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Prevention of Intraoperative Myocardial Ischemia during Noncardiac Surgery with Intravenous Diltiazem: A Randomized Trial *Versus* Placebo

G. GODET,* P. CORIAT,† J. F. BARON,‡ M. BERTRAND,* B. DIQUET,§ C. SEBAG,¶ P. VIARS**

When patients suffering from coronary artery disease (CAD) are scheduled for noncardiac surgery, prevention of myocardial ischemia is a major concern.[1] The efficacy of Diltiazem (DTZ) in controlling symptoms of coronary arterial spasm[2] and in attenuating the ischemic manifestations induced by pacing or exercise in patients with fixed coronary artery stenosis has been demonstrated.[3-7] Nevertheless, the efficacy of this drug in preventing intraoperative myocardial ischemia has not yet been evaluated. We conducted a double-blind, randomized protocol to study whether iv DTZ minimizes the risk of intraoperative myocardial ischemia during noncardiac surgical procedures.

The other main objectives of this study were to determine hemodynamic response to induction of anesthesia, intubation of the trachea, skin incision, and recovery during fentanyl–N_2O–pancuronium anesthesia with iv DTZ or placebo infusion.

MATERIALS

Thirty consecutive patients scheduled for vascular surgery (carotid endarterectomy or aortobifemoral bypass grafting) were studied with a clear history of stable, effort-related angina pectoris provoking slight or marked limitation of physical activity. All patients were chronically treated for their symptoms. All gave informed consent for the study after approval by our institutional review committee.

The following criteria were used to exclude patients from the study:

1. Cardiothoracic ratio greater than 55% on the chest radiograph;
2. heart rate of less than 50 beats/min;
3. left bundle branch block and left ventricular hypertrophy with strain pattern, all of which render interpretation of the ST segment difficult; and
4. congestive heart failure.

Patients were randomly assigned to receive either iv DTZ (DTZ group, n = 15) or placebo (P group, n = 15).

Both groups were identical in age, infarction dating more than 6 months, grade of angina, and previous history of hypertension (table 1). The type of surgical procedure was the same in both groups: carotid endarterectomy, 11 *versus* 8; aortobifemoral bypass grafting, 1 *versus* 4; and axillary femoral bypass, 3 *versus* 3. Duration of surgery was similar in both groups (2.8 ± 2.2 h *vs.* 2.7 ± 1.0 h), as was intraoperative blood loss (2.9 ± 2.3 *vs.* 1.9 ± 1 l). Antianginal and antihypertensive drugs, chronically administered, were given orally 4 h before surgery.

Anesthetic procedure was identical in both groups. Patients were given im premedication (morphine 5 mg and scopolamine 0.5 mg) 1 h preoperatively. Intravenous, radial artery, and thermodilution pulmonary catheters were inserted. Then ECG leads, anteroposterior and CM_5, were recorded continuously using a battery-operated Holter® monitor (I.C.R.).

Immediately after catheter insertion, a double-blind protocol was followed. After an iv dose of 0.15 mg/kg of DTZ or an equivalent amount of placebo, a continuous infusion of 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of DTZ or placebo was started and followed until 2 h after extubation of the trachea. Thirty minutes after continuous DTZ or P infusion had been started, anesthesia was induced with fentanyl (6 μg/kg) and flunitrazepam (0.02 mg/kg) administered slowly iv while the patient breathed 100% oxygen. Respirations were assisted at first and then controlled. When patients were unresponsive, pancuronium 0.1 mg/kg was administered and the trachea intubated.

Anesthesia was maintained under controlled ventilation with 60% N_2O and oxygen and additional fentanyl throughout anesthesia. An oscilloscopic trace (lead V_5), arterial pressure, and pulmonary capillary wedge pressure (PCWP) were monitored during surgery and the postoperative period. During surgery, fluids were infused iv at the discretion of the anesthetist. Halothane was additionally administered to patients who developed hypertension, tachycardia, or an ST segment depression in re-

* Assistant in Anesthesiology.
† Assistant Professor of Anesthesiology.
‡ Resident in Anesthesiology.
§ Assistant in Pharmacology.
¶ Assistant in Cardiology.
** Professor of Anesthesiology.

Received from the Département d'Anesthèsie Réanimation and the Départment de Pharmacologie, Hôpital Pitié-Salpêtrière, 83 boulevard de l'Hôpital, 75013 Paris, France. Accepted for publication September 15, 1986.

Address reprint requests to Dr. Coriat.

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TABLE 1. Patient Characteristics

	Group	
	P	DTZ
Age (yr)	69 ± 6	69 ± 10
Male patients	10	13
Clinical data		
Chronically treated hypertension	7	11
Previous myocardial ischemia (dating > 6 months)	9	9
Disabling angina pectoris	9	10
Preoperative cardiac treatment		
Nitrates	13	10
Diltiazem 240–360 mg/day	7	6
Nifedipine (40 mg/day)	6	3
Propranolol or acebutolol	1	2
Clonidine	2	1
Diuretics	3	2

P = placebo; DTZ = diltiazem.

sponse to surgery. Intravenous nitroglycerin was infused when PCWP remained above 17 mmHg more than 1 min or when an ischemic-type ST segment depression persisted. Postoperatively, patients were warmed while being sedated, if necessary, with fentanyl in a recovery room, and the trachea only extubated when body temperature was normal (36.5° C).

Complete hemodynamic measurements were obtained at the times indicated in table 2.

Hemodynamic measurements included mean arterial pressure (MAP), heart rate (HR), PCWP, and cardiac index (CI). Thermodilution cardiac output was made in triplicate using an Edwards Laboratory cardiac output computer. The Holter® monitor tapes were examined retrospectively and blindly using an ICR® electrocardioscanner. An ischemic episode was defined as an ischemic-type ST segment depression greater than 1 mm present for more than 10 beats in either lead. The occurrence of premature ventricular beats was noted. A digital clock synchronized to the recorded tape permitted accurate time marking. The charts were examined retrospectively to determine in which situations myocardial ischemia occurred.

TABLE 2. Hemodynamic Measurement Times

T1	Control pre-DTZ/placebo infusion
T2	30 min DTZ/placebo infusion
T3	Flunitrazepam 0.02 mg/kg + fentanyl 6 μg/kg + pancuronium 0.1 mg/kg
T4	During laryngoscopy
T5	Before incision (N_2O/O_2 60%)
T6	After incision
T7	At the end of surgery
T8	Before extubation of the trachea
T9	3 min after extubation

Immediately before induction (T2) and on extubation of the trachea (T9), blood samples were drawn for determination of plasma blood levels of DTZ. Plasma was immediately separated and frozen at −20° C and later analyzed for DTZ and deacetyl DTZ using a high-performance liquid chromatographic method.[8]

Values are expressed as mean ± SD. Two-way analysis of variance was used for statistical analysis of hemodynamic changes. The Wilcoxon-Mann-Whitney rank-sums test was used to perform intergroup comparison of ordinal data.

RESULTS

ST Segment Depression during Anesthesia and Recovery. Continuous monitoring of the ECG revealed ischemic-type ST segment depression in 11 patients receiving placebo and in six patients receiving DTZ (no significance [NS]). These depressions lasted for more than 3 min; they were observed more than once in nine patients in the P group and in two patients in the DTZ group. Twenty-five ischemic episodes were noted in 11 patients of the P group, eight ischemic episodes were noted in six patients of the DTZ group ($P < 0.02$). The ST segment depressions started during laryngoscopy (P group, n = 3, DTZ group, n = 2); following skin incision (P group, n = 6, DTZ group, n = 2); during the surgical procedure (P group, n = 11, DTZ group, n = 2); and at recovery (P group, n = 5, DTZ group, n = 2).

In the P group, nine out of 25 ischemic episodes were associated with an increase of more than 20% in systolic arterial blood pressure; 15 were associated with an increase of more than 20% in heart rate. During 11 ischemic episodes, an increase in PCWP above 17 mmHg occurred, but only four that persisted despite fentanyl–halothane administration required nitroglycerin infusion.

In the DTZ group, myocardial ischemic episodes were associated with an increase in heart rate in six cases, with an increased systolic arterial blood pressure in five cases, and in three cases with an increased PCWP. None required nitroglycerin infusion.

Myocardial ischemia was associated with more than five premature ventricular beats during 1 min in seven patients in the P group and in two patients in the DTZ group.

One patient in each group experienced a large increase in PCWP at recovery associated with myocardial ischemia which led to acute pulmonary edema. In these patients the return to mechanical ventilation, under fentanyl sedation and continuous nitroglycerin infusion at a level that restored the PCWP to normal, led to the resolution of the pulmonary edema.

All the other patients had no problems postoperatively. There were no perioperative myocardial infarctions. In five patients in the P group and in four patients in the

TABLE 3. Hemodynamic Variations (mean ± SD) for the DTZ Group (n = 15) and the P Group (n = 15)

	Time								
	1	2	3	4	5	6	7	8	9
MAP (mmHg)									
DTZ	98 ± 17	89 ± 12*	66 ± 11*	79 ± 15*	65 ± 4*	86 ± 4*	96 ± 16	96 ± 16‡	91 ± 18‡
P	91 ± 15	92 ± 15.8	77.5 ± 17.5†	85 ± 19	76 ± 20†	94 ± 15	93 ± 14	116 ± 21*	117 ± 20*
HR (beats/min)									
DTZ	72 ± 19	65 ± 16†	60 ± 18*	62 ± 16*	59 ± 16*	69 ± 22	58 ± 10*	75 ± 15	78 ± 16
P	64 ± 14	62 ± 13	58 ± 14	61 ± 20	59 ± 14	79 ± 22*	59 ± 11	86 ± 27*	91 ± 27*
CI ($l \cdot min^{-1}/m^2$)									
DTZ	3.1 ± 0.46	3.2 ± 0.7	2.5 ± 0.6*	2.8 ± 0.6	2.5 ± 0.6*	2.2 ± 0.5*	2.7 ± 0.8	3.7 ± 0.95*	4.0 ± 1.1*
P	3.1 ± 0.4	3.3 ± 0.6	2.7 ± 0.7*	3.1 ± 1.1	3.0 ± 1.1	2.8 ± 1.1	3.1 ± 0.8	3.8 ± 1.2*	4.0 ± 1.2
PCWP (mmHg)									
DTZ	9.5 ± 4.8	10.9 ± 4.4	7.7 ± 4.2†	8.4 ± 3.6	8.1 ± 3.9	13.1 ± 3.7	12.7 ± 5.3	13.8 ± 9	10.9 ± 10
P	7.6 ± 3	7.8 ± 3.5	7.2 ± 3.8	9.5 ± 4.3†	6.6 ± 4.2	14.8 ± 3.4*	14.0 ± 4.1*	12.2 ± 8†	14.1 ± 7.9†

Measurement times are indicated in Table 2.
MAP = mean arterial pressure; HR = heart rate; CI = cardiac index; PCWP = pulmonary capillary wedge pressure.
Intragroup comparison: * = $P < 0.01$ *vs.* control T1; † = $P < 0.05$ *vs.* control T1.
Intergroup comparison: ‡ = $P < 0.01$ *vs.* group P.

DTZ group, inverted T-waves appeared on the postoperative ECG.

The hemodynamic measurements performed during induction, incision, and recovery in both groups are shown in table 3. Analysis of hemodynamic data in each group revealed that before induction of anesthesia, iv DTZ caused a 10% decrease in MAP without affecting the HR, PCWP, or CI. After fentanyl–pancuronium administration, a 25% decrease in MAP appeared with a slight but significant decrease in HR and CI. Contrary to the P group, no increase in HR was noted at incision and recovery, no increase in MAP was observed at recovery, and no significant increase in PCWP was noted at intubation and at recovery. In one patient receiving DTZ, the occurrence of a bradycardia less than 40 beats/min with sinus block but without ST modification led us to discontinue DTZ infusion.

Comparison of hemodynamic data between the two groups revealed no significant difference until recovery. Before and after extubation of the trachea, MAP was significantly lower in group DTZ ($P < 0.01$).

Intraoperative fluid infusion was not significantly different between the two groups: 1.6 ± 0.7 l of colloids/crystalloids in the P group, 1.5 ± 0.4 l in the DTZ group.

An increase in arterial blood pressure in response to surgical stress led to halothane administration in 11 patients in the P group and in seven patients in the DTZ group (NS).

In the DTZ group, plasma blood levels varied at induction between 50 and 204 ng/ml (114 ± 52) and at recovery between 136 and 336 ng/ml (201 ± 60). Plasma blood levels of deacetyl DTZ were 20 ± 18 ng/ml at induction and 27 ± 15 ng/ml at recovery.

In the P group, among the seven patients chronically treated by DTZ, five had detectable plasma levels of DTZ at induction that varied from 44 to 93 ng/ml.

Using linear regression analysis, no correlation was found in the DTZ group between the decrease in MAP during induction of anesthesia and the plasma levels of DTZ.

DISCUSSION

Patients suffering from angina pectoris are particularly prone to developing intraoperative myocardial ischemia. The narcotic anesthetic techniques are often used in patients with coronary disease because these have the advantage of minimal myocardial depression.[9] With this approach, however, the increase in myocardial oxygen consumption needs to be minimized by controlling HR and/or blood pressure during stress of anesthesia, surgery, and recovery.[10] We postulated that prophylactic iv infusion of DTZ would provide optimal myocardial oxygenation during the operative period and minimize the risk of intraoperative myocardial ischemia. An iv DTZ infusion was tested in this study because its effects in exercise-induced angina and variant angina are well established.[11] In particular, a single oral dose or iv administration of DTZ increased exercise tolerance in patients with stable angina, as assessed by increases in exercise time and decreases in the magnitude or time to onset of ST segment depression.[3–7]

The kinetic profile of DTZ led us to determine the DTZ infusion rate.[11] An initial bolus of 0.5 mg/kg was administered because it results in a therapeutically active plasma concentration without negative effect on atrioventricular conduction.[12]

The high incidence of intraoperative myocardial ischemia despite PCWP monitoring and fentanyl–flunitrazepam–pancuronium–N_2O/O_2 anesthesia should be respected in relation to the severity of the coronary artery disease of the patients studied. In other studies in patients

with angina pectoris, a similar incidence of intraoperative myocardial ischemia was detected by continuous ECG monitoring[10,13] or measurements of myocardial lactate production.[14] These studies confirm that the ischemic changes are in most cases associated with increases in HR and MAP in relation to intra- and postoperative stressful situations.[10,13,14] The significantly lower frequency of ischemic ST segment depression observed in the patients receiving DTZ infusion suggests that iv DTZ is a potentially useful drug in decreasing the incidence of intraoperative myocardial ischemia during noncardiac surgery. DTZ may exert its beneficial antiischemic effects not only by decreasing myocardial oxygen demand by afterload reduction without increasing the HR, but also by improving myocardial oxygen supply through direct coronary vasodilatation or prevention of coronary vasoconstriction.[15-17]

Two of the 30 patients of the study experienced postoperative pulmonary edema. This 7% incidence of acute pulmonary edema might appear high. However, the study of Goldman *et al.*[18] revealed that acute pulmonary edema is the cardiac complication encountered most frequently during the operative period. Among the 1,000 patients over 40 yr of age studied by Goldman, 36 experienced such a complication. In our study, patients were included on the basis of a clear history of angina pectoris, which probably accounted for the higher incidence of postoperative acute pulmonary edema.

During surgery and at recovery, fewer patients in the DTZ group showed an increase in systolic arterial blood pressure and/or in HR of more than 20% in relation to the pressure or HR noted at control time. The reduction in blood pressure and HR associated with the use of DTZ suggests that a reduction in myocardial oxygen demand was a mechanism by which DTZ acts in ischemia induced by surgical stress. However, other potential mechanisms of action of DTZ, which cannot be demonstrated by the hemodynamic measurements of the study, may have played a part.

The capacity of DTZ to improve myocardial perfusion may play an important therapeutic role, even in patients without coronary spasm.[15-17] Several experimental studies have observed an increase in myocardial blood flow of the ischemic zone with DTZ.[19,20] Other studies suggest that DTZ exerts its beneficial effects through a direct metabolic effect on the myocardium.[21,22] Because CI and PCWP were unchanged after continuous DTZ infusion, the possible depressant effect of DTZ on myocardial contractility is counterbalanced by the systemic arterial vasodilatation induced by the drug. Similar hemodynamic findings have been noted in most of the studies in which a bolus of DTZ had been administered.[11]

Our data are of interest because they provide further knowledge of the hemodynamic effects and blood levels of DTZ administered by continuous iv infusion. Furthermore, they permit assessment of the interaction of DTZ with anesthetic agents (*e.g.*, fentanyl, pancuronium, and N_2) and response to stressful situations of the operative period (such as intubation, incision, or recovery). Continuous cardiovascular monitoring used in this study does not reveal profound vasodilatation and hypotension due to a combination of fentanyl–N_2O and iv DTZ. The hemodynamic response to anesthesia in patients with CAD receiving iv DTZ seems to indicate that the effect of DTZ and fentanyl–pancuronium–N_2O on cardiac function and peripheral vasculature are probably close to being additive. However, the negative chronotropic action of DTZ, which has a beneficial effect on myocardial oxygen balance, necessitates continuous intraoperative controls because the direct suppressive effect on the sinoatrial node may lead to a marked bradycardia with sinus blockade.[23] Among seven patients chronically treated with DTZ included in the P group, only two presented plasma levels of DTZ between 80 and 100 mg/ml, considered as minimal active plasma levels.[24] This seems to indicate that oral administration of DTZ 4 h before surgery does not always lead to sufficient plasma levels during anesthesia.

Since in contrast to patients receiving the placebo, no significant increase in HR and/or arterial blood pressure was observed at incision and recovery, it appeared that DTZ is potentially useful in controlling these hemodynamic parameters during such stressful situations. However, the hemodynamic changes due to recovery were the most obvious influence in the patients receiving iv DTZ. During such periods several factors point to provoking increased global oxygen consumption and preload and afterload stress. It is interesting to note the lack of impairment of hemodynamic function in the DTZ group during the stressful situation of anesthesia, while HR and blood pressure response is limited.

The lack of increases in arterial blood pressure at recovery in the DTZ group is not surprising because during exercise testing in CAD patients, a significant reduction in arterial blood pressure is observed following single-dose oral administration of DTZ (18–360 mg).[6,25,26] In hypertensive patients this effect is particularly clear.

In conclusion, we found that iv DTZ, at the dose giving serum levels varying from 100 to 300 ng/ml, could be safely used with fentanyl–pancuronium–N_2O anesthesia in patients with angina pectoris during noncardiac surgery. Our study demonstrates that iv DTZ is a potentially useful drug in decreasing the incidence of intraoperative myocardial ischemia during noncardiac surgery. As patients suffering from coronary artery disease must be considered as individuals, these results should be appreciated with respect to the age of the patients studied, the severity of their angina, their preoperative treatment, and their peripheral vascular disease. Further investigations are re-

quired to study the efficiency of DTZ in preventing intraoperative ischemic episodes for other types of coronary artery disease and for cardiac surgery.

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