High-dose fentanyl for rapid induction of anaesthesia in patients with coronary artery disease

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Nine premedicated patients, chronically maintained on beta-adrenergic blocking agents and demonstrating good ventricular function without significant valvular or left main coronary artery disease, were investigated to determine their haemodynamic responses to rapid induction of anaesthesia and tracheal intubation during elective coronary artery bypass surgery. Fentanyl $50 \mu\text{g}\cdot\text{kg}^{-1}$ and pancuronium $0.15 \text{ mg}\cdot\text{kg}^{-1}$ were administered intravenously over 20 seconds followed by tracheal intubation 90 seconds thereafter. The rapid sequence of anaesthetic induction and tracheal intubation was well tolerated by all patients. Though statistically significant changes were detected in heart rate, pulmonary capillary wedge pressure and systemic vascular resistance, these changes were small and not considered clinically significant and no signs of ischaemia were detected on the ECG. The present study demonstrates that high-dose fentanyl is capable of inducing anaesthesia rapidly and protecting against the haemodynamic changes associated with tracheal intubation.

Key words

ANAESTHESIA: cardiovascular; INDUCTION: anaesthesia; ANAESTHETICS, INTRAVENOUS: fentanyl.

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High-dose narcotic anaesthesia, particularly using the synthetic drug fentanyl or one of its congeners, has become a popular anaesthetic technique for cardiac surgery, purportedly because of the greater haemodynamic stability it confers. Because some patients with coronary artery disease may be at increased risk of pulmonary aspiration during the induction of anaesthesia (i.e., full stomach, oesophageal reflux), we investigated the use of high-dose fentanyl for rapid induction of anaesthesia.

Recent work utilizing a slow intravenous infusion of fentanyl $8.6 \mu\text{g}\cdot\text{kg}^{-1}$, has demonstrated a significant time lag between peak fentanyl concentration in plasma and maximal changes in the electroencephalograph (EEG).¹ The use of larger doses given rapidly might be expected to speed the onset of fentanyl's actions. We have previously observed unconsciousness and abrupt slowing of the EEG (delta waves) characteristic of fentanyl anaesthesia within 30 seconds of an IV bolus of fentanyl $50 \mu\text{g}\cdot\text{kg}^{-1}$.² In another clinical study, however, hypertension occurred in response to laryngoscopy and tracheal intubation after a fentanyl dose of $50 \mu\text{g}\cdot\text{kg}^{-1}$ injected in 60 seconds.³

The present study was designed to assess the efficacy of fentanyl in rapidly inducing anaesthesia and obtunding haemodynamic responses to intubation.

Methods

Following institutional approval and after obtaining informed consent, nine patients maintained on chronic beta-adrenergic receptor blocker therapy and scheduled for elective coronary artery bypass (CABG) surgery, were studied. Patients with left

TABLE I Patient characteristics

PATIENT	AGE (yr.)	SEX	WT (kg)	ASSOCIATED CONDITIONS	MEDICATIONS (Daily dose in mg)	EJECTION FRACTION	CABG (Vessels grafted)
1	60	M	83	- hypertension	- propranolol 120 - topical nitroglycerin - chlorthalidone 100	0.60	4
2	63	F	93	- hypertension - chronic bronchitis - obesity - hiatus hernia	- nadolol 40 - nifedipine 30 - topical nitroglycerin - triamterene 50 - hydrochlorothiazide 25 - cimetidine 900	0.65	3
3	54	M	89	- hypertension	- nadolol 80 - nifedipine 40 - digoxin 0.25 - furosemide 40	0.65	3
4	58	M	86	- peptic ulcer	- timolol 20 - procainamide 1000	0.65	5
5	47	F	79	- hypertension	- propranolol 160 - nifedipine 60 - topical nitroglycerin - triamterene 50 - hydrochlorothiazide 25	0.50	3
6	67	M	84	- hypertension	- atenolol 50 - diltiazem 240 - isosorbide dinitrate 40 - topical nitroglycerin	0.65	3
7	44	M	99	- obesity - hiatus hernia	- propranolol 80 - diltiazem 240 - topical nitroglycerin	0.65	2
8	55	M	97	- obesity - bronchiectasis	- propranolol 80	0.60	4
9	50	M	70	- none	- propranolol 80	0.55	1

main coronary artery disease, an ejection fraction less than 0.5, or significant valvular heart disease were excluded. All patients displayed sinus rhythm on their electrocardiogram (ECG). On the morning of surgery, all patients received their usual anti-anginal medications, including beta-blockers, one to four hours preoperatively (Table I). Premedication consisting of morphine $0.15 \text{ mg} \cdot \text{kg}^{-1}$ and scopolamine $5 \mu\text{g} \cdot \text{kg}^{-1}$ IM and diazepam $0.15 \text{ mg} \cdot \text{kg}^{-1}$ PO was administered 90 minutes prior to surgery. A radial artery cannula, two large bore IV cannulae, and a pulmonary artery catheter were inserted percutaneously under local anaesthesia and prior to induction of general anaesthesia. ECG leads II and V5 were displayed continuously on an oscilloscope throughout the study period and were simultaneously recorded, along with systemic and pulmonary artery pressures, on a calibrated Hewlett-Packard strip chart recorder running continuously throughout the study period at a speed of 5 mm/sec. Following administration of lactated Ringer's solution to produce a pulmonary capillary wedge pressure (PCWP) of at least 10 mmHg and after five minutes with the patient breathing 100 per

cent oxygen by mask, fentanyl $50 \mu\text{g} \cdot \text{kg}^{-1}$ and pancuronium $0.15 \text{ mg} \cdot \text{kg}^{-1}$ were simultaneously administered intravenously over 20 seconds.

Heart rate (HR), cardiac output (CO), mean arterial (MAP), central venous (CVP) and pulmonary arterial (PAP) and pulmonary capillary wedge pressures (PCWP) were obtained and cardiac index (CI) and systemic vascular resistance (SVR) were calculated. Control (C) haemodynamic measurements were obtained prior to oxygenation and 1 min, 3 min, and 5 min following fentanyl administration. Patients were intubated 90 seconds after the completion of fentanyl administration. Hypertension (increase in MAP $25\% > \text{C}$) was treated with thiopentone 100 mg, and hypotension (decrease in MAP $25\% < \text{C}$) was treated with ephedrine 5 mg intravenously. After the study, anaesthesia was maintained at the anaesthetist's discretion and included diazepam, fentanyl, and enflurane or isoflurane. Results are presented as the mean $\pm$ SEM. Data were analyzed by two-way analysis of variance; $p < 0.05$ was considered significant.

TABLE II Haemodynamic variables before and after fentanyl*

	HR§ bpm (range)	CI $L \cdot min^{-1} \cdot m^{-2}$ (range)	MAP mmHg (range)	SVR† $dyne \cdot sec \cdot cm^{-5}$ (range)	PCWP§ mmHg (range)
Control	57 ± 3 (45-76)	2.6 ± 0.2 (1.7-3.5)	85 ± 3 (68-95)	1209 ± 78 (903-1511)	12 ± 1 (10-16)
1 min	65 ± 3 (50-78)	2.8 ± 0.2 (1.8-4.2)	79 ± 4 (63-103)	1062 ± 88 (706-1455)	12 ± 1 (9-14)
1.5 min		(Intubation)			
3 min	66 ± 3 (55-81)	2.9 ± 0.2 (1.9-3.8)	78 ± 3 (60-92)	1021 ± 86 (723-1400)	11 ± 1 (8-14)
5 min	66 ± 3 (55-84)	2.9 ± 0.2 (2.0-3.6)	77 ± 4 (56-90)	999 ± 72 (789-1470)	10 ± 1 (7-13)

*Values are means ± SEM. Data analyzed by two-way analysis of variance. †p < 0.05;

§p < 0.01

Results

In all patients, loss of responsiveness to voice occurred at 30 ± 15 seconds following fentanyl administration. Laryngoscopy and intubation commenced 90 seconds following completion of fentanyl administration and was accomplished within 30 seconds. Intubating conditions were considered good. No patient had recall of intubation or any intraoperative event.

There was no statistically significant change in the mean group values for CI or MAP, but two patients (patient 2 and patient 5) had a transient 30 per cent decrease in MAP. The systolic blood pressure remained greater than 95 mmHg in both patients and treatment was not required. Statistically significant changes were found in HR, PCWP, and SVR (Table II). In three patients HR increased by more than 30 per cent from control (patient 1: 64 to 84; patient 4: 45 to 57; patient 7: 47 to 71) but no patient developed a HR greater than 85 or less than 50 and no arrhythmias or ST-T wave changes occurred during the study period. The SVR remained within $700-1500 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$ in all patients, and in two patients (patient 2 and patient 8) the CI decreased by less than 15 per cent from the control values. None of these changes were felt to be clinically important, and they did not require any intervention.

Discussion

A $50 \mu\text{g} \cdot \text{kg}^{-1}$ dose of fentanyl administered intravenously in 20 seconds has previously been shown

to reliably produce plasma fentanyl concentrations in excess of $20 \text{ ng} \cdot \text{ml}^{-1}$ for up to seven to eight minutes and results in the rapid production of unconsciousness (i.e., loss of response to commands) and EEG slowing.² Patients were not intubated during that study, however, thus their haemodynamic responses to the stresses of laryngoscopy and intubation were not assessed.

By administering fentanyl as a slow infusion, Scott *et al.*¹ demonstrated a delay in the onset of fentanyl's effect on the EEG. In contrast, with rapid administration of high doses of fentanyl, anaesthetic conditions were produced within 90 seconds in our patients. Because of its high lipid solubility, if tissue perfusion remains constant then diffusion of fentanyl into the brain is primarily determined by the plasma/tissue concentration gradient.⁴ The rapid production of transiently high plasma fentanyl concentrations (in excess of $1200 \text{ ng} \cdot \text{ml}^{-1}$) that is achieved with the high-dose bolus technique,² produces a very large concentration gradient for diffusion of fentanyl into the brain. These high plasma concentrations produce a rapid accumulation of fentanyl in brain and cause a rapid onset of anaesthesia.^{1,5} Maximum brain concentrations have been reported to occur in rabbits within 30 seconds after intravenous injection of fentanyl $20 \mu\text{g} \cdot \text{kg}^{-1}$.⁶

All patients in this study tolerated the rapid sequence of anaesthetic induction and tracheal intubation without problem. Though not describing a rapid sequence induction technique, Sprigge *et al.*

observed similar haemodynamic stability during induction and intubation in a group of patients receiving fentanyl $50 \mu\text{g}\cdot\text{kg}^{-1}$ and pancuronium $0.15 \text{ mg}\cdot\text{kg}^{-1}$ for induction of anaesthesia.⁷ Though blood pressure, PCWP, CI and SVR did not change significantly, they did observe a statistically significant increase in heart rate of approximately 15 per cent following induction, and 25 per cent following intubation, slightly greater than the increases in HR of 10 and 15 per cent observed in our study at similar times. This study differed from ours however in that their rate of administration of fentanyl was $1 \text{ mg}\cdot\text{min}^{-1}$ versus our rate of $50 \mu\text{g}\cdot\text{kg}^{-1}$ over 20 seconds. Similarly, in their study 1 to 2 mg of pancuronium preceded the administration of fentanyl and was followed by the remainder of the $0.15 \text{ mg}\cdot\text{kg}^{-1}$ total dose of pancuronium upon loss of consciousness, whereas in our study the total dosages of both fentanyl and pancuronium were administered concomitantly over 20 seconds. The patients of Sprigge *et al.* also had a slightly higher control heart rate of 62 ± 2 versus 57 ± 3 in our patients, presumably because only eight of ten of their patients were chronically maintained on beta-adrenergic receptor blockers. The higher incidence of hypertension observed by Kentor *et al.*³ may be due to several factors: slower fentanyl administration producing lower peak fentanyl concentrations in plasma and brain, delayed administration of relaxants leading to hypercarbia with secondary sympatho-adrenal stimulation, possibly absent or inadequate beta-adrenergic receptor blockade and a greater interval between fentanyl administration and intubation (approximately 6.5 min) allowing fentanyl concentrations to decline. Higher plasma fentanyl concentrations generally produce greater haemodynamic stability⁷ and fentanyl appears to more directly antagonize the chronotropic effects of pancuronium when the two drugs are administered concomitantly. In A.S.A. physical status class I-II patients who had not received preoperative beta-adrenergic receptor blockers and who were anaesthetized with a combination of meperidine-diazepam, administration of pancuronium in a dosage of twice its ED_{95} produced a mean increase in heart rate of greater than 20 per cent.⁸ A different group of investigators, however, found this same dose of pancuronium when utilized with fentanyl in a balanced anaesthetic technique produced a heart rate rise of more than 20 per cent

above control values in only two of ten patients and it was promptly reversed with additional fentanyl $100\text{--}150 \mu\text{g}$.⁹

Because of the propensity of narcotics, particularly fentanyl, to produce a centrally mediated reduction in heart rate,¹⁰ we elected to use pancuronium, a muscle relaxant with vagolytic properties,¹¹ in a dosage (twice the ED_{95}) shown to reliably produce rapid onset of muscular paralysis,^{8,9} in order to antagonize the fentanyl-induced vagotonia. Succinylcholine was avoided as it would not prevent and might even exacerbate the bradycardia that is produced when fentanyl is administered rapidly and in a large dosage to these patients with a high degree of pre-existing beta-receptor blockade.¹² No difference in the heart rate response to an ED_{95} dosage of either pancuronium or a pancuronium-metocurine combination was found when these drugs were administered to patients receiving chronic propranolol therapy and undergoing CABG surgery.¹³ Patients receiving the pancuronium-metocurine combination did have a lower MAP and SVR compared to the pancuronium treated group however, and it was this potential for hypotension that mitigated against using this combination of relaxants for rapid administration in our study. It has also been demonstrated that occurrence of maximum neuromuscular blockade is more rapid when using an intubating dosage of pancuronium (twice the ED_{95}) as opposed to a comparable dosage of the pancuronium-metocurine combination; 1.8 versus 2.6 minutes, respectively.⁸

The patients in the current study were all maintained on chronic beta-adrenergic receptor blocker therapy and received their last dose orally between one and four hours prior to the induction of anaesthesia. We believe the continuation of this therapy contributed significantly to their haemodynamic stability during induction of anaesthesia. We have previously observed hyperdynamic responses to the rapid induction and intubation technique described here in two other patients who were not receiving beta-blockers preoperatively. Differences in the haemodynamic responses of patients chronically maintained with beta-adrenergic receptor blocker therapy and those not receiving this therapy have been previously reported.^{14,15} In a group of patients undergoing CABG surgery, Stanley *et al.* observed a lesser incidence of intraoperative hypertension and the dosage require-

ments for narcotic anaesthesia were lower in the population maintained on beta-blockers.¹⁴ In patients undergoing CABG surgery who received propranolol two hours preoperatively versus those in whom it was withdrawn 10–48 hours preoperatively, Oka *et al.* demonstrated a significantly lower heart rate–blood pressure product (RPP) both in response to intubation and at all other times during halothane-N₂O anaesthesia.¹⁵

We have demonstrated that intravenous administration of a 50 µg·kg⁻¹ dose of fentanyl over 20 seconds is well tolerated and provides rapid induction of anaesthesia and stable haemodynamics during laryngoscopy and tracheal intubation in patients with coronary artery disease who are receiving beta-adrenergic receptor blockers. Before the technique used in this study can be recommended for general use in other patients under different conditions, it will have to be evaluated under a variety of clinical circumstances (e.g., hypovolemia, sepsis, poor ventricular function, varying degrees of beta-adrenergic receptor blockade). Whether vecuronium, one of the new generation of muscle relaxants reported to have lesser cardiovascular side-effects,¹⁶ might prove to be a superior relaxant in combination with high doses of fentanyl remains to be seen.

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Résumé

Neuf patients prémédiqués sous thérapie chronique aux bêta-bloquants et démontrant une bonne fonction ventriculaire sans atteinte valvulaire significative ou atteinte du tronc commun étaient investigués afin de déterminer leur réponse hémodynamique à l'induction rapide de l'anesthésie et l'intubation trachéale durant le pontage aortocoronarien électif. Du fentanyl $50 \mu\text{g}\cdot\text{kg}^{-1}$ et du pancuronium $0.15 \text{ mg}\cdot\text{kg}^{-1}$ ont été administrés par voie intraveineuse en 20 secondes suivis 90 secondes plus tard par l'intubation trachéale. Cette séquence rapide d'induction anesthésique et d'intubation trachéale a été bien tolérée par tous les patients. Des changements statistiquement significatifs ont été détectés dans la fréquence cardiaque, la pression capillaire pulmonaire et la résistance vasculaire systémique. Cependant ces changements étaient minimes et considérés comme non cliniquement significatifs car aucun signe d'ischémie n'était détecté à l'électrocardiogramme. La présente étude démontre que de fortes doses de fentanyl étaient capables d'induire l'anesthésie rapidement et de protéger contre les changements hémodynamiques associés à l'intubation trachéale.