Hemodynamic and Anesthetic Effects of Sufentanil as the Sole Anesthetic for Pediatric Cardiovascular Surgery

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The efficacy, safety, and hemodynamic response to 5 μg/kg, 10 μg/kg, or 20 μg/kg of sufentanil and 0.1 mg/kg pancuronium was evaluated in children between 4 and 12 years of age scheduled for open heart surgery. Systolic time intervals, 2-D echocardiograms, systolic blood pressures (SBP), diastolic blood pressures (DBP), and heart rates (HR) were recorded before and after induction of anesthesia. Significant changes 10 min following induction of anesthesia but before intubation included increases in SBP in the 5 μg/kg group (P < 0.01) and in the ratio of prejunctional period to left ventricular ejection time in the 20 μg/kg group (P < 0.05). Instances of myoclonic jerking and coughing episodes were observed in all three study groups.

Following intubation there were significant (P < 0.05) increases in SBP in all groups, in DBP in the 5 μg/kg group, and in HR in the 5 μg/kg and 10 μg/kg groups. Smaller increases in SBP, DBP, and HR were seen in all groups after skin incision and sternotomy. Mean plasma catecholamine levels showed nonsignificant increases following periods of intraoperative stimulation with wide patient variations.

Recovery of responsiveness to command occurred in all groups within one hour from the end of surgery but extubation was impeded by shallow periodic breathing and hypcapnea. The authors conclude that for children undergoing open heart surgery use of sufentanil as a sole anesthetic in bolus form did not provide a reliable depth of anesthesia with any of the induction doses studied. (Key words: Anesthetics, intravenous; sufentanil. Analgesics: narcotic, sufentanil. Anesthesia: pediatric cardiovascular.)

SUFENTANIL is a new synthetic narcotic closely related to fentanyl and recently approved for clinical use. The suggested advantages of this agent over fentanyl include higher potency, higher therapeutic index, and improved blockade of stress response.1-3 Sufentanil has been used as an anesthetic for adults undergoing cardiac surgery.4-6 The only study of sufentanil for children undergoing open heart surgery was performed with infants who received supplemental nitrous oxide.7

This study evaluated the efficacy, safety, and hemodynamic response to three induction doses of sufentanil in children undergoing cardiovascular surgery. In addition, sufentanil's adequacy as a sole anesthetic for each of these groups was evaluated on the basis of catecholamine and hemodynamic responses during high-stress points of the surgical procedure. Recovery from anesthesia was assessed for each induction group by comparison of times with awakening and extubation.

Methods and Materials

After obtaining institutional review board approval and individual parental consent, 10 pediatric patients (ASA 2 or 3) between the ages of 4 and 12 yr scheduled for open heart surgery were randomly assigned to receive either 5 μg/kg or 10 μg/kg induction doses of sufentanil. An additional 10 patients who received an induction dose of 20 μg/kg sufentanil were added to the study.

Induction

Sixty minutes prior to surgery, all patients were premedicated with intramuscular scopolamine 0.01 mg/kg, morphine 0.2 mg/kg, and pentobarbital 2 mg/kg; and an intravenous catheter was placed in the hand. In the operating room each patient had an electrocardiogram, Doppler blood pressure cuff, precordial stethoscope, and systolic time interval carotid pulse and phonocardiogram apparatus placed. Patients were assessed by the anesthesiologist as either sleeping, quiet, or upset. Following 5 min of breathing 100% oxygen, baseline systolic time intervals and two-dimensional echocardiograms were recorded.

Systolic time intervals were obtained using an IREX® system II multichannel recorder at a paper speed of 100 mm/s to record simultaneous electrocardiogram, phonocardiogram (200–500 Hz frequency band), and external carotid pulse tracings (IREX® 120-012D0002 pulse transducer). Regression equations of Cantor et al.8 were used to index total electromechanical systole (QS),

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left ventricular ejection time (LVET), and preejection period (PEP) to heart rate (QS2I, LVETI, PEPI). The uncorrected PEP and LVET were used in the calculation of PEP/LVET. Left ventricular ejection fraction was calculated from apical four-chamber views obtained with a Diasonics® 3400 R real time ultrasonograph and a 3.5 MHz phased array transducer. The heart rate and systolic and diastolic blood pressures were recorded.

Either 5, 10, or 20 μg/kg sufentanil then was infused over a 2-min period. Upon loss of the eyelash reflex, pancuronium 0.1 mg/kg was given intravenously and controlled ventilation started. Heart rate and systolic and diastolic blood pressures were noted 2, 5, and 10 min following initiation of induction. Between the 5- and 10-min postinduction points, a percutaneous radial artery cannula was inserted. At 10 min postinduction the systolic time interval and 2D echocardiogram were repeated for all children in the 5 and 10 μg/kg induction groups and for five of the children in the 20 μg/kg induction group.

**Maintenance**

Heart rate and blood pressure (systolic, diastolic, and mean from the radial arterial line) were recorded: preintubation; 2 and 5 min postintubation; pre-skin incision; 2 and 5 min post-skin incision; preternotomy; and 2 and 5 min postternotomy. Plasma catecholamines were measured: preintubation; 5 min postintubation; pre-skin incision; 5 min post-skin incision; and 5 min postternotomy in all patients (5 min post-skin incision, and preternotomy times were concurrent). Fractionated catecholamine analysis was performed by Consolidated Biomedical Laboratories using a Catecholamine Radioenzymatic assay kit** with a sensitivity of 10 pg/ml.

Supplemental sufentanil was given to any patient who had increases in heart rate or systolic pressure greater than 20% over resting preinduction levels. The supplemental sufentanil dose was 1 μg/kg for the 5 μg/kg induction group, 2 μg/kg for the 10 μg/kg induction group, and 5 μg/kg for the 20 μg/kg induction group. Additional pancuronium was given whenever a patient showed muscular activity and just before initiating cardiopulmonary bypass. The amount and timing of additional drug doses were noted for each patient. Following the surgical procedure, the anesthesiologist assessed the adequacy of anesthesia as good, satisfactory, or poor, based on the patient's hemodynamic stability during intraoperative stimuli and apparent lack of intraoperative awareness.

**Recovery**

After transfer to the intensive care unit, the time to recovery of eyelash reflex, awakening, and extubation were recorded. During the postoperative visit, any complaints the patient had concerning the anesthetic were recorded. The anesthesiologist also assessed the adequacy of recovery from anesthesia as good, satisfactory, or poor, based on the completeness of return to awareness and orientation.

Qualitative evaluation between induction groups concerning sex, preinduction state, incidence of side effects, adequacy of anesthesia, and adequacy of recovery from anesthesia was performed using the Fisher's exact test and the Mantel-Haenszel test. Quantitative comparisons of age, height, weight, preoperative hemodynamic data, and duration of surgery were evaluated with one-way analysis of variance followed by a Bonferroni test in the presence of significant F ratios. Statistical comparisons at different time intervals for hemodynamic data, systolic time intervals, echocardiographic data, and catecholamine data within groups was performed using the paired t test. Between-group comparisons of data were made using a one-way analysis of variance, followed by Bonferroni test to make pair-wise comparisons in cases of significant F ratios. Statistical significance was considered to exist with P values < 0.05.

**Results**

**Induction**

Patients in the 5, 10, and 20 μg/kg sufentanil groups were comparable in regard to age, sex, height, weight, preinduction hemodynamic variables, level of preinduction awareness, and time to loss of eyelash reflex. The congenital heart defects for the children in each of the groups are indicated in Table 1.

Within treatment groups there was a significant increase in systolic blood pressure (P < 0.01) at the 10-min postinduction point for the 5 μg/kg sufentanil group and in heart rate (P < 0.05) for the 10 μg/kg group at the 2- and 5-min postinduction points (see figs. 1 and 2). Between treatment group comparisons failed to show significant group differences (P > 0.05).

Within treatment groups there was a significant increase in the QS2I (P < 0.05) in the 10 μg/kg sufentanil group, and in the PEPI (P < 0.05) and PEP/LVET (P < 0.03) in the 20 μg/kg sufentanil group. Between treatment groups there were no significant differences. Comparison of per cent change in ejection fraction within groups and between groups were not statistically significant (Table 2).

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* Cat-A-Kit, Upjohn Diagnostics, Kalamazoo, Michigan 49001.
During induction there were myoclonic jerks and dystonic movements of the arms and legs in five patients in the 5 μg/kg group, three patients in the 10 μg/kg group, and seven patients in the 20 μg/kg group. Coughing was noted in one out of five patients in the 5 μg/kg group, one patient in the 10 μg/kg group, and 3 patients in the 20 μg/kg group.

**MAINTENANCE**

Duration of operation between groups was not significantly different (table 1). All groups required supplemental doses of sufentanil. The mean dose of standard error of the mean of sufentanil received by the 5 μg/kg group was 11 ± 3 μg/kg (range of 6–20 μg/kg), by the 10 μg/kg group was 19 ± 2 μg/kg (range of 13–23 μg/kg), and by the 20 μg/kg group was 30 ± 2 μg/kg (range of 21–43 μg/kg). The mean dose of pancuronium for the 5, 10, and 20 μg/kg groups was 0.21 ± 0.015 mg/kg (range 0.16–0.23 mg/kg), 0.27 ± 0.022 mg/kg (range 0.22–0.34 mg/kg), and 0.27 ± 0.016 mg/kg (range 0.21–0.36 mg/kg), respectively.

Adequacy of anesthesia during the course of the operation was judged by the anesthesiologist to be poor in two patients in the 5 μg/kg group, one patient in the 10 μg/kg group, and one patient in the 20 μg/kg group. Three patients with pulmonary infundibular hypertrophy (one patient in each induction group) had sudden decreases develop in PaO₂ prior to initiation of cardiopulmonary bypass, which was felt to be a result of infundibular spasm.

**HEMODYNAMIC VARIABLES**

Within each sufentanil group, comparison of per cent change from the preinduction systolic blood pressure with the pressure obtained at each of the other data points showed significant increases (P < 0.05) in each group following periods of intraoperative stress (intubation, skin incision, and sternotomy). The only exception to this was for the 10 μg/kg group, where significant increases were approached but not reached at the post-skin incision and poststernotomy periods (fig. 1). Intergroup differences at the stress points were insignificant.

Within each sufentanil group comparison of per cent change from the preinduction diastolic blood pressure with the diastolic pressure obtained at each of the other data points showed significant increases (P < 0.05) for all groups only in the poststernotomy period (fig. 1). Intergroup comparisons failed to show significant between-group differences.
Fig. 1. The mean systolic and diastolic pressures with standard error of the mean at each of the data points for the 5, 10, and 20 μg/kg sufentanil induction groups.

Within each sufentanil group, comparison of per cent change from the preinduction heart rate with the heart rate obtained at each of the other data points showed a significant increase in heart rate during the postintubation and poststernotomy periods for the 5 μg/kg group ($P < 0.05$) and during the postintubation, preincision, and pre sternotomy points for the 10 μg/kg group ($P < 0.05$). There was no significant increase in HR at any of the stimulus points for the 20 μg/kg group, but a decrease in the HR occurred during the preincision period ($P < 0.05$). Intergroup comparisons showed the HR in the 5 μg/kg group to be significantly greater ($P < 0.05$) than the 20 μg/kg group at the postintubation and pre sternotomy points and the 10 μg/kg group to be significantly greater than the 20 μg/kg group at the postintubation, preincision, post skin incision, and pre sternotomy points ($P < 0.05$). The overall trend was for the 20 μg/kg group to have lower heart rates than the other two groups (see fig. 2).

**Catecholamines**

Statistical within-group comparisons of changes from mean preinduction epinephrine levels with each of the other sampling points as well as pre-post stimulus analysis failed to show within-group differences for any induction

| Table 2. Systolic Time Intervals Prior to and 10 min Following Induction of Anesthesia |
|--------------------------------|--------------------------------|--------------------------------|--------------------------------|----------------|------------|
| Sufentanil Group | 5 μg/kg | Before | After |
| Qo₂ Δ (ms)       | 514 ± 6.0 | 559 ± 12.0 |
| LVETI (ms)       | 384 ± 9.5 | 382 ± 8.6 |
| PEPI (ms)        | 137 ± 7.5 | 155 ± 11.4 |
| PEP/LVET (ms)    | 0.319 ± 0.04 | 0.379 ± 0.05 |
| EF (%)           | 53.5 ± 4.8 | 52.5 ± 3.2 |

| Sufentanil Group | 10 μg/kg | Before | After |
| Qo₂ Δ (ms)       | 496 ± 8.7 | 518 ± 6.5* |
| LVETI (ms)       | 354 ± 6.3 | 362 ± 7.2 |
| PEPI (ms)        | 146 ± 12.1 | 158 ± 9.8 |
| PEP/LVET (ms)    | 0.379 ± 0.04 | 0.429 ± 0.05 |
| EF (%)           | 51.7 ± 3.0 | 52.7 ± 2.3 |

| Sufentanil Group | 20 μg/kg | Before | After |
| Qo₂ Δ (ms)       | 503 ± 9.8 | 511 ± 6.2 |
| LVETI (ms)       | 376 ± 7.2 | 369 ± 6.8 |
| PEPI (ms)        | 132 ± 7.6 | 147 ± 5.6* |
| PEP/LVET (ms)    | 0.306 ± 0.03 | 0.367 ± 0.02* |
| EF (%)           | 62.8 ± 3.8 | 66.8 ± 6.4 |

* After value significantly ($P < 0.05$) greater than before value.
dose (fig. 3). Intergroup comparisons revealed the 5 and 10 μg/kg groups had significantly greater plasma epinephrine levels than the 20 μg/kg group \( (P < 0.05) \) at the postintubation point.

Statistical within-group comparisons of changes from mean preinduction norepinephrine level with each of the other sampling points showed no significant changes (fig. 4). Intergroup comparisons revealed that the 5 and 20 μg/kg groups were significantly lower than the 10 μg/kg group \( (P < 0.05) \) at both the postincision and poststernotomy points.

**Recovery**

Treatment groups had comparable times to recovery of the eyelash reflex and times to awakening (responding to commands) (see table 1). The 5 μg/kg sufentanil group had a significantly \( (P < 0.05) \) shorter time to extubation (median of 19.3 h with a range of 7.4–22.9 h) compared with either the 10 μg/kg group (median of 23 h with a range of 21.9–51.2 h) or the 20 μg/kg group (median of 25.3 h with a range of 22.1–47.9 h).

In all groups, in spite of the child showing awareness when stimulated within one hour after surgery, early extubation could not be performed due to shallow periodic breathing and carbon dioxide retention when attached to a T-piece and unstimulated. Because of this, morphine was given to nearly all patients in the postoperative period and controlled ventilation was continued until the following day when extubation could be performed. Except for one patient in the 5 μg/kg sufentanil group, all patients claimed amnesia during the intraoperative period. The one patient without amnesia did not experience pain but remembered “many bad things” and pointed at his sternum. Recovery from anesthesia was considered to be good to satisfactory by the anesthesiologists for all study patients.

**Discussion**

Sufentanil recently has been investigated as an alternative to fentanyl. Because of the nine times greater potency of sufentanil compared with fentanyl (4,521 times greater than morphine), sufentanil was felt to provide greater cardiovascular stability and fewer side effects.\(^1,12\) Though initial clinical evaluation seemed to support sufentanil’s superiority in providing hemodynamic and hormonal stability during surgery,\(^2,3,15\) further use found sufentanil inadequate in reliably suppressing cardiovascular responses to intraoperative stimulus.\(^5,6\) In evaluating sufentanil, a separation should be made between its cardiovascular effects during induction of anesthesia and its ability to provide a physiologically unresponsive state during maintenance of anesthesia.

In our group of pediatric cardiac patients, bolus doses of 5, 10, and 20 μg/kg of sufentanil provided a hemodynamically stable state during induction of anesthesia. The 1-4 min interval between initiation of anesthetic induction and loss of eyelash reflex was comparable with induction times found by others.\(^5,7\) However, the de-
crease in blood pressure observed by others during induction of anesthesia with sufentanil was not observed. Although sufentanil is reported to produce more severe bradycardia than fentanyl, concurrent use of pancuronium as a muscle relaxant has been found to prevent the decrease in heart rate. The increased heart rate seen in our patients may have resulted from early use of pancuronium.

The systolic time interval data supported the hemodynamic observations that sufentanil induction had little effect on the cardiovascular system. Of some concern was the significant increase in PEP/LVET for the 20 μg/kg group. The absence of appreciable changes in ejection fraction or diastolic pressure in this group of patients raises the possibility of a mild negative inotropic effect for sufentanil at the higher dosage range. This conclusion is not supported by one study that shows sufentanil in a 4 μg/kg dose increased left ventricular dp/dt max by 18% and in a dose as high as 500 μg/kg produced little cardiovascular depression.

A disturbing noncardiovascular side effect observed for each induction dose of sufentanil was the occurrence of myoclonic jerks and dystonic movements of the arms and legs. High bolus doses (2.5 mg/kg) of sufentanil in mice and dogs have been associated with seizure activity, but clinically relevant doses have not been found to produce seizures. Two minutes following a bolus of fentanyl, EEG sharp wave activity in adult men has been observed though this finding has not been substantiated by others. The presence of myoclonic jerks for all three induction doses argues against this being a dose-related central nervous system excitative response.

During induction of anesthesia, sufentanil produces chest wall rigidity in adults more frequently than fentanyl. However, the children in our study had a very low incidence of chest wall rigidity (1 out of 20 patients). Perhaps the early use of muscle relaxants or a difference in the physiologic effects of sufentanil in adults and children may have been responsible for this observation.

The maintenance phase of anesthesia for each sufentanil induction group was evaluated by comparing the hemodynamic responses before and after periods of intraoperative stimulation. For all groups, increases in systolic and diastolic blood pressure and heart rate were observed. However, the 20 μg/kg group did tend to respond less than the other two groups. This agrees with other reports that hypertensive responses to stimulation under sufentanil are inversely related to the dose. Similar observations of increases in blood pressure during skin incision and sternotomy were made for children who received either 5 or 10 μg/kg of sufentanil.

Urine and plasma catecholamine levels have been used as an indicator of anesthetic depth and adequacy of analgesia, and a correlation has been seen between sympathetic discharge and increases in plasma epinephrine and norepinephrine levels. A number of studies have been performed showing fentanyl prevents intraoperative increases in catecholamines, cortisol, antidiuretic hormone, and growth hormone. This is surprising, considering the high incidence of hemodynamic stress responses observed in patients receiving fentanyl anesthesia. De Lange et al. saw no change in antidiuretic hormone or growth hormone during the prebypass period in patients receiving 30 μg/kg of sufentanil, but Rolin et al. observed increases in epinephrine and norepinephrine at 30 and 60 min following skin incision in patients anesthetized both with fentanyl and sufentanil. Changes in plasma catecholamine levels in our patients did not reach significant levels due to major individual patient variation within each group.

Individual patient variation in hemodynamic and catecholamine response within groups may have resulted from many factors. Since sufentanil was provided by a bolus technique rather than a continuous infusion, a lack of serum steady state drug level between patients existed. Variations in volume of distribution, speed of distribution to different tissue beds, speed of metabolism, quantity of drug receptors, affinity of drug receptors, and availability of the receptors to the drug for each patient could have been responsible for the observed within-group variability. Though a dose–response relationship between sufentanil groups seemed to exist with higher sufentanil doses having better suppression of hemodynamic and hormonal responses, the marked individual patient differences within each group precluded a bolus sufentanil technique from providing a reliable anesthetic depth for all patients, even in the higher dosage range.

The occurrence of hemodynamic responsiveness to intraoperative stress with sufentanil anesthesia was of particular concern for children having infundibular pulmonary hypertrophy. Three of the children in our study were thought to have had episodes of infundibular pulmonary spasm prior to initiation of extracorporeal circulation that led to an increased hypoxic state; this was attributed to light anesthesia. Since sufentanil in any of the studied induction dose levels was not able to reliably provide a hemodynamic steady state, use of this agent as a sole anesthetic should be questioned for patients who might be harmed by tachycardia or a hypercontractile response.

One patient whose anesthesia was induced with 5 μg/kg sufentanil had a lack of amnesia during the operation. This seems to be the only instance of intraoperative awareness under sufentanil anesthesia in the literature, though two cases of awareness with seemingly appropriate levels of fentanyl anesthesia have been reported.
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After recovery from the muscle relaxant in the intensive care unit, the most striking feature noted in the study children was a dramatic startle followed by a period of extreme agitation. When attached to a T-piece and left unstimulated, the patients returned to a sleepy state with periodic respiration and CO2 retention. Because of the vigorous reaction to stimulation, most of the patients received sedation in the intensive care unit and were not ready for extubation until the following day. If sedation had not been used perhaps extubation could have been accomplished earlier. Sufentanil has been found to produce greater postoperative respiratory depression than fentanyl15 and episodes of apnea.25,26

Use of sufentanil as a sole anesthetic in bolus form did not provide a reliable depth of anesthesia for suppression of cardiovascular responses in any of the induction doses studied for children undergoing open heart surgery. However, sufentanil prevented major changes in blood pressure, heart rate, ejection times, and ejection fractions during the induction phase of anesthesia. Further evaluation of this agent in pediatric surgery might be directed toward constant infusion techniques or use of the agent as an adjunct to other inhalational or intravenous anesthetics.

References