;0.1*§</td>
</tr>
</tbody>
</table>

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**TABLE IV. Heart rate (beat min⁻¹), systolic arterial pressure (mm Hg) and rate—pressure product values (HR; SAP) (mean ± SEM). Significant differences: * from (1) group 1 (P < 0.05); † from (1) group 2 (P < 0.05); ‡ from (2) group 1 (P < 0.05); †§ from (2) group 2 (P < 0.05); ‡§ from (3) group 1 (P < 0.05); § from (4) group 2 (P < 0.05); †∥ from (5) group 2 (P < 0.05); ‡∥ from (6) group 2 (P < 0.05); †∥ between HFA and BLA groups (P < 0.05)**

<table>
<thead>
<tr>
<th>Sample</th>
<th>HR (beat min⁻¹)</th>
<th>SAP (mm Hg)</th>
<th>RPP (unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 2</td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td>(1)</td>
<td>90±3</td>
<td>73±7§</td>
<td>136±8</td>
</tr>
<tr>
<td>(2)</td>
<td>96±3†</td>
<td>83±10</td>
<td>110±5†</td>
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<td>(3)</td>
<td>85±3*</td>
<td>76±9‡</td>
<td>104±10‡</td>
</tr>
<tr>
<td>(4)</td>
<td>86±6</td>
<td>73±8</td>
<td>117±8†</td>
</tr>
<tr>
<td>(5)</td>
<td>89±5</td>
<td>72±9</td>
<td>137±8§</td>
</tr>
<tr>
<td>(6)</td>
<td>81±8*</td>
<td>69±8§</td>
<td>122±3</td>
</tr>
<tr>
<td>(7)</td>
<td>77±5†</td>
<td>69±8§</td>
<td>139±4*§</td>
</tr>
</tbody>
</table>
increases during intubation and the concentrations of adrenaline and noradrenaline remained low until the start of surgery. These findings accord with other studies which showed blunting of the circulatory response to intubation when thiopentone was combined with low doses of fentanyl (Dahlgren and Messeter, 1981; Martin et al., 1982).

Unlike other anaesthetic agents such as morphine, halothane and nitrous oxide, thiopentone, by itself, reduces sympathoadrenal activity (Joyce, Roizen and Eger, 1983), and to obtain the same degree of suppression with fentanyl alone would have required much larger doses than the 5 μg kg⁻¹ given here. This has been shown in an earlier study (Hamberger and Järnberg, 1983), in which a dose of 10 μg kg⁻¹ used in a neurolept anaesthesia induction sequence, without thiopentone, failed to suppress the increase in plasma adrenaline concentration associated with intubation. In that study, plasma adrenaline concentration varied significantly depending on the degree of surgical stress. Because of the short plasma half-life of adrenaline, interruption of surgery for 10 min was sufficient to allow the plasma adrenaline concentration to return to baseline values.

During surgery noradrenaline concentrations in both groups and the adrenaline concentration in group 2 increased, while the adrenaline concentrations in group 1 remained at their post-induction values during the entire surgical procedure. Plasma adrenaline concentration and the rate-pressure product were both significantly higher in group 2 during the two periods of active surgical stress. The catecholamine concentrations obtained during these periods were comparable to those found in previous studies, and during exercise (Galbo, Holst and Christensen, 1975) or hypoglycaemia (Garber et al., 1976). The intraoperative adrenaline concentrations in group 2 were comparable to those found by Stratton and colleagues (1985) to induce significant increases in HR and SAP, associated with an increase in cardiac output of approximately 60%. It is, therefore, probable that the differences in the catecholamine concentrations are reflected in the differences in rate-pressure product before and during surgery, and between the two groups.

Increased sympathoadrenal activity is caused by many factors, including surgical trauma/stress (Halter, Pflug and Porte, 1977), hypoxia, hypercarbia, haemorrhage and decreases in arterial pressure (Callingham, 1975). In this study, adequate oxygenation and ventilation were provided—as shown by the blood-gas tensions—and minimal blood loss occurred during the surgical procedure. Thus it may be reasonable to assume that the differences in sympathoadrenal activity observed were the result of an altered response to the stress of surgery, brought about by the different anaesthetic techniques.

The high-dose fentanyl anaesthesia technique is, at present, used almost exclusively in open-heart surgery, although fentanyl is usually given as an infusion of 200–300 μg min⁻¹. It has, however, been shown that the rapid administration of fentanyl, comparable to that used in this study (50 μg kg⁻¹ min⁻¹) can be used without negative cardiovascular effects (Kentor, Schwab and Lieberman, 1980). During coronary artery surgery, high-dose fentanyl anaesthesia has been shown to induce a stable haemodynamic state (Stanley, Philbin and Coggins, 1979; Zuric et al., 1982) without increases in plasma adrenaline concentration in the period before bypass (Stanley et al., 1980; Sebel et al., 1981). The low adrenaline concentrations in this study are comparable to those shown by Stanley and colleagues (1980) during a fentanyl–oxygen anaesthesia with fentanyl 75 μg kg⁻¹, but are slightly lower than in other studies.

High-dose fentanyl plus nitrous oxide in oxygen anaesthesia during upper abdominal surgery also reduces the perioperative metabolic response to surgery (Cooper et al., 1981; Haxholdt, Kehlet and Dyrberg, 1981), although the profound respiratory depression found in these patients immediately after the completion of surgery can be a major problem. In our study, this was prevented by maintaining the mechanical ventilation for a few hours into the postoperative period. Fentanyl was combined with oxygen and nitrous oxide in our patients because awareness during surgery has been reported during fentanyl–oxygen anaesthesia even with a bolus dose of fentanyl 150 μg kg⁻¹. No awareness was reported in either group.

The main indication for this type of anaesthesia, excluding cardiac surgery, would probably be major abdominal surgery. These operations usually take a long time and may be associated with large blood losses. Even after routine anaesthesia, such patients are usually transferred into the ICU, and extubation delayed. Especially in poor-risk cases such as patients with concomitant cardiovascular disease, the circulatory stability achieved
during high-dose fentanyl anaesthesia could be advantageous.

The present study demonstrated significant differences between the high-dose fentanyl technique and the conventional balanced i.v. technique. Evidence of increased perioperative stress (measured by increases in plasma adrenaline concentration) was found in group 2, while group 1 remained essentially "stress free". Secondary to this, there was marked cardiovascular stability in group 1, while the rate-pressure product, which can be used as an index of myocardial oxygen consumption (Gobel et al., 1978), showed significant fluctuations in group 2. However, the overall effects of these differences on the whole organism during anaesthesia and operation require further clarification.

ACKNOWLEDGEMENTS
This study was supported by the Swedish Medical Research Council (04X-2330) and Torsten and Ragnar Söderbergs Stiftelse.

REFERENCES


