THE INFLUENCE OF CHRONIC PREOPERATIVE PROPRANOLOL THERAPY ON CARDIOVASCULAR DYNAMICS AND NARCOTIC REQUIREMENTS DURING OPERATION IN PATIENTS WITH CORONARY ARTERY DISEASE

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ABSTRACT

We measured the dose of sufentanil required for unconsciousness as well as the entire operation in 44 patients (22 taking propranolol and 22 not taking propranolol) undergoing coronary artery bypass grafting (CABG) operations. The incidence of hypertension during operation, requirements for supplements to treat hypertension and recovery times were also determined. The data indicate that patients undergoing CABG operations taking propranolol require significantly less sufentanil for unconsciousness and the entire operation than patients not taking this drug. In spite of requiring less sufentanil, patients taking propranolol had less hypertension during operation and thus required less supplements. However recovery times in both groups were the same.

The results of this study may partially explain the varying incidence of hypertension reported during high dose fentanyl and other narcotic-oxygen anaesthetic techniques.

KEY WORDS: ANAESTHESIA, Cardiovascular; ANAESTHETICS, Intravenous, Sufentanil; BLOOD PRESSURE, Drug Effects, Hypertension; SURGERY, Coronary Artery Bypass.

SUFENTANIL (N-[4-methoxymethyl]-1-[2-(2-thienyl) ethyl]-piperidinyl] N-phenylpropanamide) is a new synthetic narcotic chemically related to fentanyl (Figure 1). Sufentanil is 5 to 10 times as potent as fentanyl, but has the same duration of activity and a much greater margin of safety in animals.[1-3] Preliminary studies have suggested that at comparable doses sufentanil may be superior to fentanyl as a "narcotic anaesthetic" because of its ability to prevent hypertension during operation and to reduce requirements for anaesthetic supplements during coronary artery surgery.[3] During investigations comparing the cardiovascular actions of sufentanil with fentanyl we noted that patients who were routinely taking beta-adrenergic blocking drugs for angina or hypertension before opera-

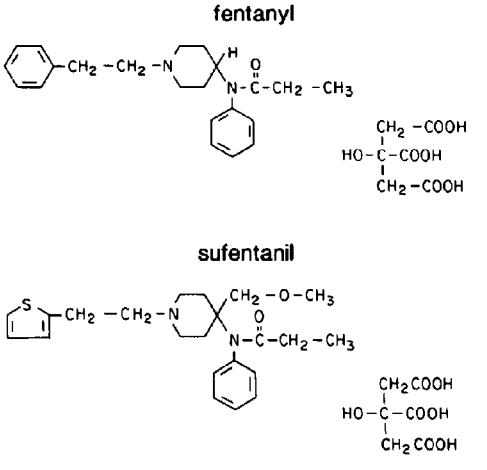

FIGURE 1 Structural formulae of sufentanil and fentanyl.

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tion seemed to require less narcotic (sufentanil or fentanyl) during coronary artery operations and had less evidence of hypertension with severe surgical stress (sternotomy and sternal spread) than similar patients not taking beta blockers. Similar observations have been made by one of us (Stanley, T.H., unpublished data) during high dose morphine-oxygen anaesthesia. Unfortunately, the group sizes in all these studies were small and thus the significance of preoperative beta-adrenergic blocker therapy was difficult to demonstrate. The objectives of this investigation were to carefully measure the "sleep dose" and subsequent requirements of sufentanil, as well as the incidence of hypertension and requirements for supplements to treat hypertension, in 44 patients (22 taking preoperative propranolol, group I, and 22 not taking proranolol, group II) during coronary artery bypass grafting (CABG) operations.

Methods

The protocol was approved by the University Hospital of Leiden Human Experimentation Committee. Informed consent to do the study was obtained from each patient at the time of the preoperative visit.

Forty patients scheduled to undergo CABG operations requiring two or more bypass grafts made up the experimental subjects. The patients were taking propranolol (80–240 mg per day by mouth, group I) or were not taking any beta-adrenergic blockers preoperatively (group II). Once the study was started patient selection was sequential (the first 22 patients fulfilling the criteria and agreeing to be accepted into the study in each of the two groups). All but six patients, three in each group, were taking nitroglycerin or some other oral vasodilator preoperatively. Patients were premedicated with lorazepam 0.08 $mg \cdot kg^{-1}$, by mouth two hours before operation and atropine 0.1 mg/15 kg intramuscularly 30 minutes before arrival in the operating room. Patients in group I received their usual morning oral dose of propranolol at the time of the oral premedication. Upon arrival in the operating room catheters were placed in a hand vein and a radial artery and a bipolar lead II electrocardiogram was recorded continuously. Before induction of anaesthesia a thermal dilution flow-directed balloon tipped pulmonary artery catheter (Instrumentation Laboratories triple-lumen 110 cm model 44166 7F) was introduced into the pulmonary artery through an antecubital vein in an upper extremity, using a 7 FR Cordis Introducer.

After a five minute stabilization period and while breathing oxygen, control measurements of heart rate (beats/min), cardiac output (l/min),* systolic and mean arterial (torr), mean pulmonary artery (torr) and mean right atrial (torr) pressures were made. Two minutes later pancuronium 0.02 $mg \cdot kg^{-1}$ was administered intravenously. Three minutes after the pancuronium, patients were given sufentanil at 300 μg/min intravenously. Respirations were first spontaneous, then assisted and finally controlled, using a face mask and semi-closed system to maintain Pa_{CO_2} at 4.6–5.3 kPa (35–40 torr) as measured in radial arterial blood every 15–45 minutes. During infusion of sufentanil, patients were requested to open their eyes and/or take a deep breath every 5–10 sec. Failure to respond to three consecutive requests was equated with unconsciousness. When unconscious, the patients were paralyzed with intravenous succinylcholine 1.5 $mg \cdot kg^{-1}$ and their tracheas were intubated with cuffed Portex tracheal tubes. After intubation an amount of sufentanil equal to the dose producing unconsciousness was infused over the next 30 minutes, and the operation was then begun. Additional sufentanil was given intravenously in 50 μg doses throughout the operation whenever systolic arterial blood pressure increased more than 15 per cent of preanaesthetic (control) values. When three successive supplemental doses of sulfentanil failed to decrease systolic blood pressure to within 15 per cent of control value before or during bypass, the patients were given phentolamine in 1–3 mg divided doses until blood pressure decreased to control values. After bypass nitrous oxide 25–50 per cent was added to the inspired mixture of gases to treat hypertension not responding to supplemental doses of sufentanil. If nitrous oxide was ineffective in decreasing post-bypass hypertension to within 15 per cent of control systolic arterial blood pressure within 10 minutes a sodium nitroprusside infusion (0.5–2.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was started. The incidences of increases in systolic arterial arterial blood pressures above 20 per cent of control values during tracheal intubation, chest incision, sternotomy and maximal sternal spread were recorded for both groups.

*Measured by thermal dilution with 10 ml of 10–15°C dextrose five per cent in water as the injectate.

Patients were paralyzed with pancuronium (0.08 mg·kg^{-1} given slowly, intravenously) 15 minutes after they had received succinylcholine. Paralysis was maintained with increments of pancuronium 0.04 mg·kg^{-1} every 45–60 minutes up until cardiopulmonary bypass. A saline-glucose solution (4.5 per cent glucose and 0.1 per cent normal saline in water) was administered at a rate of 1000 ml/h during preanaesthetic preparations and 200–250 ml/h throughout the remainder of the operation. Whole blood was given after cardiopulmonary bypass and in the postoperative period to maintain right atrial pressure at preanaesthetic values. The extracorporeal system was primed with Ringer's solution (1500 ml) and glucose 5 per cent in water (500 ml) and 500 ml of a solution containing 100 g of albumin and 5000 units of heparin. Patients were cooled to 26–28°C during extracorporeal support and rewarmed to 37°C at its conclusion.

Cardiovascular dynamics were recorded before anaesthetic induction (control) at the time patients became unconscious, one minute after tracheal intubation, immediately before and five minutes after chest incision, before sternotomy, and 5 and 10 minutes after sternal spread.

The presence of chest wall rigidity during induction of anaesthesia was evaluated by the following scoring system: none = no apparent change in pulmonary compliance and no difficulty with ventilation during manual positive pressure ventilation; mild = can ventilate but with some difficulty due to some chest wall rigidity; severe = virtually impossible to ventilate before succinylcholine administration due to marked rigidity.

Patients were all ventilated mechanically until the morning after operation. During the first eight postoperative hours they were evaluated for return of consciousness every 15 minutes. Patients were considered conscious when they could give correct affirmative responses to three consecutive questions.

Data were analyzed for statistical significance using Student's paired and unpaired t-tests and the Chi-square test. $P < 0.05$ was considered statistically significant.

Results

The ages (53 ± 8 years, mean ± SD) and weights (77 ± 8 kg) of the two groups were similar. Preoperative heart rates (61 ± 9 vs 72 ± 10 beats/min) and systolic arterial blood pressure (118 ± 11 vs 134 ± 10 torr) of group I were slightly but significantly lower than those in group II; however all other cardiovascular variables measured were similar in the two groups.

Patients in group I required an average of 3.8 ± 0.3 μg·kg^{-1} (mean ± SD) of sufentanil for unconsciousness while those in group II needed 4.9 ± 0.3 μg·kg^{-1}. For the entire operation doses of sufentanil required were 11.1 ± 0.8 and 15.0 ± 1.0 μg·kg^{-1} in groups I and II, respectively. Differences in sufentanil requirements between groups I and II at unconsciousness and for the entire operation were statistically significant ($P < 0.025$, Student's unpaired t-test). Induction times in the two groups were also statistically different, $P < 0.05$, and averaged 0.9 ± 0.2 and 1.3 ± 0.1 minutes in groups I and II respectively. The incidence of chest wall rigidity on induction of anaesthesia was similar in the two groups (18 per cent). Only one patient (group II) became severely rigid, according to our criteria, during induction. Succinylcholine given before intubation relaxed this patient rapidly.

Induction of anaesthesia with sufentanil produced small but significant decreases in systolic arterial blood pressure in both groups but no change in any other cardiovascular variable measured. Changes in systolic blood pressure were transient and had returned to control values at the time of incision. Heart rate, cardiac output and mean right atrial, systolic and mean pulmonary arterial pressures remained unchanged throughout the study period in both groups.

Increases in systolic arterial blood pressure >20 per cent of preoperative (control) values during sternotomy and sternal spread occured significantly more frequently in group II than in group I (Table I). Phentolamine was required to control arterial blood pressure in 18 per cent of patients in group II before bypass, almost always during sternal spread or dissection of the aorta before aortic cannulation, and 27 per cent of this group during bypass (Table II). Only five per cent of group I patients needed phentolamine before bypass and none during bypass. Differences between groups I and II during bypass were statistically significant. Twenty-three per cent of group II patients required nitrous oxide and 14 per cent required sodium nitroprusside after bypass for blood pressure control. No patient in group I required either of these drugs after bypass.

All patients were conscious within six hours of the end of operation. Mean time for recovery of consciousness after operation was similar in

TABLE I

PER CENT OF PATIENTS WITH INCREASES IN SYSTOLIC ARTERIAL BLOOD PRESSURE GREATER THAN 20 PER CENT OF CONTROL VALUES DURING STRESSFUL STIMULATION*

	Intubation	Incision	Sternotomy	Sternal spread
Group I (+ propranolol)	0	0	0	0
Group II (− propranolol)	0	0	27(6)†	27(6)†

*Numbers in ( ) indicate the number of patients.
†$P < 0.05$, Chi-square test, when compared to group I at the same time.

TABLE II

PER CENT OF PATIENTS REQUIRING SUPPLEMENTATION WITH PHENTOLAMINE, NITROUS OXIDE AND NITROPRUSSIDE DURING CABG OPERATIONS WITH SUFENTANIL

	Phentolamine		Nitrous oxide	Nitroprusside
	Before bypass	During bypass	After bypass	After bypass
Group I (+ propranolol)	5(1)	0	0	0
Group II (− propranolol)	18(4)	27(6)*	23(5)*	14(3)

*$P < 0.05$, Chi-square test, when compared to group I at the same time.

the two groups and averaged 2.0 ± 0.7 hours in Group I and 1.7 ± 0.7 hours in Group II. When interviewed 48 hours postoperatively, no patient in either group remembered being rigid or any other aspect of their anaesthetic induction, laryngoscopy, tracheal intubation or operation.

DISCUSSION

The results of this study demonstrate that patients with coronary artery disease taking propranolol preoperatively require less sufentanil for induction of anaesthesia and for CABG operations than patients not taking this drug. Our findings indicate that, in spite of receiving less sufentanil, patients taking propranolol preoperatively have less hypertension during operation and are more responsive to additional narcotic for control of hypertension and, thus, require less "other drug" supplementation than patients not taking propranolol. These data suggest that sufentanil-oxygen anaesthesia and perhaps anaesthesia with high doses of other narcotics is associated with less hypertension during CABG operations when patients are taking propranolol preoperatively.

A legitimate criticism of this study is that the degree of preoperative beta-adrenergic blockade using an infusion of a beta-adrenergic stimulating compound was never evaluated and compared in patients in the two groups. The reason this step was not in our protocol was that we considered this evaluation an unacceptable risk in patients with coronary artery disease. However, the significantly lower systolic arterial blood pressure and heart rate in patients in group I as compared to patients in group II suggests that at least some degree of beta-adrenergic blockade was probably present in the former.

The mechanism by which propranolol potentiates sufentanil (reduces sufentanil requirements) or blunts hypertensive responses during open heart surgery is unclear from our results. Whether potentiation or blunting also occur during non-cardiac surgery when narcotics are used in lower doses as supplements, or when they are used for analgesia outside the operating room has not, to our knowledge, been studied. Possible mechanisms by which propranolol could potentiate sufentanil include alteration (increase) of opiate central nervous system receptor occupation, stimulation of opiate central nervous system receptors, reduction of plasma volume, changes in the distribution volume of sufentanil, decreased sufentanil metabolism, or alteration in central nervous system membranes which increases the transfer of sufentanil into the brain.[4,5]

The high incidence of hypertension during fentanyl-oxygen anaesthesia in patients undergoing CABG operations reported by some investigators[6] but not by others[7–9] may also be explained in part by preoperative propranolol or other beta-adrenergic blocker therapy and/or management. Stanley and co-workers reported a zero incidence of hypertension during operation (increases in systolic arterial blood pressure >20 per cent of preoperative values) in one study and a 10 per cent incidence in another in Salt Lake City, Utah.[7]* Wynands[9] has had a similar experience. In contrast, Waller, *et al.*[6] reported a much higher incidence of hypertension during operation especially after severe surgical stress (maximal sternal spread) during CABG operations with high does fentanyl anaesthesia. Although it is unreported, all of Stanley, *et al.*'s patients in one study and most in the other were taking propranolol and received their last doses of this compound on the morning of operation. While most of Waller and co-workers' patients were taking propranolol preoperatively, none of these patients received the drug before operation on the day of surgery. Because of the short half life of propranolol, it is doubtful whether Waller, *et al.*'s patients had much beta-adrenergic blockade present during operation. Thus, it is reasonable that they would be more likely to develop hypertension with severe surgical stress during fentanyl anaesthesia.

Whether other problems with high dose fentanyl or sufentanil-oxygen anaesthesia, including tachycardia during operation,[6] rigidity during anaesthetic induction[3,6,9] and incomplete amnesia,[10] are also related to preoperative use or management of propranolol or other medications (vasodilators) is unclear from our data. It is likewise unclear whether our observations made during sufentanil anaesthesia with patients taking propranolol will also be true of patients taking other beta-adrenergic blockers and/or anaesthetized with other narcotic compounds. Tachycardia and incomplete amnesia were not observed at any time in any patient in this study. Tachycardia was observed with tracheal intubation, incision and sternotomy in the study of Waller, *et al.*[4] during high dose fentanyl anaesthesia but may have been caused by a large bolus of pancuronium ($0.1\ mg \cdot kg^{-1}$) immediately before intubation. Kopriva and co-workers[9] have shown that patients taking preoperative propranolol have lower heart rates before, during and after tracheal intubation (using thiopentone and succinylcholine for induction of anaesthesia) than patients not taking propranolol, but similar rises in heart rate with intubation. Heart rate does not increase with tracheal intubation after a high dose narcotic induction with fentanyl, sufentanil, or alfentanil, when the narcotic is followed by succinylcholine for muscle relaxation, but may when it is followed by pancuronium.[3,7,9,12]

It is likely that the incidence and degree of rigidity after fentanyl or sufentanil is not affected by preoperative propranolol therapy since they were similar in the two groups in this study. Recent work (de Lange, S., Stanley, T.H. unpublished data) suggests that the incidence of rigidity found with induction of anaesthesia with fentanyl and its newer cogeners (sufentanil, alfentanil) can be decreased by reducing the speed of narcotic administration and by using a small amount of a non-depolarizing muscle relaxant immediately before administering the narcotic.

In conclusion, our results indicate that patients undergoing CABG operations taking propranolol require less narcotic and other supplements with sufentanil-oxygen anaesthesia than patients not taking propranolol. The data also demonstrate that narcotic-oxygen anaesthesia in patients with coronary artery disease is associated with less hypertension when patients are taking propranolol than when they are not.

*de Lange, S., Stanley, T.H., Boscoe, M.J.: Fentanyl-oxygen anesthesia: Comparison of anesthetic requirements and cardiovascular responses in Salt Lake City and Leiden, Holland, Abstracts 7th World Congress of Anesthesiologists, Hamburg, 1980, p. 313.

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RÉSUMÉ

Cette étude a été effectuée chez 44 malades ayant subi un pontage aorto-coronarien. Vingt deux des patients avaient reçu du propranolol avant l'intervention, les vingt-deux autres n'en avaient pas reçu. Nous avons noté, dans chacun des cas, les doses de sufentanil nécessaires à la production de l'inconscience ainsi que les doses totales de cet agent requises au cours de l'intervention. Nous avons également noté tous les cas d'hypertension per-opératoire, les interventions médicamenteuses requises au traitement de l'hypertension et le temps d'éveil après l'intervention.

Les doses de sufentanil produisant l'inconscience ainsi que les doses totales de cet agent requises en cours d'intervention étaient significativement moindres chez les patients qui avaient reçu du propranolol avant leur intervention que chez ceux qui n'en avaient pas reçu. Même avec des doses de sufentanil inférieures, les patients qui avaient reçu du propranolol ont présenté moins d'hypertension per-opératoire et ont requis moins d'interventions médicamenteuses pour traiter cette complication. Les temps d'éveil après l'intervention ont été les mêmes chez les patients des deux groupes.

Les résultats de ce travail peuvent expliquer partiellement l'incidence variable d'hypertension rapportée au cours d'anesthésie au fentanil à haute dose ou avec d'autres techniques à base d'analgésiques et d'oxygène.