Multicentre Trial

Sufentanil anaesthesia for major surgery: the multicentre Canadian clinical trial

John M Murkin MD FRCPC

One hundred and forty-one investigators from 45 institutions across Canada participated in the phase 4 clinical trial of sufentanil citrate involving 616 patients. All patients were ASA physical status class I, II, or III, undergoing elective, non-cardiac, major surgical procedures. The average duration of surgery was 1.98 hr and mean dosage of sufentanil was 1.24 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. Supplemental inhalational anaesthesia was administered to 266 patients (43 per cent). Eighty-six patients required naloxone in the immediate postoperative period. Eighty per cent of these patients had received in excess of 1.0 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ of sufentanil. One hundred and twenty-nine adverse reactions were reported as disturbing and possibly drug-related. Profound bradycardia or sinus arrest was reported in four cases and disturbing hypotension in 37. None of these events required termination of the procedure. The induction, maintenance and recovery phases were rated as good or satisfactory by the participating investigators in 94, 92 and 93 per cent of cases respectively.

Key words
ANAESTHESIA, INTRAVENOUS: sufentanil; SURGERY: general.

Sufentanil citrate (Sufenta®) is an extremely potent narcotic/anaesthetic of the anilopiperidine series. Sufentanil has a very high stereospecific binding affinity for μ-opiate receptor sites, demonstrating 7.7-fold greater affinity than fentanyl.[1] This correlates closely with clinical observations that sufentanil is five to ten times more potent than fentanyl. It may also account for the apparent ability of sufentanil to provide complete anaesthesia as shown by a greater than 90 per cent reduction in halothane MAC in rats.[2] Highly lipophilic, sufentanil rapidly penetrates biological membranes to produce onset of clinical effects more quickly than fentanyl.[3] Although the plasma clearance of sufentanil is similar to that of fentanyl, because of a smaller volume of distribution, the half-life of its terminal elimination phase is shorter and thus its elimination is more rapid.[4] Because of these pharmacological attributes, sufentanil is a potentially advantageous new anaesthetic agent.

Beginning in October 1985, before its national release for clinical use, sufentanil underwent a multi-centre trial evaluating its efficacy and safety (Phase 4 Canadian clinical trial) in patients undergoing elective major surgery. This study represents the largest cumulative experience reported with the use of this agent, involving 141 anaesthetists and over 600 patients.

Methods

Before its commencement, approval for the study was obtained from the institutional review board, or its local equivalent. Patients who were undergoing elective major surgery, less than 70 years of age, American Society of Anesthesiologists (ASA) Physical Status class I, II, or III, and not experiencing any type of arrhythmia, were included in the study (Tables I, II). In addition to those not meeting the above requirements, specific exclusion criteria included control heart rate > 90 bpm or body weight less than 40 kg. All concurrent medications were administered as necessary on the day of surgery (Table III). Anaesthetic premedication included diazepam 5–10 mg

TABLE I   Patient demographics (data are mean ± SD)

Age (yrs.)	46±0.6
Sex (M/F)	406/210
Weight (kg)	69.3±0.6
ASA I	57.6%
ASA II	36.1%
ASA III	6.3%
Procedure	
Gastrointestinal	184
Genitourinary	176
Orthopaedic	163
Neurosurgical	34
Other	59
Duration of surgery (hr)	1.98±0.05

TABLE II   Frequency of abnormal body systems

	n	%
Heart	67	10.8
Cardiovascular	101	16.4
Pulmonary	103	16.7
Gastrointestinal	114	18.5
Metabolic	47	7.6
Renal	25	4.0
Central nervous system	38	6.2
Other	127	20.6

n = number of patients; % = percentage of 616 patients.

and droperidol 0.625–1.25 mg. Following pre-oxygenation, 0.05 mg·kg^{-1} of d-tubocurarine, 1–3 μg·kg^{-1}·sufentanil (dosage to be calculated as 1 μg·kg^{-1}·hr^{-1}), sufficient thiopentone for loss of eyelash reflex (0–2 mg·kg^{-1}), and 1.5 mg·kg^{-1} succinylcholine were administered followed by tracheal intubation. An-aesthesia was maintained with N$_2$O/O$_2$ (70:30) and pancuronium 0.07–0.1 mg·kg^{-1}, given in increments of 2 mg each. Additional 10–25 μg increments of sufentanil and supplementation with low concentrations of a volatile inhalational agent were administered as necessary for haemodynamic stability.

   Heart rate (HR) and systolic, diastolic and mean arterial pressures (SAP, DAP, MAP) were recorded prior to induction of anaesthesia, and one minute following sufentanil administration, post-intubation, and post-incision, five minutes post-incision, and at ten-minute intervals thereafter until the end of the procedure. The duration of anaesthesia and surgery and times until arousal, response to verbal commands, and extubation were recorded. All adverse effects (Table IV) occurring during induction, maintenance and recovery from anaes-thesia were recorded and classified by the attending anaesthetist as either disturbing, or non-disturbing, and as possibly drug-related or non-drug-related. Investigators also rated sufentanil for induction, maintenance and recovery on a three-point scale: good, satisfactory, or bad. Patients were asked to select their last recollection

TABLE III   Concomitant medications

	n	%
Beta-blocker	33	5
Calcium blocker	5	0.8
Diuretic	46	7.5
Antihypertensive	21	3.4
Antiinflammatory	82	13.3
Sedative/tranquilizer	121	19.6
Antihistamine	32	5.2
Hypoglycaemic	15	2.4

prior to surgery from the following: in the ward before operation, journey to the operating room (OR), in the OR, or falling asleep (induction), and their first recollection upon awakening from among the following: during the operation, postoperatively in the OR, or in the intensive care unit.

   Categorical data were summarized as frequencies whereas mean values were determined for continuous variables. Cardiovascular variables were analysed using ANOVA, where measurements over time were compared with control values using the Bonferroni correction for multiple comparisons to determine statistical signifi-cance. Chi-square analysis was applied to demographic data and to determine the relationship between dosage of sufentanil (greater than or less than 1 μg·kg·hr^{-1}) and naloxone administration. Following initial analysis, pa-tients were grouped into two categories, those requiring supplemental volatile agents (supplement group) and those not (non-supplement group). Haemodynamic and demographic data were then compared between these groups. Data are reported as mean ± SEM where P < 0.05 was required for statistical significance.

Results

One hundred and forty-one anaesthetists from 45 institu-tions investigated 616 patients. In fifteen patients a finishing time was not recorded, therefore these patients were excluded from the dosage–time analysis. Patient demographics are shown in Tables I to III, while haemodynamic data, divided into supplement and non-supplement groups, appear in Figures 1 and 2.

Use of volatile supplements

Fifty-seven per cent of patients, 350, did not require supplementation with volatile agents. There was a signifi-cantly greater proportion of males, and a significantly higher incidence of less fit patients (41 vs 32 per cent ASA II; 9 vs 4.2 per cent ASA III) in the supplement vs non-supplement groups, respectively. Preoperatively, this group contained more "tense" and fewer "sleeping" patients than the non-supplement group.

   Overall the duration of surgery was greater in the

N (+)   263 264 264 261 262 264 264 262 259 248 230 209 188 167 152 136 118 100 82 64 56   48 39
N (−)   348 349 349 343 350 350 350 344 322 295 248 208 170 138 115 88 78 67 56 38 33   30 26
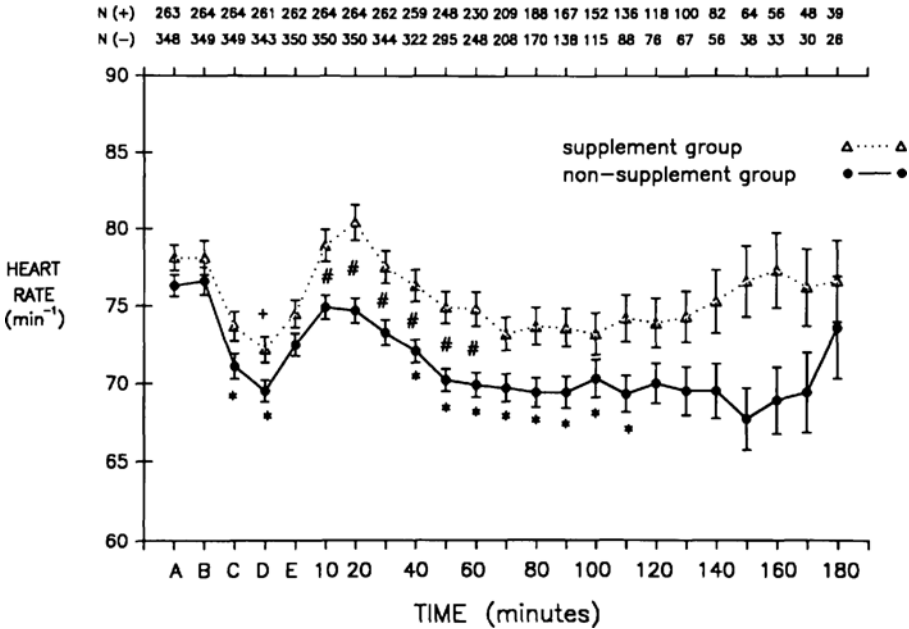

FIGURE 1   Average heart rate for all cases where N(+) represents numbers of patients in the supplement group and N(−) the numbers of patients in the non-supplement group. Data are mean ± SEM. A = control, B = one minute after sufentanil, C = one minute after intubation, D = one minute post-incision, E = five minute post-incision. * Indicates P < 0.05 compared with control in the non-supplement group; + indicates P < 0.05 compared with control in the supplement group; # indicates P < 0.05 between groups.

supplement vs the non-supplement groups (2.33 vs 1.71 hr) and patients requiring volatile supplements also received a significantly greater dosage of sufentanil 2.2 vs 1.98 µg·kg⁻¹. There was a significant difference in mean times to awakening (11.4 vs 7.8 min) and correct orientation (37.8 vs 30.6 min) but not in times to extubation in the supplement vs the non-supplement groups.

Haemodynamic data

The haemodynamic data are presented in Figures 1 and 2, divided into supplement or non-supplement groups. There was no significant change in heart rate in either group 1 min after initial sufentanil administration. Heart rates during 50 per cent of the time periods in the non-supplement group were significantly lower than control. Heart rates for the supplement group were significantly higher than this, and except at 1 min post-incision, did not differ significantly from control (Figure 1). The percent difference relative to control (difference/control × 100) shows the greatest heart rate

TABLE IV   Adverse experiences*

	Number of patients	
	n	%
Hypotension	37	6.01
Bradycardia	21	3.41
Chest wall rigidity	18	2.92
Vomiting	13	2.11
Nausea	10	1.62
Tachycardia	8	1.30
Hypertension	6	0.97
Coughing	2	0.32
Allergic skin reaction	1	0.16
Venous irritation	1	0.16
Laryngospasm	1	0.16
Other	11	1.79

*Reported as both "disturbing" and "possibly drug-related."

change of −8.9 to occur in the non-supplement group 1 min post-incision while 1 min after intubation there was a change of −6.8 per cent.
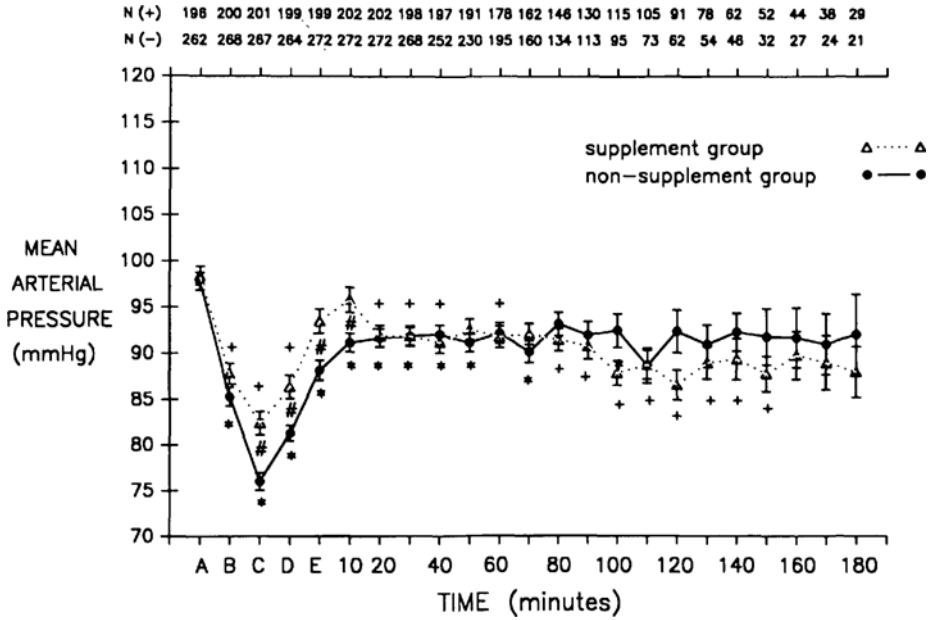
FIGURE 2   Average mean arterial pressure for all cases where N(+) represents numbers of patients in the supplement group and N(−) is numbers of patients in the non-supplement group. Data are mean ± SEM. A = control, B = one minute after sufentanil, C = one minute after intubation, D = one minute after post-incision, E = five minute post-incision. * Indicates P < 0.05 compared with control in the non-supplement group; + indicates P < 0.05 compared with control in the supplement group; # indicates P < 0.05 between groups.

For MAP, over half of all measurements in both groups were significantly lower than baseline (Figure 2). In the non-supplement group there was a 12.8 per cent reduction in MAP after sufentanil administration followed by a 22.3 per cent reduction following intubation. This represented the greatest reduction in mean arterial pressure which thereafter remained about ten per cent lower than baseline from 5 min after incision in both groups. From 1 min after

TABLE V   Number of adverse experiences reported

Number of experiences reported per patient	n	%
None	185	30.0
1	171	27.8
2	157	25.5
3	58	9.4
4	33	5.4
5	9	1.5
6	3	0.5

intubation until 10 min after incision MAP was significantly lower in the non-supplement vs the supplement group. Both SAP and DAP were also reduced about ten per cent with initial sufentanil administration and were reduced approximately 18.5 per cent 1 min after intubation. From 5 min post-incision the reductions in both SAP and DAP were less than ten per cent of baseline values.

Adverse experiences

A total of 854 adverse experiences were reported, of which 30.7 per cent, 263, were considered by the reporting anaesthetist as "possibly" drug-related. Of these, 15.1 per cent, 129, were reported as both "disturbing" and "possibly drug-related." As indicated in Table V, the number of adverse experiences reported ranged from none, 30 per cent, to six, 0.5 per cent, per patient. Adverse experiences included hypotension, hypertension, bradycardia, tachycardia, chest wall rigidity, nausea, vomiting and laryngospasm (Table IV). There were no significant differences in incidence between the supplement or non-supplement groups.

Of the adverse reactions reported to be both disturbing and drug-related, there were 21 episodes of bradycardia, four of which involved either extreme bradycardia, <10 bpm, or sinus arrest of up to 20 sec. All episodes occurred shortly following initial sufentanil administration or during laryngoscopy and intubation, and responded to atropine and/or ephedrine, or resolved spontaneously. There was no significant correlation with ASA status, chronic usage of beta adrenergic (n = 3) or calcium entry blockers (n = 0), or diuretics (n = 3), in comparison with the study group as a whole.

Disturbing hypotension was observed in six per cent of cases. The majority of these cases involved a progressive reduction in blood pressure following sufentanil administration that resolved, untreated, following surgical stimulation. In at least two cases, however, profound hypotension necessitated both fluid and vasopressor administration. Excessive thiopentone administration does not seem to have been a significant factor as neither of these patients received more than 2 mg·kg^{-1} thiopentone during induction of anaesthesia. Chronic beta-blocker usage (n = 6) did correlate significantly with occurrence of hypotension (P < 0.05) whereas diuretic (n = 4) or calcium blocker (n = 0) usage did not. Similarly, there was a significantly (P < 0.001) higher incidence of disturbing hypotension amongst less fit patients (ASA II or III).

Chest wall rigidity was reported as disturbing in 2.9 per cent of cases. In several instances there was complete inability to ventilate the patients' lungs until neuromuscular relaxants had been administered. Myoclonus, and seizure-like activity with concomitant chest wall rigidity, occurred during induction of anaesthesia in two patients following sufentanil administration.

Naloxone administration
Eighty-six patients received naloxone in the immediate postoperative period. There was a highly significant correlation, P < 0.002, between naloxone administration and dosage of sufentanil in excess of 1.0 μg·kg^{-1}·hr^{-1}. Only 17 of 240, 7.1 per cent, patients receiving sufentanil 1.0 μg·kg^{-1}·hr^{-1} or less required naloxone, whereas 69 of 361 (19.1 per cent) patients exceeding 1.0 μg·kg^{-1}·hr^{-1} required narcotic reversal. The average sufentanil dosage in the naloxone treated patients, 86/616, was 1.56 μg·kg^{-1}·hr^{-1} vs 1.19 μg·kg^{-1}·hr^{-1} in the non-naloxone group, 530/616. There were no significant differences in age of patients, use of volatile agents, or duration of surgery between patients receiving or not receiving naloxone.

Anaesthetic evaluations
Overall, the participating investigators rated 73 per cent

of the anaesthetic inductions as good, 21 per cent as satisfactory and six per cent as bad; 62.4 per cent of maintenance periods were rated as good, 29.7 per cent were rated satisfactory and 7.9 per cent as bad; and 64.3 per cent of recovery phases were rated as good, 28.5 per cent were satisfactory and 7.2 per cent were rated as bad. The anaesthetists' ratings of the induction, maintenance and recovery phases were all significantly better in the non-supplement group. This was most pronounced during the maintenance phase where 75 per cent in the non-supplement versus 45 per cent in the supplement group, P < 0.0001, were rated as good, although there were few significant differences between the mean hemodynamic variables of either group (Figures 1, 2).

One patient, 0.18 per cent, reported transient intraoperative awareness during a total hip arthroplasty. This patient received diazepam 7.5 mg PO and droperidol 1.25 mg IV as premedication, a total of 100 μg sufentanil, 0.66 μg·kg^{-1}·hr^{-1}, and 70 per cent N$_2$O intraoperatively. Fifteen per cent of patients had their first post-anaesthetic recollection in the operating room, 82 per cent in the recovery room and three per cent in their room.

Discussion
This study represents the largest cumulative experience reported to date with sufentanil. The clinical acceptability, haemodynamic variables, and type and incidence of complications reported here represent over 600 sufentanil anaesthetics. Due to the large number of investigators enrolled, these experiences are representative of a broad range of clinical anaesthetic practice. By virtue of its multicentre design and the large number of participating investigators, inter-observer variability may have been increased in this study. The categorization of adverse experiences into "disturbing" or "drug related" is necessarily subjective, and, being derived from the observations of 141 participating anaesthetists, necessarily contains more latitude than observations made by a single author or a small group. The absence of a control group makes comparison between this technique and others difficult. The ratings of the anaesthetic technique as given by the anaesthetists involved in this study does, however, give a good indication of the overall clinical acceptability of sufentanil anaesthesia.

The anaesthetic protocol employed in this study was rated as good or satisfactory by the participating anaesthetists in over 90 per cent of cases. In the majority of cases a smooth and rapid induction of anaesthesia was observed, with haemodynamic stability maintained for the duration of the procedure. Although statistically significant changes from control were detected for all haemodynamic variables, due to the large sample size, small differences can be detected as statistically significant. As indicated in

Table IV, these were rarely felt to be of clinical significance by the various investigators. Of the total group 3.4 per cent, 21, of patients were reported to have had a bradycardia and six per cent, 37, experienced a hypotensive episode felt to be both "possibly drug-related" and "disturbing."

Bradycardia and chest wall rigidity are common side-effects of narcotic administration. Narcotics produce bradycardia via a centrally mediated increase in efferent vagal activity.[5] For fentanyl, this tendency is enhanced by succinylcholine administration but responds to prompt administration of atropine.[6]

Rigidity appears to be mediated by μ receptors located in the caudate nucleus.[7] Chest wall rigidity can produce difficulty with ventilation as a result of contraction of both thoracic and abdominal musculature, and may also involve glottic and supraglottic obstruction.[8] Rigidity may be provoked or enhanced by auditory or tactile stimulation of the patient and is readily treated by administration of neuromuscular blocking agents.[8] Concomitant myoclonic activity of the extremities may appear as seizure-like but is not accompanied by cortical excitation and appears rather to be a particular manifestation of rigidity.[9]

Sufentanil does not cause hypotension due to myocardial depression or histamine release[10] but it is a potent inhibitor of central sympathetic outflow and may thus unmask relative hypovolaemia. In dogs, the reduction in arterial pressure following fentanyl administration has been shown to correlate directly with the level of circulating catecholamines.[11] Hypovolaemia should thus be sought actively and treated before induction of anaesthesia. As indicated in this study, concomitant beta-blocker usage, particularly in less fit patients, may aggravate the potential for hypotension, possibly by impairing compensatory mechanisms.

Respiratory depression from sufentanil is dose-related and reversible with a narcotic antagonist. In this study, patients receiving in excess of $1.0 \ \mu g \cdot kg^{-1} \cdot hr^{-1}$ of sufentanil were significantly more likely to require naloxone, $P < 0.002$, than those receiving a lower dose, consistent with the recommended administration guidelines. Patients requiring a deeper level of anaesthesia can be readily treated with low concentrations of an appropriate volatile inhalational agent.

Careful preoperative assessment of the patient's circulatory volume, the administration of muscle relaxants concomitantly with sufentanil, the ready availability of vagolytic agents, and the administration of a cumulative dosage of sufentanil no greater than $1.0 \ \mu g \cdot kg^{-1} \cdot hr^{-1}$ should prevent the majority of adverse reactions.

References
1 *Leyson JE, Gommeren W, Niemegeers CJE.* (^{3}H) Sufentanil, a superior ligand for μ-opiate receptors: binding properties and regional distribution in rat brain and spinal cord. Eur J Pharmacol 1983; 87: 209–25.

2 *Hecker BR, Lake CL, DiFazio CA, Moscicki JC, Engle JS.* The decrease of the minimum alveolar anesthetic concentration produced by sufentanil in rats. Anesth Analg 1983; 62: 987–90.

3 *DeLange S, Boscoe MJ, Stanley TH, Pace NC.* Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. Anesthesiology 1982; 56: 112–8.

4 *Bovill JG, Sebel PS, Blackburn CL, Dei-Lim V, Heykants JJ.* The pharmacokinetics of sufentanil in surgical patients. Anesthesiology 1984; 61: 502–6.

5 *Reitan JA, Stengert KB, Wymore ML, Martucci RW.* Central control of fentanyl-induced bradycardia during halothane anesthesia. Anesth Analg 1978; 57: 31–6.

6 *Sorensen M, Engbaek J, Viby-Mogensen J, Guldager H, Molke Jensen F.* Bradycardia and cardiac asystole following a single injection of suxamethonium. Acta Anaesthesiol Scand 1984; 28: 232–5.

7 *Havemann U, Kuschinsky K.* Further characterization of opioid receptors in the striatum mediating muscular rigidity in rats. Naunyn Schmiedebergs Arch Pharmacol 1981; 317: 321–5.

8 *Benthuysen JL, Smith NT, Sanford TJ, Head N, Dec-Silver H.* Physiology of alfentanil-induced rigidity. Anesthesiology 1986; 64: 440–6.

9 *Murkin JM, Moldenhauer CC, Hug CC, Epstein CM.* Absence of seizures during induction of anesthesia with high-dose fentanyl. Anesth Analg 1984; 63: 489–94.

10 *Flacke JW, Flacke WE, Bloor BC, Van Etten AP, Kripke BJ.* Histamine release by four narcotics: a double blind study in humans. Anesth Analg 1987; 66: 723–30.

11 *Flacke JW, Davis LJ, Flacke WE, Bloor BC, Van Etten AP.* Effects of fentanyl and diazepam in dogs deprived of autonomic tone. Anesth Analg 1985; 64: 1053–9.

Résumé

Cent quarante et un chercheurs de 45 centres canadiens participaient à cette 4^{ieme} phase d'une étude portant sur l'usage du citrate de sufentanil en clinique et impliquant 616 patients de classe ASA I, II ou III. Toutes ces interventions majeures étaient électives et autres que cardiaques. Elles duraient en moyenne 1.98 h avec une dose moyenne de sufentanil de 1.24 $\mu g \cdot kg^{-1} \cdot h^{-1}$ et ont nécessité l'adjonction d'anesthésiques volatils dans 43 pour cent des cas (266 patients). En post-opératoire immédiat, on a du injecter de la naloxone à 86 patients dont 80 pour cent avaient reçu plus de 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ de sufentanil. On a aussi noté 129 "incidents" ennuyeux, possiblement secondaires au médicament dont quatre cas d'arrêt sinusal ou de bradycardie sévère et trente sept cas d'hypotension importante. Cependant, dans tous les cas, on a pu continuer la chirurgie. Les chercheurs ont qualifié de satisfaisantes les phases d'induction, de maintien et d'émergence dans 94, 92 et 93 pour cent des cas respectivement.