SUFENTANIL AND NITROUS OXIDE ANAESTHESIA FOR CARDIAC SURGERY

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The ability to obtund cardiovascular responses to surgical stimuli may be an intrinsic property of very potent opioids [1]. Sufentanil is a potent opioid analgesic relatively recently introduced into anaesthetic practice [2]. Its higher potency and shorter elimination half-life [3] when compared with fentanyl [4] may make it a more suitable drug for cardiac anaesthesia. Indeed, it has been shown in a comparative trial, that sufentanil 12–30 μg kg\(^{-1}\) has a superior modifying effect on cardiovascular responses compared with fentanyl in doses up to 120 μg kg\(^{-1}\) [5]. However, neither Rosow and colleagues [6] nor Howie and co-workers [7] using similar dose ranges were able to show any significant differences between the two drugs.

One would expect the shorter half-life of sufentanil to confer an advantage in clinical practice, as there is a trend towards progressively earlier extubation of the trachea after cardiac surgery. However, there are conflicting reports about the clinical significance of the shorter half-life of sufentanil when compared with fentanyl. For example, Howie and co-workers [7] and de Lange and associates [5] found no difference in recovery times; Sanford and colleagues [8], using the same dose as Howie and co-workers [7], found that recovery from sufentanil was significantly quicker. However, there were some differences in premedication and method of sufentanil administration that could account for this discrepancy.

These previous studies have been conducted using opioid-oxygen anaesthesia. There have been few studies of the cardiovascular effects of the combination of sufentanil and nitrous oxide (in oxygen). When used in balanced anaesthesia with nitrous oxide, relatively low doses of sufentanil (2.5 μg kg\(^{-1}\)) have been associated with suppression of cardiovascular responses to surgical stress in patients undergoing non-cardiac surgery [9].

The present study was designed to investigate the effects of three different doses of sufentanil, during balanced anaesthesia with nitrous oxide, on the haemodynamic responses and the recovery times in patients undergoing cardiac surgery. The

**SUMMARY**

We have investigated the use of sufentanil 3.75–15 μg kg\(^{-1}\) by supplementing anaesthesia with nitrous oxide and midazolam. Thirty patients with ejection fractions exceeding 30% were studied while undergoing scheduled coronary artery vein graft surgery. Even in the lowest dose group (3.75 μg kg\(^{-1}\)), haemodynamic responses to surgical and anaesthetic stimuli were sufficiently obtunded that no patient exhibited an increase in heart rate or systolic arterial pressure greater than 20% of the control value. Marked hypotension occurred in some patients during unstimulated periods. Such periods of hypotension were associated with equally marked decreases in systemic vascular resistance. The mean recovery times to spontaneous ventilation after the end of surgery ranged from 6 to 12 h. This is longer than would be expected from other studies using a similar dose of sufentanil. This may be related to the use of benzodiazepines during anaesthesia and to their use after surgery in those patients who became restless.
aim was to determine if balanced anaesthesia with an appropriate dose of sufentanil plus nitrous oxide produced a stable anaesthetic, compatible with early recovery.

PATIENTS AND METHODS

Following Ethics Committee approval, informed consent was obtained from 30 patients with left ventricular ejection fractions exceeding 30% and who were scheduled to undergo coronary artery vein graft surgery (CAVG). They were allocated randomly to three equal groups to receive sufentanil as follows: group 1, 3.75 μg kg⁻¹; group 2, 7.5 μg kg⁻¹; group 3, 15 μg kg⁻¹.

Patients were premedicated with diazepam 15–20 mg by mouth followed by papaveretum 15–20 mg and hyoscine 0.3–0.4 mg i.m. Half their normal daily dose of beta-adrenoceptor blocking agent was given with their normal morning dose of calcium channel blocker, when relevant.

Pulmonary artery and radial artery catheters were inserted under local anaesthesia before the induction of general anaesthesia. Five minutes later, standard haemodynamic variables were measured at the following times:

- Event 1 = baseline
- Event 2 = 2 min after induction of anaesthesia
- Event 3 = 2 min after administration of sufentanil
- Event 4 = 2 min after intubation
- Event 5 = 2 min after skin incision
- Event 6 = 2 min after sternotomy

The standard haemodynamic variables measured were heart rate, systemic and pulmonary artery pressures, right atrial pressure, pulmonary artery wedge pressure and cardiac output. Other data (stroke work indices, vascular resistances) were derived using standard equations.

Anaesthesia was induced with midazolam 1–4 mg. Pancuronium was administered in a dose of 0.1 mg kg⁻¹; two-thirds of the sufentanil dose was administered at 2.5 μg kg⁻¹ min⁻¹. The lungs were

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<th>TABLE 1. Cardiovascular variables for group 1 sufentanil 3.75 μg kg⁻¹; group 2 sufentanil 7.5 μg kg⁻¹; group 3 sufentanil 15 μg kg⁻¹. SVR = Systemic vascular resistance; CVP = central venous pressure</th>
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ventilated with 60% nitrous oxide in oxygen as soon as anaesthesia commenced. Before sternotomy, the remainder of the sufentanil was given. A further bolus of midazolam 5 mg was given on establishing cardiopulmonary bypass (CPB).

The times after the end of surgery were noted for the return of consciousness and of spontaneous ventilation, the latter defined by satisfactory blood-gas tensions ($P_{\text{a}CO_2} < 45$ mm Hg and $P_{\text{a}O_2} > 85$ mm Hg) without prompting.

Statistical analysis was by repeated measures analysis of variance. The data do not fulfil the requirement of conventional analysis of variance because the individual data points in our study are not independent. Significant differences were further investigated by multiple $t$ testing and the $P$ values corrected by Bonferroni's adjustment.

RESULTS

The three groups of patients were not statistically different with respect to age, weight and sex. Measured and derived cardiovascular indices are shown in table I. Statistical analysis of the cardiovascular variables showed significant changes within the three groups associated with anaesthesia and surgery, but only the left ventricular stroke work index (LVSWI) differed significantly between groups.

There was a statistically significant increase in heart rate after the administration of sufentanil and intubation, but this was small and of the order of 5-7 beat min$^{-1}$ (fig. 1). Systolic arterial pressure and systemic vascular resistance (SVR) showed a uniform trend during the procedure, with no significant differences between any of the groups (figs 2, 3). There was a marked decrease in systolic arterial pressure after the administration of sufentanil, associated with a similar decrease in SVR. There was very little change in systolic arterial pressure after intubation and a small increase towards pre-induction values after sternotomy. Left ventricular stroke work index showed a modest decrease associated with anaesthesia (fig. 4). There was a significantly greater decrease in group 1 than in group 3 after sufentanil administration, and a significantly greater decrease in group 2 compared with group 3 after intubation.

Recovery times showed highly significant differences between the three groups: mean times for spontaneous ventilation to resume were 6.1 h for group 1, 9.1 h for group 2 and 12.0 h for group 3 (fig. 5).

FIG. 1. Heart rate during anaesthesia with three different doses of sufentanil and surgery. Event 1 = baseline; event 2 = after midazolam; event 3 = after sufentanil; event 4 = after intubation; event 5 = after first skin incision; event 6 = after sternotomy. Values are means (with one SE shown). $F$ value for difference between groups: 1.61 ($P = 0.21$). $F$ value for differences within groups: 5.53 ($P = 0.0008$).

FIG. 2. Systolic arterial pressure during anaesthesia with three different doses of sufentanil and surgery. Event 1 = baseline; event 2 = after midazolam; event 3 = after sufentanil; event 4 = after intubation; event 5 = after first skin incision; event 6 = after sternotomy. Values are means (with one SE shown). $F$ value for differences between groups is 0.69 ($P = 0.51$). $F$ value for differences within groups is 31.8 ($P < 0.0001$).
DISCUSSION

One problem of cardiac anaesthesia is how to suppress cardiovascular and hormonal responses to surgical stimuli and simultaneously provide a stable cardiovascular system during rapidly changing degrees of stimulation. Whilst inhalation agents can provide satisfactory conditions for cardiac surgery, their use requires considerable "fine tuning" [10]. In 1969, Lowenstein and colleagues [11] investigated the haemodynamic changes associated with large doses of morphine in cardiac patients. They demonstrated that morphine 0.5–3 mg kg⁻¹ had no depressant effect on cardiac function and that, in patients with valve disease, the vasodilator properties of morphine actually promoted an increase in stroke volume. In addition, in most patients there was a high degree of cardiovascular stability. Since then, anaesthetists have shown increasing interest in high-dose opioids to provide stable cardiovascular conditions. High-dose morphine has been superseded by the newer opioids, mainly because of the extremely long period of emergence from morphine anaesthesia [8]. The use of fentanyl in cardiac surgery has been extensively researched both as a high-dose sole anaesthetic and as an analgesic supplemented with nitrous oxide, benzodiazepines or inhalation agents [12].
Some workers have found high-dose fentanyl-oxygen anaesthesia only partly successful in blocking the cardiovascular and hormonal responses to surgery [5, 13]. Others have found that fentanyl effectively obtunded these responses [14, 15]. However, the studies are not strictly comparable. Patients in the latter study [15] were undergoing mitral valve surgery and not CAVG surgery. There were also differences in the premedication regimens: patients in the former group [14] received nitrous oxide, while half of the patients in the second study [15] were given diazepam during the surgical procedure.

Sufentanil is a potent opioid (about seven times as potent as fentanyl) and has been studied in cardiac surgery as an alternative to fentanyl. The effects on the suppression of hormonal responses in the period before bypass have been encouraging [16], but may not be better than fentanyl [7]. However, the effects of sufentanil on cardiovascular dynamics are less certain. Some researchers using sufentanil at a dose between 11 and 30 μg kg⁻¹ have found little difference between this drug and a comparable dose of fentanyl [6, 7]. However, de Lange and co-workers [5], using sufentanil 12 μg kg⁻¹, did find a significant advantage over fentanyl. They found that the sufentanil group required significantly less vasodilator therapy for hypertension compared with the fentanyl group. Furthermore, they noted that patients in the sufentanil group who were receiving preoperative beta-adrenergic blockers required no vasodilator intervention. Elsewhere, Stanley, de Lange and Boscoe [17] have commented on the reduction of opioid requirements in patients receiving beta-blockers before operation.

None of our patients exhibited any hypertensive responses at any time. On the contrary, there was a significant decrease in systolic arterial pressure after the induction of anaesthesia; this was marked in two patients who needed a vasopressor. Marked decreases in systolic arterial pressure associated with sufentanil have been described previously [18, 19] when i.v. benzodiazepines were used in the anaesthetic sequence. The decrease may be partly associated with experimental design creating unusually long periods without stimulation.

The changes in heart rate were also minimal and were probably associated with the vagotonic effects of sufentanil. In spite of the concomitant administration of pancuronium, three patients required vagolytic drugs. There was thus a small increase in mean values of heart rate after sufentanil administration (and after intubation). Previous research has shown that, where pancuronium is given before sufentanil, serious bradycardia does not occur, but a similar increase in heart rate still occurs [20]. They found that bradycardia requiring vagolytic drugs occurred with atracurium and vecuronium when anaesthesia was induced with sufentanil 15 μg kg⁻¹.

The LVSWI was the only haemodynamic index to show any significant differences between the groups. There was a 40% decrease in group 1 after induction and a significant difference at this point between groups 1 and 3. This may be partly explained by group 1 patients also exhibiting the greater decrease in systolic arterial pressure. Changes in LVSWI are difficult to interpret as the index fails to differentiate between (useful) flow work and (wasteful) pressure work.

The marked suppression of cardiovascular responses in our study is probably associated with the use of nitrous oxide and midazolam. Interactions between opioids, nitrous oxide and benzodiazepines have been well described. Tomich et al. [21] described marked hypotension when diazepam was given before high-dose fentanyl. This was associated with equally marked decreases in systemic vascular resistance and, interestingly, marked decreases in plasma catecholamine concentrations. Stroke volume index was, however, unchanged. Other reports [22] suggest direct myocardial depression. The effects of nitrous oxide–opioids have also been well described. McDermott and Stanley [23] found a 36% decrease in stroke volume with 50% nitrous oxide and morphine. Lappas and co-workers [24] found a 21% decrease in stroke index using 50% nitrous oxide, but this was associated with a decrease in the rate–pressure product. This impairment may occur only in patients with coronary disease and high left ventricular end diastolic pressure [25, 26]. Of greater concern is the potential for nitrous oxide to create ischaemic conditions in cardiac patients anaesthetized with opioids [27, 28].

The interaction between nitrous oxide and midazolam should be considered. Samuelson and associates [10] found the effect of nitrous oxide on an induction dose of midazolam innocuous in cardiac patients. Falk and co-workers [29] reported a case of marked vasodilatation with diazepam and nitrous oxide during induction of anaesthesia.
The recovery times after high dose sufentanil–oxygen anaesthesia are sometimes still prolonged in spite of its slightly shorter half-life. Comparing sufentanil with fentanyl, Howie and colleagues [7] and de Lange and co-workers [5] found no significant difference in recovery times. Sanford and associates [8] found that patients given sufentanil breathed spontaneously and could have the tracheal tube removed significantly sooner than those given fentanyl.

Our times for the return of spontaneous ventilation were significantly different between groups and this is obviously a dose-related effect. Mean recovery time after sufentanil 15 μg kg⁻¹ was 11.7 h. This is long compared with 5.6 h in Sanford’s group (given 15 μg kg⁻¹) or de Lange’s group (given 12 μg kg⁻¹). Howie and colleagues [7] using orientation as the endpoint, found mean recovery time was 7 h after 20 μg kg⁻¹ and mean extubation time was 17 h. We decided to take spontaneous ventilation as our endpoint rather than extubation, as the latter depends on a variety of factors including patient build, preoperative respiratory status, and the absence of surgical bleeding. Even our low dose group (sufentanil 3.75 μg kg⁻¹) took 5.7 h (mean) to resume spontaneous ventilation. Our premedication probably produced greater sedation than that in the three other groups described earlier. Unlike them, we used a combination of an opioid and a benzodiazepine as premedicant. In addition, midazolam was given for the induction of anaesthesia and before the start of cardiopulmonary bypass. Some patients also received small boluses of midazolam in the early postoperative period. They were clearly free of pain, but awoke extremely restless and confused. Thus in our patients we did not find our technique compatible with a policy of early extubation.

Sufentanil, even in our lowest dose of 3.75 μg kg⁻¹, provided a satisfactory suppression of cardiovascular responses. It would be interesting to substitute a potent inhalation agent for both nitrous oxide and midazolam and to observe whether similar haemodynamic trends prevailed. If so, concerns about nitrous oxide and myocardial metabolism could be forgotten and a decrease in the dose of midazolam may allow earlier recovery.

ACKNOWLEDGEMENTS

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REFERENCES


