Safety and efficacy of alfentanil and halothane in paediatric surgical patients

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Alfentanil, a congener of the opioid fentanyl, possesses properties that make it an attractive choice for use during short operative procedures. Since the pharmacodynamic aspects of alfentanil have not been well documented in children, this study was undertaken to evaluate the safety, efficacy, and dose requirements of alfentanil when used with nitrous oxide or halothane in paediatric patients. Eighty unpremedicated patients, ASA physical status I or II and aged 2–12 yr were studied. Patients were randomly assigned to one of four groups. After induction of anaesthesia with nitrous oxide, oxygen, and halothane, the groups were treated as follows. In Group 1 (n = 19), after halothane was discontinued, alfentanil 50 $\mu g \cdot kg^{-1}$ was infused over 30 sec. In Group 2 (n = 20), the end-tidal halothane was maintained at 0.5% and alfentanil 25 $\mu g \cdot kg^{-1}$ was infused. In Group 3 (n = 20), the end-tidal halothane concentration was maintained at 1% and alfentanil 12.5 $\mu g \cdot kg^{-1}$ was infused. In Group 4 (n = 21), the end-tidal halothane concentration was maintained at 1.5% and no alfentanil was administered. Patients in Groups 1, 2, and 3 received bolus doses of alfentanil 12.5 $\mu g \cdot kg^{-1}$ as needed to maintain haemodynamic stability. After alfentanil administration, there were transient decreases in systolic blood pressure in Groups 1 and 2, and in heart rate in Group 2. With surgical stimulation, haemodynamic stability was well maintained except in patients in Group 1, who had an increase in systolic blood pressure.

Key words

ANAESTHESIA: paediatric;
ANAESTHETICS, INTRAVENOUS: alfentanil.

Children Group 1 were alert sooner and their tracheas were extubated earlier than those in Groups 2, 3, and 4. The four groups were similar in postoperative narcotic analgesic administration and incidence of vomiting. In summary, alfentanil (12.5–50.0 $\mu g \cdot kg^{-1}$) was a safe anaesthetic, whether combined with nitrous oxide alone or with nitrous oxide and halothane.

On connaît mal la pharmacocinétique de l'alfentanil chez les enfants même si certaines des propriétés de ce parent du fentanyl devraient en favoriser l'usage lors de courtes interventions. Nous avons donc évalué chez 80 enfants la sûreté et l'efficacité de diverses combinaisons d'alfentanil et d'halothane en présence de protoxyde d'azote. On randomisait d'abord les enfants de 2 à 12 ans et de classe ASA I ou 2 en quatre groupes. Sans prémédication, on induisait l'anesthésie de façon habituelle avec de l'oxygène, du protoxyde d'azote et de l'halothane. Puis, on cessait l'halothane chez les enfants du groupe 1 (n = 19) pour leur injecter 50 $\mu g \cdot kg^{-1}$ d'alfentanil en 30 secondes. Pour le groupe 2 (n = 20), on ajustait l'halothane en fin d'expiration à 0,5% et on y ajoutait 25 $\mu g \cdot kg^{-1}$ d'alfentanil. Le groupe 3 (n = 20) avait une combinaison d'halothane 1,0% et 12,5 $\mu g \cdot kg^{-1}$ d'alfentanil et enfin, le groupe 4 (n = 21) n'avait que 1,5% d'halothane sans alfentanil. On injectait subséquemment des doses de 12,5 $\mu g \cdot kg^{-1}$ d'alfentanil aux enfants des groupes 1,2 et 3 afin d'assurer la stabilité hémodynamique. Transitoirement, avec l'injection d'alfentanil, la tension artérielle systolique diminua dans les groupes 1 et 2 et le pouls ralentit dans le groupe 2. Il n'y eut pas de changement hémodynamique associée à la stimulation chirurgicale sauf dans le groupe 1 où la tension artérielle systolique s'éleva. Les enfants du groupe 1 s'éveillèrent plus rapidement et purent être extubés plus tôt que ceux des autres groupes. En postopératoire, les besoins en analgésiques et l'incidence de vomissement furent semblables chez les quatre groupes. Bref, en doses de 12,5 à 50 $\mu g \cdot kg^{-1}$, l'alfentanil associé au protoxyde d'azote constitue un anesthésique sûr, qu'il soit ou non combiné avec de l'halothane.

Alfentanil, a congener of the opioid fentanyl, possesses pharmacokinetic properties which make it an attractive choice for use during short operative procedures. Its rapid onset, large margin of safety, small volume of distribu-

tion, short elimination half-life, and stable haemodynamic properties have led to its use in adults both as a total opioid anaesthetic, and as an analgesic supplement to nitrous oxide anaesthesia.[1-3] Although studies have revealed alfentanil to have a smaller volume of distribution and a shorter elimination half-life in children than in adults,[4] the pharmacodynamic aspects of alfentanil in children have not been as well documented. This study was undertaken to evaluate the safety, efficacy, and dose requirements of alfentanil administered as a bolus, with nitrous oxide or with halothane, in paediatric patients undergoing short surgical procedures.

Methods

The study was approved by the hospital's Human Rights Committee, and informed, written consent was obtained from a parent and, when age appropriate, from the patient. Eighty unpremedicated patients of ASA physical status I or II and ages 2–12 yr were studied. All were undergoing orthopaedic, general surgical, or otorhinolaryngologic procedures lasting less than one hour. Patients with known liver or kidney disease were excluded from the study.

Patients were routinely monitored with ECG, pulse oximetry, oscillometric measurements of blood pressure (Dinamap®), and end–tidal gas analysis (Puritan-Bennett® Anesthetic Agent Monitor 222). General anaesthesia was induced with nitrous oxide, oxygen, and halothane by mask. An intravenous catheter was inserted and atracurium besylate, 0.5 mg·kg^{-1} was administered to facilitate tracheal intubation and to prevent chest wall rigidity. After the induction of anaesthesia the patients were randomly assigned to one of four groups that differed from each other with respect to the amount of alfentanil and/or halothane that was administered.

In Group 1 (alfentanil only, n = 19), halothane was discontinued following the induction of anaesthesia. With the patient breathing 70% nitrous oxide and 30% oxygen, and the end–tidal halothane concentration measuring less than 0.1%, alfentanil 50 µg·kg^{-1} was infused over 30 sec. Three minutes after the injection of alfentanil, the trachea was intubated. Anaesthesia was maintained with 70% nitrous oxide and 30% oxygen, and ventilation was controlled to maintain an end–tidal PCO$_2$ between 30–40 mmHg. Increases in heart rate or systolic blood pressure greater than 20% above baseline values were treated with incremental bolus injections of 12.5 µg·kg^{-1} of alfentanil, while decreases in heart rate of greater than 25% below baseline values were treated with 20 µg·kg^{-1} of atropine.

Patients in Groups 2 and 3 (n = 20 each) received nitrous oxide and oxygen as well as halothane and

alfentanil. In Group 2, end–tidal halothane was maintained at 0.5% and the initial alfentanil infusion was 25 µg·kg^{-1}. In Group 3 the end–tidal halothane concentration was maintained at 1% and the initial alfentanil infusion was 12.5 µg·kg^{-1}. As in Group 1, increases in blood pressure and heart rate greater than 20% above baseline values in Groups 2 and 3 were treated with incremental injections of 12.5 µg·kg^{-1} of alfentanil, and decreases in heart rate greater than 25% below baseline values were treated with 20 µg·kg^{-1} of atropine.

For patients in Group 4 (halothane only, n = 21) nitrous oxide and oxygen were continued after induction and the end–tidal halothane concentration was maintained at 1.5%. No alfentanil was administered. Increases in heart rate or blood pressure greater than 20% of baseline values were treated with 0.5% increments in the halothane concentration. Atropine (20 µg·kg^{-1}) was administered for decreases in heart rate greater than 25% below baseline values.

Haemodynamic measurements were made at the following times: on admission to the hospital (baseline), on arrival in the operating room, one minute before alfentanil injection, one minute after alfentanil injection, one minute before intubation, one minute after intubation, one minute before first surgical stimulation, and one minute after first surgical stimulation. Vital signs were recorded at five-minute intervals during the operative procedure and on admission to the postanaesthetic recovery area.

The anaesthetic gases were discontinued at the end of the surgical procedure, and residual neuromuscular blockade was antagonized. Recovery from anaesthesia was assessed by the investigators as the time from discontinuation of the last anaesthetic gas to (1) extubation and (2) alertness. Respiratory depression, evidenced by a slow respiratory rate or a requirement for a narcotic antagonist, was recorded. In the postanaesthetic recovery room, pain and vomiting were evaluated every five minutes by recovery room nurses who were unaware of group assignment. In preverbal children, pain was quantified as the use of opioid analgesics, which were administered to children who could not be comforted by swaddling, tactile soothing, or an oral pacifier. In older children opioid

TABLE I Demographic data

Group	n	Age (yr)	Weight (kg)	Duration of anaesthesia (min)
1	19	6.2 ± 2.7	23.3 ± 8.5	50 ± 21
2	20	6.1 ± 2.3	21.6 ± 6.1	45 ± 15
3	20	6.1 ± 2.8	25.3 ± 10.6	44 ± 10
4	21	6.9 ± 2.7	25.3 ± 10.6	48 ± 19

TABLE II   Dose of alfentanil (mean ± SD) and atropine requirements

Group	Dose of alfentanil (μg·kg⁻¹·min⁻¹)*	Number of patients receiving atropine
1	1.59 ± 0.48†	6 (31.5%)
2	0.79 ± 0.29	7 (35.0%)
3	0.61 ± 0.36	3 (15.0%)
4	0 ± 0	1 (4.7%)

*Calculated as the total dose divided by body weight and duration of anesthesia.
†Significantly higher than doses in Groups 2 and 3.

analgesics were administered when pain was expressed verbally. Vomiting and retching were recorded as either present or absent.

Statistical analysis included repeated measures analysis of variance, the Student-Newman-Keuls test, and the chi-square test. Significance was considered for $P < 0.05$.

Results

There were no statistical differences in age, weight, type of surgery, or duration of anaesthesia among the four groups (Table I). Alfentanil dosage requirements were similar in Groups 2 and 3 and significantly lower in these groups than in Group 1 (Table II). There were no statistical differences among the groups in the number of patients requiring atropine (Table II).

The haemodynamic values obtained on admission to the operating room were elevated, probably because of anxiety; therefore, the values obtained on admission to the hospital were used as the baseline values for the study. After induction of anaesthesia, but before the alfentanil injection, systolic blood pressure and heart rate remained similar to control values (Tables III and IV). After the administration of alfentanil, however, there were transient significant decreases in mean systolic blood pressure in Groups 1 and 2 (from 103 to 86 mmHg and from 101 to 88 mmHg, respectively, $P < 0.01$) and in heart rates in Group 2 (from 108 to 83 beats per min). After tracheal intubation both heart rate and systolic blood pressure returned to near control values. With surgical stimulation, haemodynamic stability was well maintained except in patients in Group 1, who had an increase in systolic blood pressure (from 111 to 121 mmHg).

The patients in Group 1 were alert in a shorter time and the tracheas were extubated sooner than those in Groups 2-4 (Table V).

The four groups were similar in postoperative administration of narcotic analgesics. A single small dose of naloxone hydrochloride was administered to two patients in Group 1. In both these children an incremental dose of alfentanil (12.5 μg·kg⁻¹) had been administered less than two minutes before the completion of surgery. In both patients spontaneous ventilation resumed promptly and subsequently recovery was uneventful.

There was no difference among groups in incidence of postoperative vomiting (Table V).

TABLE III   Systolic blood pressure (mmHg)

Group	Baseline	On arrival at OR	Before alfentanil	After alfentanil	Before intubation	After intubation	Before incision	After incision
1	103 ± 10	115 ± 14	96 ± 6	86 ± 10†	90 ± 9*	104 ± 13	111 ± 13	121 ± 11*
2	101 ± 10	117 ± 14*	95 ± 8	88 ± 9†	87 ± 8†	98 ± 10	101 ± 12	111 ± 16
3	98 ± 14	115 ± 15†	98 ± 10	92 ± 16	91 ± 16	97 ± 14	97 ± 13	106 ± 15
4	100 ± 8	116 ± 15*	92 ± 8	90 ± 7	91 ± 8	104 ± 10	98 ± 8	105 ± 11

*$P < 0.05$ vs baseline.
†$P < 0.01$ vs baseline.

TABLE IV   Heart rate (beats per minute)

Group	Baseline	On arrival at OR	Before alfentanil	After alfentanil	Before intubation	After intubation	Before incision	After incision
1	100 ± 16	111 ± 20	88 ± 16	79 ± 17*	83 ± 17	104 ± 23	114 ± 20	117 ± 20
2	108 ± 14	115 ± 23	96 ± 17	83 ± 17†	84 ± 17*	103 ± 21	105 ± 24	113 ± 23
3	101 ± 17	113 ± 17	100 ± 20	89 ± 23	84 ± 26	106 ± 23	105 ± 25	118 ± 27
4	94 ± 19	109 ± 22	91 ± 16	91 ± 16	90 ± 17	113 ± 18	100 ± 16	110 ± 21

*$P < 0.05$ vs baseline.
†$P < 0.01$ vs baseline.

TABLE V   Emergence times and recovery characteristics

Group	Time to extubation	Time to alertness	Number of patients requiring naloxone	Number of patients receiving opioids in the recovery room	Number of patients vomiting in the recovery room
1	3 ± 2*	10 ± 9*	2 (10%)	5 (26%)	10 (52%)
2	6 ± 2	25 ± 11	0 (0)	7 (35%)	11 (55%)
3	8 ± 4	21 ± 11	0 (0)	12 (60%)	9 (45%)
4	8 ± 3	24 ± 12	0 (0)	11 (52%)	4 (19%)

*$P < 0.05$ compared with Groups 2, 3, and 4.

Discussion

Ideal intravenous anaesthetics for paediatric patients should provide an adequate depth of anaesthesia. haemo-dynamic stability, rapid induction and emergence, and minimal postoperative side-effects. In adult volunteers, low-dose alfentanil results in no significant haemo-dynamic changes. At high doses, however, alfentanil decreases heart rate, mean blood pressure, and systemic vascular resistance, and increases pulmonary capillary wedge pressure, right atrial pressure, and pulmonary vascular resistance.[5,6] Less information is available regarding alfentanil's cardiovascular effects in children. Marlow et al. reported a 20% decrease in mean arterial pressure in premature infants following a two-minute infusion of 20 μg·kg^{-1} of alfentanil.[7] In contrast, Davis et al. found no significant haemodynamic changes in premature infants receiving 25 μg·kg^{-1} alfentanil.[8]

Like the other opioid compounds, alfentanil has a vagotonic effect. The differences among groups and the need for atropine following the initial dose of alfentanil did not reach statistical significance. Although the incidence of bradycardia ranged from 5 to 35%, it was not statistically significant among groups. It is our belief that no matter what the aetiology, it is preferable to prevent bradycardia in all patients rather than treat it in a few. Thus, we routinely administer atropine before the injection of alfentanil.

In healthy children, 50 μg·kg^{-1} of alfentanil as a bolus for induction of anaesthesia does not appear to suppress completely the haemodynamic response to a surgical stimulus 15 min later. Extrapolated data from our previous pharmacokinetic studies in children suggest that this time interval would correspond to a plasma concentration less than 200 ng·ml^{-1}.[8] Ausems et al. suggest that the effective plasma concentrations for 50% of patients (cp50) for intubation, lower abdominal incision, and upper abdominal incision were 425, 309, and 412 ng·ml^{-1}, respectively.[9] Although additional increments of 12.5 μg·kg^{-1} controlled the hypertensive response, it appears that for procedures lasting less than one hour,

either a higher initial bolus dose or a continuous infusion of alfentanil should be considered.

The mean dose requirements for alfentanil were calculated for each group by dividing the total dose of alfentanil administered during the surgery by the patient's weight and the duration of anaesthesia. The dose requirements were diminished in patients who also received halothane (1.59 ± 0.48 μg·kg^{-1}·min^{-1} in Group 1 vs 0.79 ± 0.29 μg·kg^{-1}·min^{-1} in Group 2, $P < 0.05$). The requirement of 1.59 μg·kg^{-1}·min^{-1} alfentanil with nitrous oxide and oxygen is similar to that in adults.[10] Although dose requirements for alfentanil decreased with increasing concentrations of inspired halothane, there were no statistical differences in dose requirements between Groups 2 and 3. The time to extubation and time to alertness were statistically shorter in Group 1 than in Groups 2, 3, and 4. More rapid awakening with an alfentanil anaesthetic than with either isoflurane or halothane has been reported in adults.[11,12]

Nausea, vomiting, and pain are common problems during the recovery period. The incidence of vomiting in the four groups ranged between 19 and 52%, but the differences did not achieve statistical significance. Although we are unable to document a significant difference between the four groups, this may be a function of our sample size. The overall incidence in this study was 42%, a value comparable to those reported in adults after alfentanil.[10] Although the incidence of vomiting among children receiving alfentanil appears similar, this study may have underestimated the true incidence of postoperative vomiting, since only vomiting occurring in the recovery room was recorded. The reported incidence of postoperative vomiting following general anaesthesia in paediatric patients ranges from 5% to 42%.[13,14] In a study of paediatric outpatients, Patel and Hannallah reported that postoperative vomiting was the most frequent complication, occurring in 35% of patients, and that protracted vomiting accounted for one-third of the unscheduled admissions to the hospital following outpatient surgery.[15] Postoperative vomiting following the use of

opioids may be a major drawback to their intraoperative use. Medication with antiemetics can reduce the incidence of postoperative vomiting following anaesthesia as has been demonstrated in patients having strabismus surgery.[16] However, whether such medication would be effective with other surgical procedures and with opioid anesthesia remains an important question to be answered.

The occurrence of postoperative pain in preverbal children is difficult to assess objectively. Behaviour caused by separation from parents, fear, or thirst can easily obscure or be mistaken for postoperative pain. Realizing these limitations, we indirectly assessed pain by evaluating postoperative opioid administration by recovery room nurses who judged the need for analgesics and were unaware of the patient's anaesthetic. In preverbal children, opioids were administered when crying could not be comforted by an oral pacifier, tactile soothing, or swaddling. The absence of significant differences in postoperative analgesic requirements between Group 1 and Groups 2, 3, and 4 may be due to the very short half-life of alfentanil. However, we cannot rule out the variability of the subjective assessment of pain by the nursing staff. Thus, patients receiving intraoperative alfentanil may still need postoperative pain medication.

In summary, we found alfentanil ($12.5-50.0 \mu g \cdot kg^{-1}$) to be a safe anaesthetic, whether combined with nitrous oxide alone or with nitrous oxide and halothane. When used with nitrous oxide, alfentanil provided a rapid emergence from anaesthesia. An initial bolus injection of $50 \mu g \cdot kg^{-1}$, however, does not blunt the response to surgical incision in children. Consequently, a larger initial bolus or a continuous infusion is required.

Acknowledgements

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