

Propranolol treatment in children with tetralogy of Fallot alters the response to isoprenaline after surgical repair

C BARAZZONE,* C JACCARD,* M BERNER,* P DAYER,† J-C ROUGE,‡
I OBERHANSLI,§ B FRIEDLI§

*From the *University Paediatric Clinic of Geneva; †Clinical Pharmacology Unit, Department of Medicine, University of Geneva; ‡Department of Anaesthesia, University Hospital of Geneva; §Paediatric Cardiology Unit, University Paediatric Clinic of Geneva*

SUMMARY When propranolol is given to prevent hypoxaemic episodes in children with tetralogy of Fallot who are awaiting operation it is advisable to continue the treatment until shortly before the induction of anaesthesia. Because catecholamines are often required to maintain adequate cardiac output after surgical correction the effect of preoperative treatment with β blockers on the response to isoprenaline after the operation was investigated in nine children given propranolol before operation and nine who were not. They were studied three and 24 hours after cardiopulmonary bypass. The haemodynamic response to increasing doses of infused isoprenaline was monitored. Immediately after cardiopulmonary bypass the response to isoprenaline was significantly blunted in the patients who had been given propranolol before operation. Their dose-response curve lay to the right of that for patients not given propranolol, and this indicates competitive inhibition. Propranolol concentrations in the blood and myocardium correlated significantly with the heart rate response to isoprenaline. Twenty four hours after operation the isoprenaline response was similar in both groups and concentrations of propranolol in the blood were minimal or undetectable.

β Blockers given up to the time of operation significantly altered the postoperative response to catecholamines.

Propranolol is a β adrenergic blocking drug that is used to prevent hypoxaemic episodes in children with Fallot's tetralogy who are awaiting surgical correction.¹⁻³ To prevent anoxic spells at the induction of anaesthesia, we withdraw propranolol only the night before the operation. We use isoprenaline to sustain cardiac output after open heart surgery for tetralogy of Fallot, because these patients rely mainly on heart rate to increase their cardiac index.⁴ Persistence of β adrenergic blockade after cardiopulmonary bypass could be clinically important in these patients.

The present study was designed to investigate whether propranolol given up to the night before

the operation alters the response to adrenergic drugs given immediately after operation.

Patients and methods

Between June 1985 and April 1986, 18 patients aged 10 months to 12 years were studied immediately after surgical correction of tetralogy of Fallot. Nine patients (group 1) had been treated with daily doses of propranolol for at least two weeks before operation (1.5 to 4 mg/kg/per day). Propranolol was given every six hours until the night before induction of anaesthesia. The nine other patients (group 2) were not given β blocking drugs before operation.

Two patients in group 2 had pulmonary stenosis with atrial septal defect, all the others had typical tetralogy of Fallot. Table 1 shows the patients' characteristics and haemodynamic data at cardiac

Requests for reprints to Dr C Jaccard, Clinique de Pédiatrie, 30 Boulevard de la Cluse, 1205 Geneva, Switzerland.

Table 1 Patients' characteristics and haemodynamic data at cardiac catheterisation (mean (SD))

	Group 1 (n = 9)	Group 2 (n = 9)	p
Age (yr)	3.5 (2.1)	7.5 (4.8)	<0.05
Weight (kg)	12.2 (4.2)	22.9 (12.2)	<0.05
Haematocrit (%)	55.4 (7.1)	49.4 (9.5)	NS
CPB (min)	122.6 (15.3)	112.7 (46.0)	NS
Aortic cross clamping (min)	75.4 (35.8)	81.1 (10.2)	NS
Aortic saturation (%)	59.5 (15.4)	82.7 (7.5)	<0.05
EDVI (l/m ²)*	71.4 (47.0)	70.7 (33.1)	NS
EF (%)*	60.3 (3.9)	56.3 (8.9)	NS

*Volume and ejection fraction available in six patients from group 1 and seven from group 2.

CPB cardiopulmonary bypass, EDVI, end diastolic volume index; EF, ejection fraction.

catheterisation. The control group was significantly older and had a higher mean arterial oxygen saturation. Two patients in group 2 had palliative shunts (left aorto-pulmonary artery anastomosis with a Goretex tube). Both shunts were functioning at the time of operation. Preoperative ventricular function was similar in both groups as assessed by ventricular end diastolic volume index and ejection fraction calculated from biplane cineangiography. The operation was performed under cardiopulmonary bypass, deep hypothermia (18°C), and moderate haemodilution (haematocrit 28%). Cardiopulmonary bypass and aortic cross clamping time were similar for the two groups (table 1). Cold chemical cardioplegia was used to obtain asystole before right ventriculotomy, resection of the muscular hypertrophy, enlargement of the outflow tract, and closure of the ventricular septal defect. Five patients required a transannular enlargement of the pulmonary artery.

The study started 3–4 hours after closure of the chest when the patients were in a stable haemodynamic condition in the intensive care unit. No volume expansion was needed during the study. Heart rate, central venous pressure, systolic, mean and diastolic systemic arterial pressures, and left atrial pressure were measured with a 78353-B Hewlett-Packard pressure module. Left atrial pressure was monitored through a surgically placed line.

We assessed the degree of β blockade after cardiopulmonary bypass by measuring the dose-response curves for isoprenaline three and 24 hours after operation and correlating them with blood and tissue concentrations of propranolol. All medications were stopped 20 minutes before baseline measurements. Isoprenaline was then administered continuously at increasing doses: 0.025, 0.05, and 0.1 $\mu\text{g}/\text{kg}$ per minute. Each dose was maintained for 15 minutes before a new set of measurements was

taken. Twenty minutes after the drug had been stopped a second set of baseline values was measured. The same protocol was repeated 24 hours later.

Blood propranolol concentrations were measured at four different times: (a) immediately before the last dose given before operation (steady state level); (b) after induction of anaesthesia, immediately before cardiopulmonary bypass—that is about eight hours after the last dose; (c) three hours after cardiopulmonary bypass—that is at the beginning of the first study; (d) 24 hours after cardiopulmonary bypass, at the start of the second study period. Propranolol concentrations were measured in myocardium excised from the infundibulum during the operation. Samples were immediately frozen at -80°C in liquid nitrogen and homogenised.

Concentrations of propranolol in blood and tissue were measured by high pressure liquid chromatography with fluorometric detection.⁵ All results are expressed in ng/ml of total blood and ng/g of myocardium (wet tissue weight).

The protocol of the study was approved by the ethics committee of our department.

STATISTICAL ANALYSIS

Unpaired and paired t tests were used to compare data between the two groups. Two way analysis of variance was performed on the haemodynamic results. We used semi-logarithmic regression to compare blood and tissue concentrations with haemodynamic data and Spearman's ρ coefficient to compare tissue and blood concentrations.

Results

Baseline haemodynamic data before isoprenaline were not significantly different in the two groups on either the first or second days (tables 2 and 3).

ISOPRENALINE DOSE-RESPONSE CURVE THREE HOURS AFTER CARDIOPULMONARY BYPASS

The heart rate increased in both groups on each of the three doses of isoprenaline, however, the increases were significantly less in the group treated with propranolol (group 1): group 1: +5%, +14%, +33%; group 2: +20%, +41%, +51%. The two groups had parallel dose-response curves with the curve for group 1 being shifted to the right (fig 1).

Central venous pressure and left atrial pressure fell significantly in both groups during isoprenaline infusion but they returned to baseline values as soon as the drug was stopped. Diastolic arterial pressure was significantly reduced on the third dose of isoprenaline in group 2, whereas it increased significantly on the three doses of isoprenaline in group

Table 2 Haemodynamic response (mean (SD)) to isoprenaline (ISP $\mu\text{g}/\text{kg}$ per min) immediately after cardiopulmonary bypass in patients treated with propranolol before operation (group 1) and in those who were not (group 2)

	Baseline 1	ISP 0.025	ISP 0.05	ISP 0.1	Baseline 2
Group 1:					
HR (beats/min)	118.5 (19.1)	125.3 (23.3)**	135.2 (27.6)**	157.1 (28.3)**	118.5 (18.4)
CVP (mm Hg)	12.1 (3.2)	10.8 (2.9)	10.3 (2.3)*	10.4 (2.6)*	11.8 (2.6)
LAP (mm Hg)	14.3 (3.5)	13.1 (3.8)	12.4 (4.0)*	10.6 (3.3)**	13.9 (3.9)
SAP (mm Hg)	83.1 (11.3)	90.8 (9.7)**	96.2 (11.1)**	98.8 (10.8)**	86.1 (9.6)
DAP (mm Hg)	55.7 (9.2)	60.8 (7.2)**	64.1 (10.3)**	63.9 (10.3)**	59.8 (9.3)
MAP (mm Hg)	67.2 (10.3)	72.4 (7.5)	76.9 (11.3)**	76.5 (11.1)**	70.1 (9.2)
Group 2:					
HR (beats/min)	118.3 (24.4)	142.0 (25.2)**	166.2 (16.8)**	179.8 (17.6)**	126.2 (21.7)
CVP (mm Hg)	11.9 (2.9)	10.9 (3.2)	10.1 (3.5)*	9.6 (4.0)*	11.7 (3.8)
LAP (mm Hg)	11.8 (2.7)	10.8 (2.5)	9.3 (3.0)**	8.8 (3.1)**	12.3 (2.8)
SAP (mm Hg)	77.6 (25.8)	83.8 (23.8)	86.4 (28.6)*	80.6 (24.4)	80.6 (21.5)
DAP (mm Hg)	53.6 (17.5)	54.0 (13.3)	52.3 (13.9)	46.9 (9.6)*	55.2 (13.3)
MAP (mm Hg)	62.0 (19.7)	63.9 (15.8)	62.6 (17.5)	59.3 (12.9)	64.3 (15.3)

HR, heart rate; CVP, central venous pressure; LAP, left atrial pressure; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure.

* $p \leq 0.05$ and ** $p \leq 0.01$ compared with baseline 1.

Table 3 Haemodynamic response (mean (SD)) to isoprenaline (ISP $\mu\text{g}/\text{kg}$ per min) 24 hours after cardiopulmonary bypass in patients treated with propranolol before operation (group 1) and in those who were not (group 2)

	Baseline 1	ISP 0.025	ISP 0.05	ISP 0.01	Baseline 2
Group 1:					
HR (beats/min)	120.3 (11.4)	135.8 (17.5)**	148.8 (22.2)**	168.2 (22.0)**	126.2 (11.6)
CVP (mm Hg)	12.3 (2.1)	11.5 (1.9)	9.8 (1.8)**	8.6 (1.8)**	11.0 (2.4)
LAP (mm Hg)	14.0 (3.6)	12.0 (4.4)*	10.0 (3.1)**	8.9 (3.0)**	11.2 (3.3)
SAP (mm Hg)	71.4 (10.1)	77.0 (14.3)	82.8 (15.7)**	83.3 (13.0)**	70.1 (12.6)
DAP (mm Hg)	50.4 (8.6)	51.8 (8.8)	53.6 (9.9)	50.3 (9.9)	48.9 (10.3)
MAP (mm Hg)	57.9 (9.2)	61.2 (9.4)	63.1 (10.6)	60.2 (9.5)	56.8 (10.1)
Group 2:					
HR (beats/min)	118.3 (16.6)	134.4 (15.9)**	149.1 (20.5)**	167.9 (13.3)**	124.9 (16.7)
CVP (mm Hg)	13.3 (3.4)	12.2 (4.8)	11.4 (5.8)	11.7 (4.8)	12.2 (4.7)
LAP (mm Hg)	16.2 (4.8)	14.0 (5.4)	12.0 (5.7)*	12.3 (2.6)*	15.0 (3.7)
SAP (mm Hg)	75.8 (13.8)	83.7 (14.8)	83.9 (11.4)*	94.9 (18.1)**	81.2 (10.7)
DAP (mm Hg)	53.2 (10.9)	55.2 (7.9)	53.1 (7.5)	55.4 (11.1)	55.8 (8.5)
MAP (mm Hg)	62.0 (11.6)	65.3 (9.0)	64.0 (8.8)	67.9 (12.9)*	64.3 (9.8)

* $p \leq 0.05$ and ** $p \leq 0.01$ compared with baseline 1.

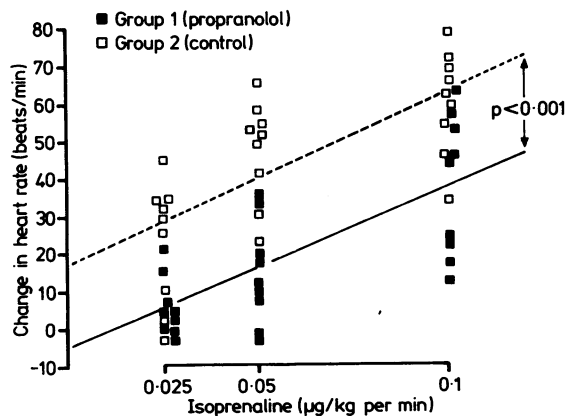


Fig 1 Heart rate response to isoprenaline three hours after cardiopulmonary bypass in patients who had been treated with propranolol and those who had not (group 1: $y = 428(x) - 4$; group 2: $y = 470(x) + 17$).

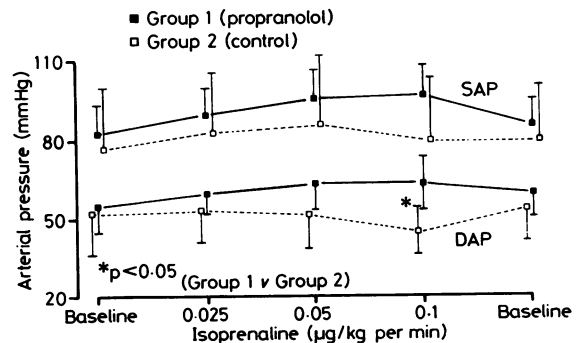


Fig 2 Mean (SD) systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) responses to isoprenaline three hours after cardiopulmonary bypass in patients who had been treated with propranolol (group 1) and those who had not (group 2).

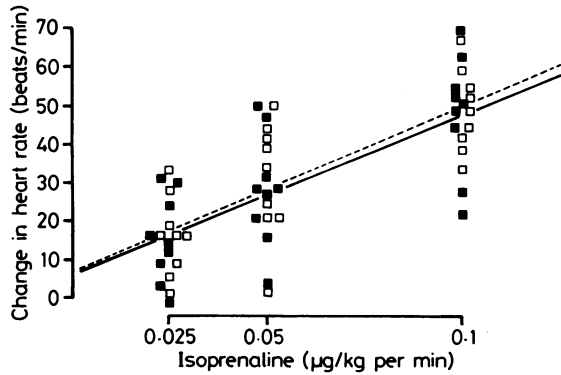


Fig 3 Heart rate response to isoprenaline 24 hours after cardiopulmonary bypass in patients who had been treated with propranolol and those who had not (group 1: $y = 426(x) + 6$; group 2: $y = 431(x) + 7$).

1 (patients given propranolol before operation) (fig 2).

DOSE-RESPONSE CURVE FOR ISOPRENALINE 24 HOURS AFTER CARDIOPULMONARY BYPASS

There were similar increases in heart rate in both groups (group 1: +12.5%, +23%, +40%; group 2: +13.5%, +26%, +41%). Figure 3 shows that the

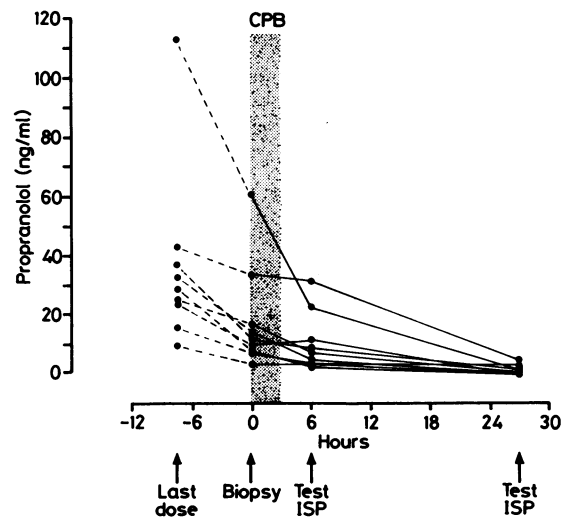


Fig 4 Change in serum concentrations of propranolol with time. The first blood sample was taken just before the last dose of propranolol was given. The second sample was taken before cardiopulmonary bypass, the third sample at the beginning of the first isoprenaline (ISP) study (three hours after cardiopulmonary bypass (CPB)), and the last sample at the time of the second isoprenaline study (24 hours after cardiopulmonary bypass). A myocardial biopsy specimen was excised from the infundibulum during cardiopulmonary bypass.

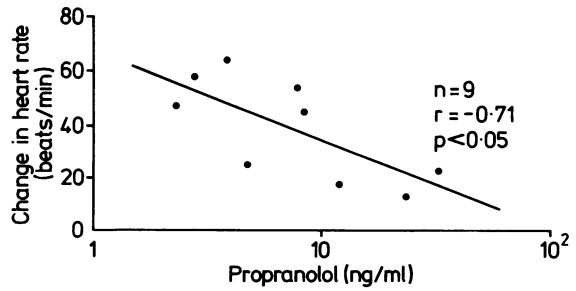


Fig 5 Inverse relation between heart rate response to 0.1 µg/kg per min of isoprenaline and serum concentration of propranolol. ($y = -34(\log x) + 68$).

dose-response curves for both groups are now superimposed.

Central venous pressure fell significantly in group 1 only, whereas left atrial pressure was significantly reduced in both groups. There was no significant difference in systolic and diastolic arterial pressures between the two groups.

PROPRANOLOL CONCENTRATIONS

The mean steady state propranolol concentration in blood was 37 ng/ml (range 10–110 ng/ml). Immediately before cardiopulmonary bypass—that is eight hours after the last dose of propranolol—the mean blood concentration had decreased to 18.7 ng/ml (range 3.4–61.5 ng/ml).

At the time of the first isoprenaline study, propranolol was still detectable in the blood (mean 10.8 ng/ml, range 2.3–32.2 ng/ml). Twenty four hours later, however, propranolol was undetectable in three patients and ranged from 1 to 5.6 ng/ml in the others (fig 4).

There was no correlation between steady state blood concentrations of propranolol and the dose administered. There was a significant inverse correlation between blood concentrations of propranolol and the chronotropic response to the

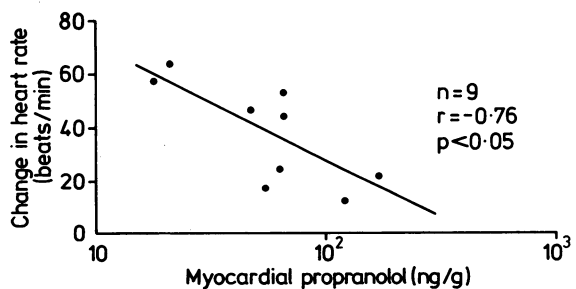


Fig 6 Inverse relation between heart rate (HR) response to 0.1 µg/kg per min of isoprenaline and myocardial concentration of propranolol. ($y = -45(\log x) + 118$).

highest dose (0.1 $\mu\text{g}/\text{kg}$ per minute) of isoprenaline ($r = -0.71$, $p < 0.05$) (fig 5).

Myocardial propranolol concentrations ranged from 17.8 to 169 ng/g of tissue and were 3–5 times higher than blood concentrations. There was a significant inverse correlation between myocardial concentrations of propranolol and the chronotropic response to 0.1 $\mu\text{g}/\text{kg}$ per minute of isoprenaline ($r = -0.76$, $p < 0.05$) (fig 6).

There was a highly significant correlation between blood concentrations of propranolol measured immediately before cardiopulmonary bypass and myocardial concentrations ($\rho = 0.93$, $p < 0.001$). One patient from group 1 had a hypoxaemic episode when anaesthesia was induced; this was controlled by an injection of intravenous morphine.

Seventeen of the 18 patients made a good recovery. In one (group 2) mumps developed three days after operation and he became comatose. This encephalopathy was not caused by hypotension or an electrolyte imbalance. He died 14 days after operation. Necropsy was not performed.

Discussion

The question of when to withdraw β blocking treatment before operation was prompted by several postoperative deaths in adults that were supposedly related to β blockade.⁶ These led to the recommendation that propranolol should be stopped two weeks before operation. But subsequent studies suggested that propranolol treatment could be continued until shortly before operation. Faulkner *et al* showed that propranolol was undetectable in plasma samples and atrial tissue 36–48 hours after withdrawal of the drug,⁷ whereas Romagnoli and Keats showed that although propranolol was still detectable in plasma samples and atrial tissue 18 hours after the drug was stopped no β blocking effects could be demonstrated at that time.⁸

We found that when propranolol was given up to the night before operation it persisted in the blood and in myocardium after cardiopulmonary bypass and modified the response to isoprenaline immediately after operation. The degree of β blockade can be assessed by measuring the acceleration of heart rate induced by isoprenaline.^{9–11} In the present study, the different chronotropic response to isoprenaline immediately after cardiopulmonary bypass indicated the persistence of significant β blockade in group 1. The rightward shift of the dose-response curve indicates competitive inhibition of the chronotropic effect of isoprenaline.

The response of diastolic arterial pressure to isoprenaline in the two groups was different and this suggests that propranolol, as well as inhibiting the

heart rate response to isoprenaline, also inhibits its systemic vasodilator effect.

In adults the response of heart rate to exercise after oral propranolol is most strongly blocked at blood concentrations of 40 ng/ml .¹² The steady state concentrations of propranolol in our patients are consistent with maximum β blockade. Somewhat surprisingly, there was no relation between the oral dose of propranolol and steady state blood concentrations in our patients. The concentrations immediately before cardiopulmonary bypass were lower, probably because of the longer interval after the last dose. None the less, a mild haemodilution related to induction of anaesthesia could have had a role. We found a linear correlation between the logarithm of plasma propranolol and the degree of β blockade (assessed by heart rate response to isoprenaline infusion), which confirmed the results of a previous study.¹³

Several workers have studied blood concentrations of intravenously administered propranolol before and after cardiac surgery.^{14,15} Plachetka *et al* found that propranolol concentrations were higher after cardiopulmonary bypass than before. They suggested that this was the result of a redistribution of the drug from the lungs to the plasma and of a reduced hepatic extraction.¹⁶ McAlister *et al* explain this phenomenon by the reduction of the volume of distribution caused by hypothermia.¹⁷

Twenty four hours after cardiopulmonary bypass, a β blocking effect was no longer seen in the propranolol treated group—the responses of the two groups to isoprenaline were similar. Propranolol concentrations measured at that time were minimal or undetectable.

We conclude from our study that propranolol treatment given up to the night before the operation influences the response to isoprenaline immediately after operation. Significant concentrations of propranolol persist in the blood and myocardium for several hours after cardiopulmonary bypass and result in a blunted response to catecholamines. Despite these findings, we advocate the administration of propranolol up to the time of the operation to avoid hypoxaemic episodes during induction of anaesthesia. The residual β blockade can be overcome by the administration of higher than usual doses of catecholamines.

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