Title: CARDIOPULMONARY BYPASS ALTERS d-TUBOCURARINE PHARMACOKINETICS

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Introduction. The literature dealing with the disposition of anesthetic agents in patients undergoing cardiac surgery is limited, although high-dose fentanyl has been studied.[1,2] Cardiopulmonary bypass (CPB) produced a marked initial decrease in the total plasma concentrations of fentanyl, presumably due to hemodilution. A constant-rate infusion of d-tubocurarine (dTC) has been used previously to produce sustained muscular relaxation in surgical patients.[3] If initiation of CPB decreases the plasma concentrations of dTC, then additional doses may be required. The present study was undertaken to investigate the effects of surgery involving CPB on the pharmacokinetics of dTC administered by a bolus and infusion technique.

Methods. 12 patients, aged 57.2 (±9.9) years, scheduled for coronary artery bypass grafting gave their informed consent. Anesthesia was induced with thiopental (100-300 mg), and maintained with nitrous oxide, halothane and fentanyl, varied according to clinical requirements. Prior to the administration of dTC single specimens of blood and urine were collected. An I.V. bolus dose of dTC (0.6 mg/kg) was administered simultaneously with the commencement of an infusion of dTC at 3 μg/min/kg. The infusion was continued until closure of the pericardium was imminent. Urine samples were collected at half hourly intervals during the infusion, the volume recorded, and an aliquot stored at -20°C for later dTC analysis. Plasma was obtained from samples taken via the catheter placed to monitor arterial blood pressure; sampling continued at appropriate intervals until 16-24 hours following the infusion. Concentrations of dTC in the plasma and urine were determined by a spectrofluorimetric technique. The renal clearance of dTC was determined from the plasma and urine data obtained during the dTC infusion and CPB. The pharmacokinetic parameters, plasma clearance (CL), elimination half-life ($T_{\frac{1}{2}\beta}$) and apparent volume of distribution (Vss) were calculated model-independently, ignoring the period of transient disruption in the plasma concentrations during the CPB. These parameters were compared with data obtained in a group undergoing noncardiac surgery.[3]

Results. The patients weighed 78 (±12) kg and received a total dose of 95.4 (±18.7) mg of dTC for the infusion period (197 ± 36 min). CPB was initiated 58 (±7) min following commencement of the dTC infusion and continued for 103 (±31) min. Initially the dTC plasma concentrations fell in a normal bi-exponential fashion to 2.16 (±0.72) μg/ml immediately prior to CPB. Upon institution of CPB, the concentrations rose to a plateau of 3.94 (±0.58) μg/ml. During this period the renal clearance of dTC was 17.7 (±9.3) ml/min. The pharmacokinetic parameters are shown in Table 1.

Discussion. Upon initiation of CPB, the plasma concentrations of dTC rose to a plateau approximately twice that prior to CPB and some three times that observed in a previous study involving noncardiac surgery.[3] These changes were presumably related to a lower CL and a longer $T_{\frac{1}{2}\beta}$ of dTC in the cardiac patients per se or as a direct result of CPB. Prolonged effect did not present a clinical problem in our patients as their routine care involved continued endotracheal intubation and mechanical ventilation. However, the low clearance suggests that large doses of dTC are likely to produce postoperative respiratory insufficiency in some patients following surgery involving CPB.

References.

1. Lunn JK, Stanley TH, Eisele J, Webster L, Woodward A: High dose fentanyl for coronary artery surgery: Plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular responses, Anesth Analg 58:390-395, 1979.
2. Koska AJ, Romagnoli A and Kramer WG: Effect of cardiopulmonary bypass on fentanyl distribution and elimination, Clin Pharm Ther 29:100-105, 1981.
3. Ramzan MI, Triggs EJ, Shanks CA: The pharmacokinetics of d-tubocurarine administered by combined I.V. bolus and infusion, Br J Anaesth 52:893-899, 1980.

TABLE 1. PHARMACOKINETIC PARAMETERS (MEAN ± S.D.) FOR d-TUBOCURARINE

	CPB Patients	Noncardiac Patients	P
$T_{\frac{1}{2}\beta}$ (mins)	590 (± 104)	172 (± 80)	<0.01
CL (ml/min/kg)	0.61 (± 0.19)	2.69 (± 1.02)	<0.01
Vss (ml/kg)	405 (± 98)	455 (± 173)	NS