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COMMUNICATIONS

Effect of cardiopulmonary bypass on plasma concentrations of diltiazem and its two active metabolites

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Abstract—Diltiazem is often used to prevent myocardial ischaemia during the perioperative period of coronary artery bypass surgery. The purpose of this study was to investigate the effect of cardiopulmonary bypass (CPB) on plasma concentrations of diltiazem and of its two main and active metabolites (*N*-monodemethyldiltiazem (*N*-desmethyldiltiazem) and desacetyldiltiazem). The patients were administered their usual treatment during the preoperative days. The last dose was administered immediately before anaesthesia. At the onset of CPB, a significant decrease in the plasma concentrations of diltiazem and its metabolites was observed, whereas the variation was slight and not significant when the plasma concentrations were corrected for haemodilution. These results confirm that the decrease observed at the initiation of the bypass procedure can be ascribed to the haemodilution induced by the CPB. During CPB, the concentrations of diltiazem and its metabolites remained constant suggesting that the rate of metabolism and excretion of the drug was altered during the bypass procedure. At the end of CPB, there was no increase of drug plasma concentrations suggesting that no redistribution of diltiazem from tissues to plasma occurred. Furthermore, this study shows that only 33% of subjects have therapeutic levels of diltiazem before anaesthesia, and that all subjects have subtherapeutic levels during and after the CPB. These results suggest that a higher chronic oral dose of the drug should be given in patients undergoing cardiac surgery with CPB.

Diltiazem is a calcium-channel blocker widely used in the treatment of variant angina (Buckley et al 1990). It can be used before anaesthesia to prevent perioperative myocardial ischaemia during coronary artery bypass surgery. Cardiopulmonary bypass (CPB) causes profound physiological changes (haemodilution, hypotension, blood flow changes) that may influence drug distribution and elimination and consequently alter plasma concentrations of the drugs (Buylaert et al 1989).

Pharmacokinetic studies with β-blockers during CPB have shown an increase of propranolol plasma levels after the end of CPB (Plachetka et al 1981) while no increase was observed with acebutolol (Mantz et al 1984). These changes observed in drug plasma concentrations at the end of CPB may have important clinical implications; increased levels suggest that additional doses of the drug could induce an overdose. On the other hand the continuation could be convenient to prevent myocardial ischaemia.

The present study was performed to investigate the effect of CPB on plasma concentrations of diltiazem and its main active metabolites, *N*-monodemethyldiltiazem (*N*-desmethyldiltiazem) and desacetyldiltiazem, in patients receiving conventional diltiazem.

Materials and methods

Patients. The study was carried out in 12 men aged from 50 to 70 years (58·5 ± 6·1, mean ± s.d.) and weighing from 71 to 105 kg (84·2 ± 10·8). All patients underwent coronary artery bypass surgery with CPB. Preoperatively, all subjects had normal renal and hepatic function and left ventricular ejection fraction was higher than 0·50. The patients received immediate-release diltiazem tablets for at least one week before surgery at a daily dose of 180 to 360 mg; eight patients received three tablets (60 mg) per day, two patients received four 60 mg tablets per day and two patients received six 60 mg tablets per day. The last dose of the multiple regimen of diltiazem was given 12 h before surgery.

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Anaesthesia was induced with fentanyl (50 μg kg^{-1}), midazolam (0·30 mg kg^{-1}) or flunitrazepam (0·03 mg kg^{-1}) with the muscle relaxant pancuronium bromide (0·10 mg kg^{-1}). Anaesthesia was maintained with increments of these drugs. The patients were ventilated with an inspired mixture of 50% nitrous oxide in oxygen before and after bypass. After anticoagulation (heparin 300 units kg^{-1}), the CPB was performed with a bubble oxygenator (Bos 10, Bentley, Plaisir, France), under normothermic conditions, total haemodilution and hyperkaliaemic cardioplegia. The priming volume consisted of Ringer's lactate (1500 mL), dextrose 5% (200–500 mL according to patient's weight), sodium bicarbonate 4·2% (100 mL), and heparin (5000 units).

The protocol of the study was approved by the Ethics Committee of University Claude Bernard Lyon I and the Hospices Civils de Lyon, and written informed consent was obtained from each patient.

Administration and blood sampling. On the day scheduled for surgery, before induction of anaesthesia, fasting subjects received one tablet of diltiazem at a dose of 60 mg with 30 mL water.

Blood samples (5 mL) were drawn from the radial artery catheter in heparinized tubes before drug administration and anaesthesia (T_0) and at the following interval times: T_1, 15 min after drug administration; T_2, 30 min after drug administration; T_3, after heparin injection and immediately before the onset of CPB; T_4, 5 min after the onset of CPB; T_5, before removal of aortic cross clamp; T_6, after restoration of pulmonary circulation; T_7, immediately before the end of CPB; T_8, 30 min after the end of CPB; T_9, T_{10} and T_{11}, 6, 8 and 24 h, respectively, after diltiazem administration. All samples were promptly centrifuged and the supernatant plasma stored at −80°C until analysis.

Additional blood samples (2 mL) were taken at each time for measurement of plasma albumin for correction of plasma concentration for haemodilution, according to the formula:

$$\text{Corrected plasma concn} = \frac{\text{Plasma concn} \times \text{albuminaemia at } T_0}{\text{Albuminaemia at time of measurement}}$$

For three subjects, blood samples were taken simultaneously from venous and arterial vessels at times T_4 and T_5 to assume that no drug was absorbed on the CPB equipment.

Analytical method. Diltiazem and metabolites were determined by an HPLC method using a solid phase extraction procedure

before analysis (Boulieu et al 1990). For an accurate determination of the concentrations of the compounds, rigorous conditions of blood sample collection and treatment were required to avoid metabolic conversions (Bonnefous et al 1992).

Statistical analysis. The comparison of uncorrected and corrected plasma concentrations at different times was performed with Student's *t*-test for paired data. The limit for significance was $P < 0.05$.

Results

Plasma concentration profiles of diltiazem, *N*-desmethyldiltiazem and desacetyldiltiazem from a patient under CPB following oral administration of diltiazem are shown in Fig. 1. Fig. 2 represents the mean plasma concentration profiles of uncorrected and corrected values after diltiazem administration. The comparisons of uncorrected and corrected diltiazem and metabolite concentrations between T_0 (before drug administration) and T_4 (5 min after the onset of CPB), and between T_7 (immediately before the end of CPB) and T_8 (30 min after the end of CPB) are shown in Table 1.

Table 1. Statistical comparison of plasma diltiazem and metabolite concentrations measured before drug administration and 5 min after the onset of CPB (T_0 vs T_4) and just before the end of CPB and 30 min after the end of CPB (T_7 vs T_8).

	Concn (ng mL^{-1})			
	T_0	T_4	T_7	T_8
Diltiazem				
Uncorrected	79·5±41·2	41·0±20·4**	40·6±23·7	38·6±23·8
Corrected	79·5±41·2	66·1±32·5	62·6±34·4	57·6±32·3
N-Desmethyldiltiazem				
Uncorrected	46·5±21·6	26·1±9·1**	26·8±12·3	27·5±13·0
Corrected	46·5±21·6	42·5±14·4	44·2±17·0	41·3±17·2
Desacetyldiltiazem				
Uncorrected	17·5±8·8	11·3±4·5*	12·3±5·9	11·7±6·1
Corrected	17·5±8·8	18·2±6·7	23·0±11·3	21·5±16·3

*$P < 0.01$, **$P < 0.001$ compared with T_0 values. There were no significant differences between T_8 and corresponding T_7 values. All values are mean ±s.d.

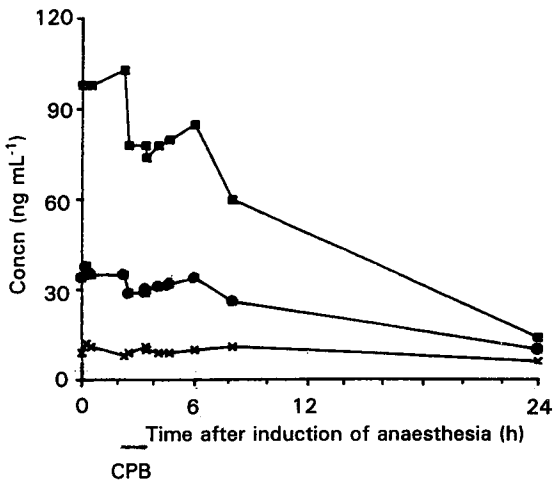

FIG. 1. Plasma concentration profile of diltiazem (■), *N*-desmethyldiltiazem (●) and desacetyldiltiazem (×), from a patient under CPB following oral administration of diltiazem.

At the onset of CPB, the concentrations of diltiazem and its two metabolites decreased significantly compared with the concentrations determined before induction of anaesthesia (T_0 vs T_4) for uncorrected values, whereas the slight variation observed in the values corrected for haemodilution was not significant.

The decline in plasma concentration observed upon initiation of CPB was followed by a plateau of about 40 min during the bypass procedure (Fig. 1).

At the end of CPB, the concentrations of diltiazem and its metabolites did not change significantly as shown in Table 1.

The influence of CPB circuit on plasma concentrations was investigated. No significant difference was found in the diltiazem and metabolite plasma concentrations between blood samples taken from arterial and venous vessels, suggesting that neither diltiazem nor the metabolites were absorbed on the material of the CPB equipment.

Discussion

The effect of CPB on plasma concentrations of diltiazem and the

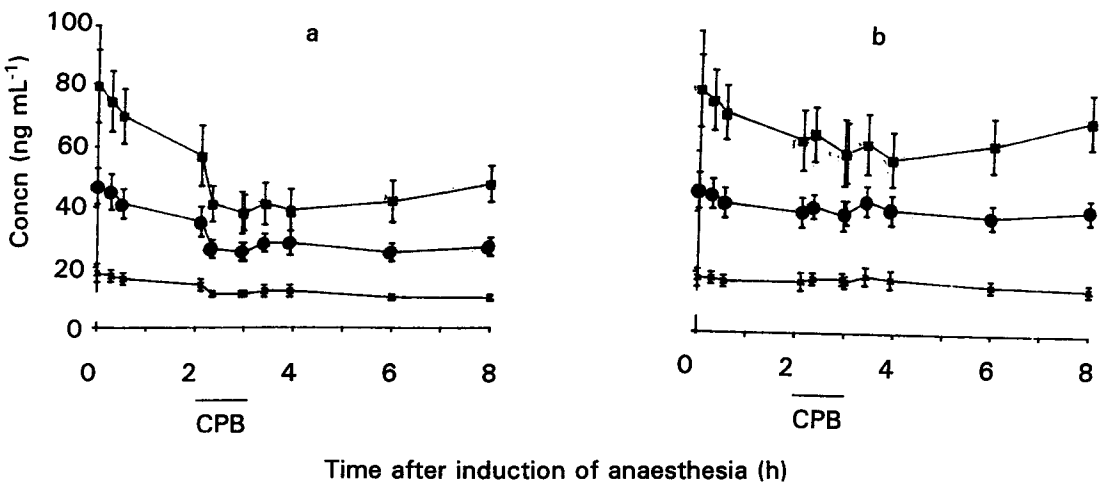

FIG. 2. Mean plasma profile of uncorrected (a) and corrected (b) concentrations following a 60-mg oral dose of diltiazem from patients under CPB. Diltiazem (■), *N*-desmethyldiltiazem (●) and desacetyldiltiazem (×).

two main active metabolites, *N*-desmethyldiltiazem and desacetyldiltiazem, was evaluated during the perioperative period. These metabolites may have pharmacological activity; desacetyldiltiazem and *N*-desmethyldiltiazem were found to have an estimated pharmacodynamic effect of 50 and 20%, respectively, of that of the parent drug (Morselli et al 1979; Sugihara et al 1984; Buckley et al 1990).

The abrupt fall in plasma concentrations upon initiation of the bypass procedure can be attributed to changes in distribution or elimination (Buylaert et al 1989). During bypass, the plasma dilution due to the addition of priming solution leads to a reduction in plasma drug concentration. In the present study, the marked decrease in the concentrations of diltiazem and the metabolites observed at the initiation of CPB can be explained by haemodilution as suggested by the comparison of the uncorrected and corrected values between T_0 (before anaesthesia induction) and T_4 (5 min after the onset of CPB). During CPB, the concentrations of the compounds remained constant. This suggests that the rate of metabolism and excretion of the drug was altered during the bypass procedure. At the end of CPB, after restoration of pulmonary circulation, the concentrations of diltiazem and its metabolites remained stable or displayed little change, suggesting that no redistribution of the drug from tissue to plasma occurred and particularly no wash-out from the lungs compared with propranolol (Plachetka et al 1981) and fentanyl (Bentley et al 1983). Likewise, no significant difference was observed in the concentrations found immediately before (T_7) and 30 min after (T_8) the end of CPB.

A trend toward augmentation of plasma diltiazem level occurred 8 h after anaesthesia induction (T_{10}). This trend may be due to a delay in drug absorption induced by CPB. According to several authors, a minimum plasma concentration of diltiazem of 100 ng mL^{-1} is associated with haemodynamic effects (Cremer et al 1985; Joyal et al 1986) and symptomatic improvement in patients with angina pectoris (Morselli et al 1979). In our study, we observed that before anaesthesia induction, only four subjects (33%) had a concentration of diltiazem higher than 100 ng mL^{-1} (1 with 6 tablets, 2 with 4 tablets and 1 with 3 tablets per day for chronic treatment). After CPB, all subjects have diltiazem plasma levels below 100 ng mL^{-1}. Larach et al (1989), on the basis of a limited number of sampling points (one before anaesthetic induction: pre-CPB, and one following weaning from CPB: post-CPB), had found that six out of eight patients (75%) receiving oral diltiazem therapy at a mean dose of 256 ± 12 mg every 6 to 8 h for at least 36 h before anaesthesia had diltiazem concentrations less than 100 ng mL^{-1} and that all patients had subtherapeutic levels post-bypass. Our study shows that oral diltiazem treatment at a dose of 180–360 mg day^{-1} for at least one week as used in clinical practice displayed subtherapeutic concentrations at the end of CPB.

Plasma concentrations of the metabolites *N*-desmethyldiltiazem and desacetyldiltiazem were about $64 \pm 20\%$ (range 35–108) and $25 \pm 14\%$ (range 9–65) of the parent drug, respectively, before anaesthesia induction (T_0), $77 \pm 27\%$ (range 40–142) and $37 \pm 34\%$ (range 14–142) at the onset of CPB (T_4) and $80 \pm 24\%$ (range 40–132) and $37 \pm 26\%$ (range 11–116) 30 min after the end of CPB (T_8). However, the differences observed were not statistically significant. Considering the large inter-individual variability in the concentrations of these metabolites and their pharmacodynamic properties, the determination of plasma concentrations of the active metabolites needs to be considered for individualization of dosage adjustment for optimal therapeutic benefit in selected patients.

With regard to diltiazem levels, our results suggest that a higher chronic oral dose of this drug should be given before surgery. The mechanism of calcium-channel blockers in preventing perioperative myocardial ischaemia is still unclear. In three prospective studies (Chung et al 1988; Slogoff & Keats 1988; Tuman et al 1989) calcium-channel blockers seemed to decrease the incidence of ischaemic episodes but their effect appeared less than the effect of β-blockers. However, these studies were not randomized and the patients received different calcium-channel blockers. Thus, further study on pharmacodynamics during the perioperative period are required to define the plasma concentration-therapeutic relationship and to optimize diltiazem dosage in patients undergoing cardiac surgery.

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