Dose-response to anaesthetic induction with sufentanil: haemodynamic and electroencephalographic effects

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Purpose: To determine the effect of a five-fold variation in sufentanil dose on the haemodynamic and electroencephalo graphic (EEG) response to anaesthetic induction and tracheal intubation.

Methods: Thirty-four patients undergoing elective coronary artery bypass grafting (CABG) participated in this randomized double-blind study. Patients in Group L (n=17) received 3 $\mu g \cdot kg^{-1}$ sufentanil and those in Group H (n=17) 15 $\mu g \cdot kg^{-1}$. Premedication was 60 $\mu g \cdot kg^{-1}$ lorazepam *po*. Anaesthesia and neuromuscular blockade were induced by infusing sufentanil and 0.15 $mg \cdot kg^{-1}$ vecuronium *iv* over five minutes. Haemodynamic data and the electroencephalographic (EEG) spectral edge were acquired by computer and compared at Control, Induction and Intubation.

Results: Sufentanil dose did not affect the haemodynamic or EEG response at end-induction. No bradyarrhythmias occurred, and the incidence of hypotension was 12% in both groups. However, during induction apparent electromyographic artifacts and a transiently greater increase in heart rate were observed in Group H. The serum sufentanil concentration at Induction was 6.1 ± 1.8 $ng \cdot ml^{-1}$ in Group L and 25.4 ± 8.8 $ng \cdot ml^{-1}$ in Group H, and did not correlate with haemodynamic changes. No patient recalled any intraoperative event.

Conclusion: Increasing sufentanil dose from 3 to 15 $\mu g \cdot kg^{-1}$ does not influence the ultimate haemodynamic response to induction. Combined with lorazepam premedication, 3 $\mu g \cdot kg^{-1}$ sufentanil produces near-maximal haemodynamic and EEG effects and is adequate for induction and tracheal intubation of patients undergoing CABG. Sufentanil 15 $\mu g \cdot kg^{-1}$ is no more efficacious, and causes transient cardiovascular stimulation.

Objectif : Déterminer les effets hémodynamiques et électroencéphalographiques (EEG) d'une dose quintuple de sufentanil sur l'induction de l'anesthésie et l'intubation de la trachée.

Méthodes : Trente-quatre patients subissant une chirurgie de revascularisation myocardique (CRVM) non urgente participaient à cette étude aléatoire conduite à double insu. Les patients du groupe L (n=17) recevaient sufentanil 3 $\mu g \, kg^{-1}$ et ceux du groupe H (n=17) 15 $\mu g \cdot kg^{-1}$. Tous étaient prémédiqués au lorazepam 60 $\mu g \, kg^{-1}$ *per os*. L'anesthésie et la curarisation étaient initiées en perfusant le sufentanil et le vécuronium 0,15 $mg \cdot kg^{-1}$ *iv* en cinq minutes. Les données hémodynamiques et l'EEG spectral comprimé étaient recueillies sur ordinateur et comparées à la phase de contrôle, à l'induction et au moment de l'intubation.

Résultats : Le sufentanil n'a pas eu d'effets hémodynamiques ou EEG à l'induction. On n'a pas observé de bradycardie et l'incidence d'hypotension a été de 12% pour les deux groupes. Cependant, pendant l'induction, des perturbations visibles à l'EEG et une augmentation transitoire plus importante de la fréquence cardiaque étaient observés dans le group H. La concentration sérique de sufentanil à l'induction était de 6,1 ± 1,8 $ng \, ml^{-1}$ pour le groupe L et de 25,4±8,8 $ng \cdot ml^{-1}$ pour le groupe H et n'était pas en corrélation avec les changements hémodynamiques. Aucun des patients n'a mentionné un rappel d'événements peropératoires.

Conclusion : L'augmentation de la posologie du sufentanil de 3 à 15 $mg \, kg^{-1}$ n'a pas d'unfluence sur la réponse hémodynamique en fin d'induction. Associé à une prémédication de lorazepam, le sufentanil 3 $\mu g \, kg^{-1}$ produit des effets hémodynamiques et EEG presque maximaux et est adéquat pour l'induction et l'intubation de la trachée de patients subissant une CRVM. Le sufentanil 15 $\mu g \cdot kg^{-1}$ n'est pas plus efficace et provoque une stimulation cardiovasculaire transitoire.

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Accepted for publication September 22, 1996.

HAEMODYNAMIC stability is an important objective when general anaesthesia is induced in patients with coronary artery disease (CAD). Synthetic opioids, including sufentanil, are often used to induce anaesthesia in patients undergoing coronary artery bypass grafting (CABG) because their administration is usually accompanied by haemodynamic stability.[1] However, disturbing bradyarrhythmias and hypotension have been associated with sufentanil administration in humans.[2,3] These adverse haemodynamic effects could be mediated by opioid-induced vagal stimulation, and/or inhibition of sympathetic tone.[4,5] In dogs, dose-related decreases in heart rate (HR) and blood pressure accompany fentanyl administration.[6,7] However, the relationship between opioid dose, opioid serum concentration, and the consequent haemodynamic response has not been systematically investigated in humans.[1] We wondered if induction-related bradycardia and hypotension might be more evident with larger opioid doses, or higher serum concentrations.

Large doses of sufentanil cause typical electroencephalographic (EEG) effects characterized by predominant high-amplitude, low-frequency activity.[8] Scott *et al.* noted that 1.4 $\mu g \cdot kg^{-1}$ sufentanil produced near-maximal EEG effects in healthy, mask-ventilated volunteers, and calculated that an effect-site sufentanil concentration of 0.68 ± 0.31 $ng \cdot ml^{-1}$ caused a 50% decrease in the 95% EEG spectral edge (SE_{95}).[9] However, the influence of sufentanil dose on the rate of onset of EEG effect, and the EEG response to endotracheal intubation has not been well characterized.

The usual dose range for induction of anaesthesia with high-dose sufentanil is stated to be 2–20 $\mu g \cdot kg^{-1}$.[1] However, Bowdle *et al.* found that only 1.3 $\mu g \cdot kg^{-1}$ of sufentanil induced unconsciousness within two minutes in 90% of patients, while Philbin *et al.* gave sufentanil 40 $\mu g \cdot kg^{-1}$ at induction to patients undergoing CABG.[10,11] Our objective was to examine the effect of sufentanil dose on the haemodynamic and electroencephalographic response to induction of anaesthesia. We compared two doses of sufentanil, 3 and 15 $\mu g \cdot kg^{-1}$, that were near the extremes of the usual range, yet in accordance with clinical practice at our institution. To compensate for inter-patient variability in pharmacokinetics, we measured serum sufentanil concentrations and correlated these with haemodynamics. At the time of this study, high-dose sufentanil anaesthesia was the standard anaesthetic for patients undergoing CABG. As a routine, our patients' lungs were mechanically ventilated overnight and their tracheas extubated the next day.

Methods

The study was approved by the Ethics Committee of the University of Manitoba, and all patients gave written informed consent. We studied 34 patients undergoing elective CABG. Those with recent myocardial infarction or unstable angina were included if they had been discharged from an acute care area more than 72 hr before surgery. We excluded patients with left ventricular (LV) ejection fraction < 0.3, or "severe" LV dysfunction detected by angiographic, radionuclide, or echocardiographic techniques. Other exclusion factors were valvular heart disease, left ventricular aneurysm, previous CABG, chronic therapy with sedative-hypnotics, gastrooesophageal reflux, and body weight > 100 kg. Patients were randomly assigned to one of two groups. Patients in Group L received sufentanil 3 $\mu g \cdot kg^{-1}$, while those in Group H received 15 $\mu g \cdot kg^{-1}$. Because therapy with ß-adrenergic blocking agents influences haemodynamics during induction of anaesthesia, patients who were receiving a ß-adrenergic blocking agent preoperatively were randomized separately from those who were not, in order to ensure similar allocation to the two groups.[12]

Antianginal medications were continued until the time of surgery. Ninety minutes before arrival in the operating room, patients were premedicated with 60 $\mu g \cdot kg^{-1}$ lorazepam po. After premedication, all patients received nasal oxygen 4 $l \cdot min^{-1}$. Prior to induction of anaesthesia, electrocardiographic (ECG) leads II and V_5 were applied and monitored continuously thereafter. Bilateral frontal and mastoid electrodes were placed and the electroencephalographic (EEG) data were processed by aperiodic analysis and displayed as a power-frequency histogram using a computerized LIFESCAN™ monitor (Neurometrics Inc.).[13] The monitor continuously displayed the EEG spectral edge (SE_{95}), defined as the ninety-fifth percentile of the power *vs* frequency distribution. Venous, arterial, and pulmonary arterial catheters were inserted under local anaesthesia. Systemic arterial pressure, pulmonary arterial pressure, central venous pressure (CVP), and end-tidal carbon dioxide tension ($P_{ET}CO_2$) were monitored continuously. Thermodilution cardiac output (CO) in triplicate, using 10 ml of room-temperature injectate, and pulmonary capillary wedge pressure (PCWP) were measured intermittently.

Each patient was hydrated with Ringer's lactate solution 7 $ml \cdot kg^{-1}$ *iv* during insertion of intravascular catheters. Prior to induction, 100% oxygen was administered by mask for five minutes. Sufentanil was prepared by our pharmacy in concentrations of either 10 $\mu g \cdot ml^{-1}$ or 50 $\mu g \cdot ml^{-1}$ and administered in a double-blind fashion. Anaesthesia was induced with sufentanil

0.3 ml·kg^{-1} *iv* over five minutes. Paralysis was achieved with 0.15 mg·kg^{-1} vecuronium *iv* given concomitantly with sufentanil. With loss of consciousness, positive pressure ventilation by mask was begun and adjusted to achieve an $P_{ET}CO_2$ of 30–35 mmHg. Upon completion of the sufentanil-vecuronium infusion, a complete haemodynamic profile was obtained and the trachea was intubated. Postoperatively, each patient was interviewed, and specifically questioned about awareness of intraoperative events.

Haemodynamic variables were maintained within predefined limits. Baseline HR and systolic arterial pressure (SAP) were determined from the average of five measurements acquired preoperatively on the ward. During induction, if HR increased 30% over the baseline value, a ß-adrenergic blocking agent was administered. If SAP increased 30% above baseline, isoflurane or *iv* nitroglycerin was given. If SAP decreased to 30% less than the baseline value, *iv* phenylephrine was infused. Bradycardia (HR < 35 beats·min^{-1}) associated with hypotension, was treated with *iv* atropine.

Haemodynamic data were acquired every five seconds and EEG data every 10 sec, using computers interfaced to corresponding operating room monitors. Data acquisition began after the patient had received O_2 by mask for four minutes and continued until five minutes after intubation. Heart rate was derived from the R-R interval of the ECG. Systemic vascular resistance index (SVRI) and cardiac index (CI) were derived from standard formulae. The following times were selected for statistical analysis: Control (fifth minute of preoxygenation), Induction (first minute after completion of sufentanil infusion), and Intubation (second minute after intubation). The values reported at these times are the average of the data collected over one minute. At each of these times, PCWP and CO were also determined. To measure the speed of onset of opioid-induced EEG effects, the time required to reach 33% of the maximal change in SE_{95} (T_{33}) was quantified. Arterial blood for determination of the serum sufentanil concentration was collected at Control and Induction. The blood was centrifuged and the serum stored at –80°C for later analysis. Serum sufentanil concentrations were determined with a commercially available radio- immunoassay kit (Janssen Biotech) used according to the manufacturer's instructions. All samples were measured in duplicate, and the average value reported. The coefficient of variation of the assay was 5.67% at a concentration of 8.0 ng·ml^{-1}.

Data are presented as mean ± standard deviation. Demographic data were compared by Student's t-test, chi-square analysis or Fisher's exact test. Haemodynamic and EEG data were subjected to analysis of variance (ANOVA) for repeated measures. Where ANOVA indicated a group·time interaction, group effect, or time effect, the Student-Newman-Keuls method was used for multiple comparisons. Linear regression analysis was used to seek correlations. A *P*-value 0.05 was regarded as statistically significant.

Results

Thirty-four patients participated, 17 in each group. The groups did not differ with respect to age, weight, sex, preoperative HR, SAP or ß-adrenergic blocker therapy (Table I). Haemodynamic and EEG data are summarized in Table II. ANOVA revealed a group·time interaction for HR. Heart rate declined in both groups at Induction, but returned to the Control value at Intubation only in Group L. Multiple comparisons revealed no intergroup differences in HR. ANOVA indicated no group·time interaction for any other haemodynamic variable, although time-related changes were apparent. Mean arterial pressure (MAP), PCWP, and CI decreased at Induction and Intubation in both groups. In Figures 1 & 2 data from each five-second interval are averaged to provide a continuous illustration of the HR and MAP response to induction and intubation in each group.

There was no difference between the groups with respect to the number of interventions. Hypotension was treated with phenylephrine in two patients in each group. A ß-adrenergic blocking agent was administered during induction, but before intubation, to one patient in Group H. No patient required atropine, nitroglycerin, or isoflurane. Data from these patients were included in the haemodynamic statistical analysis.

The average serum sufentanil concentration at Induction was 6.1±1.8 ng·ml^{-1} in Group L, and 25.4±8.8 ng·ml^{-1} in Group H. For all 34 patients there was no correlation between serum sufentanil concen-

TABLE I Demographic data

	Group L (n = 17)	*Group H (n = 17)*
Age (yr)	63 ± 9	65 ± 7
Weight (kg)	65 ± 14	69 ± 9
Sex (M : F)	14 : 3	16 : 1
ß-blockers	11	11
SAP (mmHg)	126 ± 15	126 ± 10
DAP (mmHg)	72 ± 7	75 ± 5
HR (beats·min^{-1})	63 ± 9	58 ± 5

Values are expressed as mean ± SD
SAP = systolic arterial pressure; DAP = diastolic arterial pressure; HR = heart rate

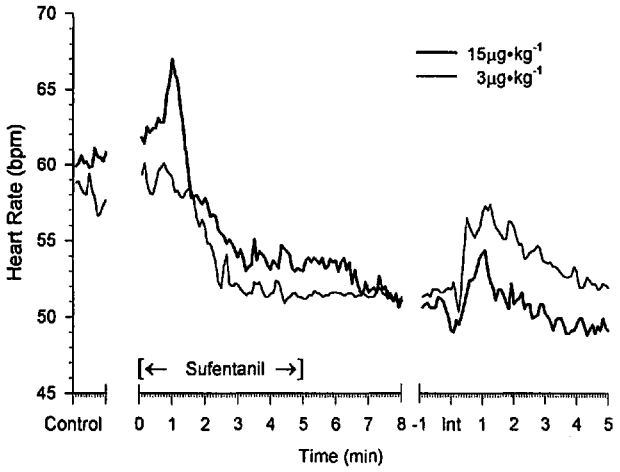

FIGURE 1 Heart rate in Groups L and H. Each point is the mean of all values in that group, plotted at five second intervals. Data from all patients were synchronized at the start of sufentanil infusion, and at intubation. No attempt is made to illustrate interpatient variability.

Ctrl = Control; Int = Intubation.
— Group H, sufentanil 15 μg·kg^{-1}
— Group L, sufentanil 3 μg·kg^{-1}

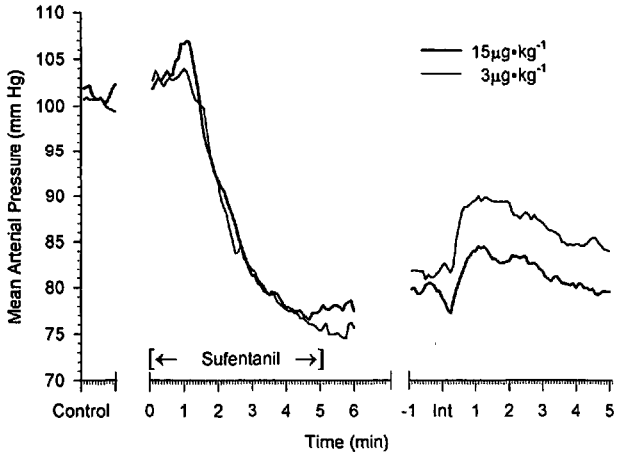

FIGURE 2 Mean arterial pressure in Groups L and H. Each point is the mean of all values in that group, plotted at five second intervals. Data from all patients were synchronized at the start of sufentanil infusion, and at intubation. No attempt is made to illustrate interpatient variability.

Ctrl = Control; Int = Intubation.
— Group H, sufentanil 15 μg·kg^{-1}
— Group L, sufentanil 3 μg·kg^{-1}

tration and changes in HR or MAP occurring between Control and Induction.

For technical reasons, satisfactory EEG data were acquired for only 15 patients in Group L. ANOVA revealed no effect of opioid dose on the EEG. The SE_{95} decreased, and to a similar extent, in both groups after induction (Table II). The EEG data are also illustrated as averages from each 10 second interval in Figure 3. The SE_{95} declined smoothly during induction in Group L, but was interrupted transiently in Group H. Opioid dose did not appear to influence the

TABLE II Haemodynamic and EEG Data

	Group	*Control*	*Induction*	*Intubation*
HR	L	58 ± 11	51 ± 8*	55 ± 9
(beats·min^{-1})	H	60 ± 11	53 ± 5*	52 ± 6*
SAP	L	156 ± 23	119 ± 21*	134 ± 26*
(mmHg)	H	152 ± 18	117 ± 20*	125 ± 21*
MAP	L	100 ± 14	76 ± 14*	88 ± 17*
(mmHg)	H	101 ± 11	78 ± 12*	84 ± 12*
CI	L	2.7 ± 0.5	2.3 ± 0.5*	2.3 ± 0.4*
(l·min^{-1}·m^{-2})	H	3.1 ± 0.6	2.5 ± 0.6*	2.5 ± 0.6*
CVP	L	10.2 ± 1.7	11.6 ± 2.1*	10.6 ± 2.3
(mmHg)	H	9.2 ± 3.0	10.1 ± 1.7	9.5 ± 1.6
PCWP	L	16 ± 4	12 ± 3*	12 ± 5*
(mmHg)	H	16± 7	11 ± 2*	11 ± 2*
SVRI	L	2737 ± 466	2299 ± 466*	2709 ± 440
(dyne·s·cm^{-5}·m^2)	H	2469 ± 551	2211 ± 412	2415 ± 655
SE_{95}	L	18.6 ± 3.5	4.8 ± 2.3*	4.8 ± 2.3*
(Hz)	H	17.9 ± 3.6	5.9 ± 1.7*	5.1 ± 2.2*

Values are expressed as mean ± standard deviation

* = $P < 0.05$ *vs* Control

EEG = electroencephalographic; HR = heart rate; SAP = systolic arterial pressure;

MAP = mean arterial pressure; CI = cardiac index; CVP = central venous pressure;

PCWP = pulmonary capillary wedge pressure; SVRI = systemic vascular resistance index;

SE_{95} = 95% spectral edge of the EEG

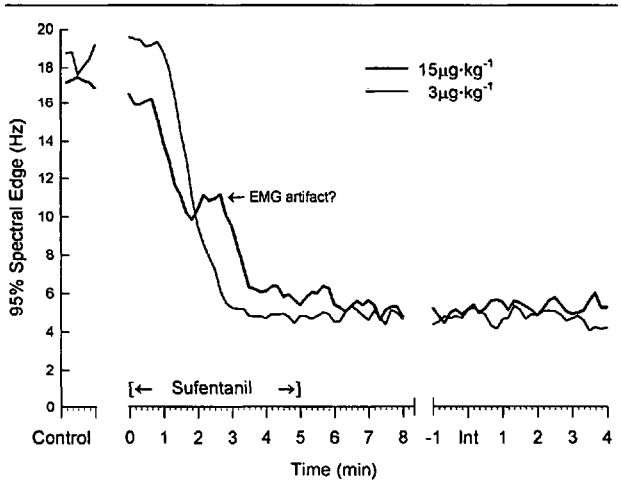

FIGURE 3 Electroencephalographic 95% spectral edge in Groups L and H. Each point is the mean of all values in that group, plotted at 10 sec intervals. Data from all patients were synchronized at the start of sufentanil infusion, and at intubation. No attempt is made to illustrate interpatient variability.

Ctrl = Control; Int = Intubation; EMG = electromyographic
— Group H, sufentanil 15 μg·kg^{-1}
— Group L, sufentanil 3 μg·kg^{-1}

rate of onset of opioid-induced EEG changes. In Group L T_{33} was 94±32 sec, compared with 77±35 sec in Group H. The decline in SE_{95} and MAP were usually temporally related. A correlation between these two variables was noted in 13/15 patients in Group L, and 14/17 in Group H. No patient recalled any intraoperative event.

Discussion

Varying sufentanil dose, over the range of 3 to 15 $\mu g \cdot kg^{-1}$, had no effect on the ultimate haemodynamic response to induction of anaesthesia. Mean arterial pressure declined similarly in both groups. However, the incidence of hypotension (12%) was low and identical in both groups. Although HR declined with both doses, no patient required atropine for bradycardia. Because bradycardia and hypotension occurred infrequently, our study is not large enough to rule out an effect of sufentanil dose on the incidence of these adverse cardiovascular events. Both sufentanil doses produced adequate anaesthetic depth, since no patient developed hypertension or tachycardia in response to intubation, and no patient had awareness.

Bazaral *et al.* examined the haemodynamic effect of fentanyl dose (15 $\mu g \cdot kg^{-1}$ *vs* 60 $\mu g \cdot kg^{-1}$) during induction of anaesthesia in patients with CAD.[14] Their patients received premedication with morphine and scopolamine *im* and muscle relaxation was achieved with the combination of 0.16 $mg \cdot kg^{-1}$ metocurine plus 0.04 $mg \cdot kg^{-1}$ pancuronium. This induction sequence resulted in an increase in HR, probably mediated by a drug-interaction involving fentanyl, scopolamine and pancuronium.[12] Interestingly, the increase in HR three minutes after induction was greater in patients who received the larger fentanyl dose. Like us, they found no effect of opioid dose on induction-related changes in MAP, CI, CVP, or PCWP. Because of the cardiovascular stimulation associated with the induction sequence, Bazaral's study cannot provide clear insight into the influence of opioid dose on induction-related cardiovascular depression.

Sprigge *et al.* found no effect of opioid dose on the haemodynamic response to anaesthetic induction with either 30, 40 or 50 $\mu g \cdot kg^{-1}$ of fentanyl.[15] However, the dose range employed was narrow, and the induction sequence (scopolamine-fentanyl-pancuronium) caused an increase in HR. In our study, we deliberately avoided the use of antimuscarinic and sympathomimetic anaesthetic adjuncts, to avoid masking any dose-related vagotonic or sympatholytic effects of sufentanil.

Sufentanil infusion in Group H was accompanied by a consistent but transitory increase in HR, averaging 7.1±9.4 $beats \cdot min^{-1}$, peaking one minute into induction (Figure 2). This was greater than the corresponding 0.4±4.8 $beats \cdot min^{-1}$ change in Group L (P=0.02). One patient from Group H received *iv* propranolol early in the induction period because of a transient tachycardia. Thus, large doses of opioids may cause transient cardiovascular stimulation early in induction, that is not seen with smaller doses.[16] The mechanism of this effect is unknown, but catecholamine release may be involved.[17] Such an effect might be magnified and prolonged by the anti-muscarinic effect of scopolamine and/or pancuronium.[12] This interaction might explain the dose-related increase in HR observed by Bazaral *et al.* in patients in whom anaesthesia was induced with fentanyl.

Animal studies examining the haemodynamic effect of opioid dose are conflicting. Liu *et al.* infused fentanyl 50–2000 $\mu g \cdot kg^{-1}$ *iv* into thiopentone-anaesthetized dogs.[6] They noted progressive, dose-related decreases in HR after 50 $\mu g \cdot kg^{-1}$ (26%) that were near-maximal after 500 $\mu g \cdot kg^{-1}$ (52%). Similar decreases in MAP were noted at 150 $\mu g \cdot kg^{-1}$ (21%) and were near-maximal at 1000 $\mu g \cdot kg^{-1}$ (34%). Arndt *et al.* administered a cumulative fentanyl dose of 167.5 $\mu g \cdot kg^{-1}$ to unpremedicated, trained dogs. Fentanyl-induced decreases in HR were maximal after a dose of only 67.5 $\mu g \cdot kg^{-1}$.[7] They concluded that, in dogs, all fentanyl's effects (analgesic, respiratory and cardiovascular) are maximal at a serum concentration of approximately 30 $ng \cdot ml^{-1}$. In our study, 3 $\mu g \cdot kg^{-1}$ sufentanil appears to have produced near-maximal EEG and cardiovascular effects.

The cardiovascular response to sufentanil is likely secondary to opioid receptor-mediated central nervous system (CNS) effects. Bilateral vagotomy abolishes 90% of the marked, dose-related decrease in HR associated with fentanyl administration in halothane-anaesthetized dogs, but does not prevent fentanyl-induced hypotension.[4] Complete autonomic denervation prevents the decrease in both HR and MAP associated with fentanyl administration.[5] Vagal stimulation by sufentanil is much less apparent in premedicated patients than in laboratory animals, as shown by the relatively small, non-dose-related, HR decreases we observed. On the other hand, the consistent, substantial decrease in MAP observed is comparable to that induced by fentanyl in laboratory animals. This suggests that loss of sympathetic tone, rather that vagal stimulation, is the predominant mechanism producing the cardiovascular response to large doses of opioids in humans. The consistent temporal association between hypotension and EEG slowing suggests that withdrawal of sympathetic tone accompanies loss of consciousness.

We found no difference between the two opioid doses with respect to the EEG response to induction. Both doses of sufentanil produced virtually identical, near-maximal alterations in the EEG power spectrum, characterized by a rapid decline in SE_{95} from approximately 18 Hz prior to induction to 5 Hz by the end of the five minute induction period. This was expected, since Scott *et al.* observed that a mean sufentanil dose of 1.4 $\mu g \cdot kg^{-1}$ caused similar, near-maximal EEG suppression in healthy, unpremedicated patients.[9] Similarly, Chi *et al.* infused sufentanil 10 $\mu g \cdot kg^{-1}$ at 0.71 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in premedicated patients undergoing CABG. They noted maximal EEG changes after three minutes (i.e. 2.1 $\mu g \cdot kg^{-1}$) but minimal change with continued sufentanil infusion.[18] We anticipated that the onset of opioid-induced EEG effect might occur earlier in Group H. However, although T_{33} was achieved an average of 17 sec earlier in Group H, this effect was not statistically significant. Thus, the speed of induction is not increased by a five-fold increase in sufentanil dose from 3 to 15 $\mu g \cdot kg^{-1}$. Importantly, we observed no evidence of EEG arousal during laryngoscopy and intubation in either group.

In response to induction, the SE_{95} declined smoothly in Group L but was transiently interrupted in Group H. An electromyographic (EMG) artifact in Group H may explain this effect. Scott *et al.* observed a similar EMG artifact in one of ten patients induced with a 125 µg *iv* bolus of sufentanil.[9] The frequent occurrence of probable EMG artifacts in Group H patients suggests that muscle rigidity might be more evident when larger sufentanil doses are employed. Our original intention was to use the time to achieve 50% of the maximal decline in SE_{95} (T_{50}) as our index of the onset of opioid effect. However, the apparent EMG artifacts in Group H frequently interfered with this measurement. Although not ideal, substituting T_{33} for T_{50} avoided this problem in all but two patients.

The blood samples for determination of serum sufentanil concentration were drawn at a time when equilibration between blood and the central nervous system would be far from complete.[9] Therefore, the serum sufentanil concentrations we report cannot be equated with effect site concentrations. Based on the findings of Scott *et al.*, we estimate that the sufentanil concentration at the effect site would approximate 30% of the blood concentration at the time we sampled. Furthermore, both serum and effect site concentrations would have been changing rapidly. Despite these limitations, it is fair to assume that the dose regimens used resulted in a substantial intergroup difference in effect-site sufentanil concentration.

Combined with lorazepam premedication and vecuronium, 3 $\mu g \cdot kg^{-1}$ sufentanil rapidly produces near-maximal opioid effects, and is clearly adequate for induction of anaesthesia and tracheal intubation in patients undergoing elective CABG. The loss of sympathetic tone accompanying EEG slowing results in a substantial decrease in blood pressure, but the accompanying HR decrease is small. Increasing sufentanil dose to 15 $\mu g \cdot kg^{-1}$ causes no additional cardiovascular depression, although transient cardiovascular stimulation early in induction is apparent. Such large doses of sufentanil are clearly unnecessary for induction of anaesthesia in premedicated patients undergoing CABG. Of course, the use of lower sufentanil doses at induction would necessitate supplemental anaesthesia during surgery. We found no evidence that sufentanil dose *per se* is a major cause of clinically important bradyarrhythmias and/or hypotension, although a much larger study would be needed to rule out such an effect.

Acknowledgements

We thank our cardiac surgeons (Drs. J Barwinsky, SK Bhattacharya, SW Kim, EA Pascoe, K Warrian) and cardiac anaesthetists (Drs. LG Brownell, RM Friesen, DJ Peters, JE Scatliff) for their cooperation. The Pharmaceutical Manufacturers Association of Canada generously provided salary support for Dr. Sareen during completion of this University of Manitoba BSc (Med) project. Laura Saward, MSc, and Peter Zahradka PhD, Department of Physiology, performed the sufentanil assays.

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