Human pharmacokinetic and pharmacodynamic studies on Ro31-1118, a new β -adrenoceptor antagonist

P. C. O'CONNOR¹, J. M. O. ARNOLD¹, A. N. BROWN², R. J. FRANCIS², M. B. FINCH¹, D. B. GALLOWAY², D. W. G. HARRON¹, D. G. McDEVITT¹ & R. G. SHANKS¹

¹Department of Therapeutics and Pharmacology, The Queen's University, Belfast and ²Departments of Drug Metabolism and Clinical Pharmacology, Roche Products Ltd, Welwyn Garden City, Hertfordshire, UK

1 The pharmacokinetic and pharmacodynamic effects of Ro31-1118 were examined in groups of healthy volunteers.

2 In three subjects given 10 mg of [¹⁴C]-Ro31-1118 orally, peak levels of radioactivity (84 ± 5 ng/ml) were 16 times those of the parent drug (~ 5 ng/ml).

3 Very little parent drug was recovered in the urine, although recovery of total radioactivity was nearly 80% in the urine by day 5.

4 In five subjects studied after both oral and intravenous administration of 20 mg Ro31-1118 the average bioavailability was 57% (range 41–73%).

5 Following intravenous infusion the apparent volume of distribution for the five subjects averaged 590 l (range 510–700 l). The elimination half-life averaged 18 h (range 17–26 h).

6 In eight subjects who received 40, 80, 160 and 320 mg of Ro31-1118 orally there was a linear relationship between dose and plasma concentration ($r = 0.999$) and between dose and AUC ($r = 0.996$).

7 Ro31-1118 had no effect on resting heart rate whereas atenolol reduced resting heart rate up to 6 h after all doses.

8 The maximum reduction of an exercise tachycardia after Ro31-1118 (320 mg) was $23.13 \pm 0.7\%$ and compared with atenolol (100 mg) was $28.2 \pm 1.25\%$. At 24 h the percentage reduction after Ro31-1118 was $21.5 \pm 1.7\%$, while after atenolol the percentage inhibition had decreased to $11.1 \pm 1.6\%$.

9 In three subjects Ro31-1118 (160 mg) orally had no effect on resting heart rate, forearm blood flow and systolic blood pressure, while atenolol (50 mg) reduced all three parameters. Atenolol had little effect on resting finger tremor, but after Ro31-1118 there was an approximate three fold increase.

10 In these three subjects the isoprenaline heart rate dose-response curve was shifted to the right in a parallel manner by both drugs. The increase in forearm blood flow induced by isoprenaline was decreased more by atenolol than Ro31-1118.

11 Most subjects complained of tremor and visual disturbances after 160 and 320 mg of Ro31-1118.

12 We conclude that Ro31-1118 is a β -adrenoceptor antagonist with partial agonist activity and a long duration of action. Ro31-1118 is at least as cardioselective as atenolol.

Keywords Ro31-1118 β -adrenoceptor antagonist pharmacokinetics pharmacodynamics

Correspondence: Professor R. G. Shanks, Department of Therapeutics and Pharmacology, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL, UK

Introduction

Ro31-1118 1- (4- (2- (4-fluorophenethyloxy)-ethoxy)phenoxy) -3-isopropylamino-2-propanol hydrochloride, whose structure is shown in Figure 1, is a new β -adrenoceptor antagonist which, in animals, has been shown to be cardioselective with partial agonist activity (PAA) and a long duration of action (Blaber *et al.*, 1983). The present studies were undertaken to determine the pharmacokinetic and pharmacodynamic properties of this novel compound in man.

Figure 1 Chemical structure of Ro31-1118, 1-(4-(2-(4-fluorophenethyloxy)ethyl)phenoxy)-3-isopropylamino-2-propanol hydrochloride. The asterisk indicates the position of the label in the ^{14}C -compound.

Methods

Observations were made in healthy male subjects who gave informed consent after the procedures had been carefully explained. The studies were approved by the Ethical Committee of the Queen's University, and, for the radio-labelled study, by the Administration of Radio-active Substances Advisory Committee.

Study 1

A 10 mg (20 μCi) solution of ^{14}C -labelled compound was administered orally to three healthy male volunteers. Heparinised blood samples were collected for radioactivity measurements and drug analysis immediately before and at 0.75, 1, 1.5, 2, 3, 4, 6, 8, 24, 27 and 48 h after drug administration. All urine and faeces were collected in pre-weighed containers for 5 days after oral dosing.

Study 2

Single 20 mg oral and intravenous doses of Ro31-1118 were given to five male subjects, in

randomised order, with at least 1 week between treatments. Their mean ages were 20.8 ± 1.6 years and weights 67.2 ± 6.2 kg. The intravenous dose was given by infusion over 10 min into a forearm vein, with blood samples being taken from the opposite arm immediately pre-infusion and at 2.5, 5, 7.5, 10, 12.5, 15, 20, 30 min from the commencement of the infusion. After both oral and intravenous administration samples were taken at 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 32 and 48 h.

Study 3

This was a randomised, double-blind comparison of Ro31-1118, atenolol and placebo, in eight healthy male volunteers, with a mean age of 25.5 ± 1.17 years and weight 66.8 ± 8.1 kg. The doses of Ro31-1118 were 40, 80, 160 and 320 mg, and of atenolol 25, 50 and 100 mg. Drugs were given at not less than weekly intervals.

Cardiovascular parameters (heart rate and blood pressure) were recorded before drug administration and at 1, 2, 4, 6, 8, 24, 32 and 48 h after dosing. At each time interval and at 12 h, 10 ml of venous blood was taken for subsequent plasma drug analysis. Cardiovascular parameters were recorded after the subjects had been lying supine for 15 min and after 3 min standing and heart rate within 5 s of completing a 3 min period of exercise which consisted of stepping on and off a box 46 cm high at a rate of 32 steps per min. Blood pressure was recorded during the last 30 s of exercise. Cardiovascular parameters were recorded using a Critikon exercise monitor (model 1165).

Study 4

In this study an assessment of the cardioselectivity of Ro31-1118 was carried out in three male volunteers (ages 19, 20 and 21 years; weights 69, 70 and 72 kg) who received randomly in a single blind study an oral dose of Ro31-1118 160 mg, atenolol 50 mg or placebo at weekly intervals. The laboratory temperature was controlled to $23\text{--}24^\circ\text{C}$. The subjects rested for 30 min 2.25 h after drug or placebo administration. An intravenous saline infusion of 8 min duration was followed by sequential 8 min infusions of isoprenaline (0.5 to 16 $\mu\text{g}/\text{min}$) with sodium metabisulphite as a preservative. During each infusion heart rate was measured from 3 to 3.5 min, blood pressure from 3.5 to 5 min, finger tremor and forearm blood flow from 5 to 8 min. The subjects rested for 30 min following the last isoprenaline

infusion, before performing the standard 3 min exercise step test. Heart rate was measured within 5 s of completing the exercise.

Heart rate was monitored continuously throughout the experiment. Blood pressure was recorded by auscultation using a Hawksley random zero sphygmomanometer, and measured as the mean of two observations, using the Korotkoff fourth sound for diastolic pressure. A piezo-resistive accelerometer (Devices Trem 1) was lightly taped to the dorsum of the middle finger of the left hand and finger tremor measured as described previously (Arnold & McDevitt, 1983). Percentage change in tremor was calculated from the tremor activity recorded during the saline infusion. Forearm blood flow was recorded by venous occlusion plethysmography employing a mercury in rubber strain gauge (Greenfield, 1960). Forearm blood flow was calculated as the mean of 10 values obtained at each infusion rate.

For all studies samples of plasma were analysed for parent drug by a standard procedure utilising capillary gas chromatography on a 25 m CPSIL 5 quartz column (Chrompak) programmed from 180°C to 285°C at 6°/min. Detection was by electron capture. An internal standard (Ro31-1117) of similar structure was added to all samples prior to extraction, and standards of known amount of Ro31-1118 were processed along with the unknowns. Extracts were treated with heptafluorobutyric anhydride followed by *t*-butyldimethylchlorosilane to form the *o*-*t*-butyldimethylsilyl, *N*-heptafluorobutyryl derivatives of Ro31-1118 and internal standard. Quantitation was from peak height ratio, with reference to the calibration curve established for the standards by linear regression. Extraction recovery for the method was 70–80% and sensitivity limit 1 ng/ml. Response was linear to 2 µg/ml, with a coefficient of variation of $\pm 25\%$ for levels < 5 ng/ml and < 5% for levels ≥ 10 ng/ml.

Individual plasma level-time course data were fitted to the appropriate (Gibaldi & Perrier, 1975) models by an extended non-linear least squares regression programme (ELSMOS) (Francis, 1984). Relevant pharmacokinetic parameters were calculated from the model coefficients. For intravenous data, results were fitted to a two- or three-compartment model. For oral data results were fitted to a one-compartment first-order absorption model. Peak time and concentration values were obtained directly from the data.

Results of the pharmacodynamic studies were examined by analysis of variance. Duncan's multiple range test was employed to

determine significant differences ($P < 0.05$) between means.

Results

Pharmacokinetics

Study 1 Three subjects were given orally 10 mg (20 µCi) of [^{14}C]-Ro31-1118 in solution. The peak level of radioactivity was 84 ± 5 ng/ml at 3.3 h, and of parent drug ~ 5 ng/ml at 4.7 h. Average elimination half-lives for radioactivity and parent drug were approximately 25 and 26 h, respectively, although considerable individual variation was evident for the parent drug, the plasma levels of which were close to the assay limit. Very little of the parent drug could be detected in the urine, although the recovery of total radioactivity was nearly 80% by day 5.

Study 2 Figure 2 shows the mean plasma concentrations from 0 to 48 h of Ro31-1118 after both intravenous and oral administration of 20 mg Ro31-1118. The plasma concentration increased rapidly during the period of infusion. After the infusion there was an initial rapid decline in levels in two out of five subjects, followed by a slower distribution phase and a final slow elimination phase. A three-compartment model was fitted and the derived coefficients indicated half-lives of approximately 5 min, 25 min and 17 h for the three phases. Plasma or central compartment volume was calculated at 12 l. In the remaining three subjects the initial rapid decline was not clearly differentiated from the slow distribution phase and a two-compartment model was fitted. The apparent volume of distribution for the five subjects averaged 590 l (range 510–700 l), or approximately 9 l/kg. Systemic clearance was 23 l/h (range 17–26 l/h) and elimination half-life 18 h (range 15–22 l/h), with the terminal phase being dominant by 2–3 h post dose in all cases.

Plasma levels after oral administration of Ro31-1118 were at all times lower than for the intravenous dose (Figure 2), although the rate of decline in levels was similar. In three out of five subjects there was little indication of drug absorption up to 1 h post-dosing, whereas, in the remaining two subjects absorption appeared to commence immediately. Average time-lag from the fitted data was 0.7 h (range 0–1.3 h). All the data sets gave a good fit to a one-compartment model with first-order absorption. Elimination half-life averaged 20 h (range 14–23 h). Peak time was 4 h (range 2–8 h) and peak

Figure 2 Mean ($n = 5$) plasma concentrations of Ro31-1118 after 20 mg given intravenously ($\square$) and orally ($\blacksquare$). The insert shows the early part of the intravenous time course in an expanded form.

concentration 16 ng/ml (range 14–19 ng/ml). Average oral, or absolute bioavailability calculated from the oral/intravenous area ratio was 57% (range 41–73%).

Study 3 In the eight subjects who received an eight-fold dose range (40, 80, 160 and 320 mg) of Ro31-1118 there was a linear relationship ($r = 0.999$) (Table 1) between dose and plasma concentration. There was also a linear relationship between dose and AUC ($r = 0.996$), whereas half-life (15–16 h) was independent of dose.

Pharmacodynamics

Study 3 The effects on heart rate and blood pressure of placebo, Ro31-1118, 40, 80, 160 and 320 mg, atenolol 25, 50 and 100 mg were compared in eight subjects. Ro31-1118 had no

effect on resting heart rate, while atenolol reduced heart rate up to 6 h after oral administration. There was no consistent pattern to the effects of either Ro31-1118 or atenolol on resting systolic or diastolic blood pressure. Both Ro31-1118 and atenolol significantly decreased standing heart rate (Table 2). Atenolol 25, 50 and 100 mg decreased standing heart rate up to 6 h post-dosing to a significantly greater degree than any dose of Ro31-1118. Neither atenolol nor Ro31-1118 had any consistent effect on standing systolic or diastolic blood pressure.

Exercise heart rate was reduced by Ro31-1118 and atenolol at all doses examined up to 24 h after oral dosing (Table 3), except for atenolol 25 mg, the effect of which was only seen to 8 h. The effects of Ro31-1118 80, 160 and 320 mg were still present at 48 h. The maximum percentage reduction of exercise heart rate after atenolol (100 mg) was $28.2 \pm$

Table 1 Pharmacokinetic values (mean $\pm$ s.e. mean) after subjects had taken orally 40, 80, 160 and 320 mg of Ro31-1118

Dose (mg)	n	Peak plasma level (ng/ml)	AUC (mg l ⁻¹ h)	Half-life (h)
40	8	37.2 $\pm$ 3.1	0.93 $\pm$ 0.07	15.2 $\pm$ 1.2
80	8	73.4 $\pm$ 5.4	1.90 $\pm$ 0.26	15.5 $\pm$ 1.9
160	8	133.9 $\pm$ 11.7	3.20 $\pm$ 0.26	15.9 $\pm$ 1.3
320	7	257.0 $\pm$ 25.0	6.34 $\pm$ 0.49	15.7 $\pm$ 2.2

Table 2 Mean ($\pm$ s.e. mean) ($n = 8$) standing heart rate after placebo, atenolol (25, 50 and 100 mg) and Ro31-1118 (40, 80, 160 and 320 mg ($n = 7$))

Time from receiving treatment (h)	Placebo	Atenolol 25 mg	Atenolol 50 mg	Atenolol 100 mg	Ro31-1118 40 mg	Ro31-1118 80 mg	Ro31-1118 160 mg	Ro31-1118 320 mg
0	97.0 $\pm$ 3.9	93.3 $\pm$ 4.4	95.5 $\pm$ 6.1	96.0 $\pm$ 5.3	94.3 $\pm$ 4.5	98.3 $\pm$ 2.4	94.9 $\pm$ 4.8	104.1 $\pm$ 6.6
2	101.3 $\pm$ 4.4	75.3 $\pm$ 3.0†	77.1 $\pm$ 3.8†	72.4 $\pm$ 3.0†	87.0 $\pm$ 2.9†	89.3 $\pm$ 3.1†	89.0 $\pm$ 3.3†	86.1 $\pm$ 4.0†
4	106.6 $\pm$ 3.0	80.1 $\pm$ 3.2†	75.5 $\pm$ 4.2†	73.6 $\pm$ 3.5†	91.3 $\pm$ 4.2†	91.9 $\pm$ 3.2†	89.5 $\pm$ 4.0†	81.0 $\pm$ 3.0†
6	107.0 $\pm$ 3.8	80.1 $\pm$ 2.9†	82.8 $\pm$ 5.3†	77.6 $\pm$ 4.4†	93.5 $\pm$ 6.0†	92.0 $\pm$ 4.1†	93.8 $\pm$ 2.5†	90.3 $\pm$ 6.0†
8	100.9 $\pm$ 4.3	79.9 $\pm$ 4.9†	83.1 $\pm$ 5.6†	76.3 $\pm$ 3.6†	90.6 $\pm$ 4.1	88.8 $\pm$ 3.1†	86.6 $\pm$ 3.0†	86.9 $\pm$ 2.5†
24	98.8 $\pm$ 2.6	88.4 $\pm$ 4.1†	89.0 $\pm$ 5.6†	80.9 $\pm$ 3.3†	88.6 $\pm$ 2.7	88.9 $\pm$ 3.7†	86.3 $\pm$ 3.6†	82.1 $\pm$ 3.7†
32	100.4 $\pm$ 3.5	91.5 $\pm$ 4.8	95.3 $\pm$ 5.0	87.3 $\pm$ 6.2†	85.5 $\pm$ 3.5†	92.9 $\pm$ 2.9	85.9 $\pm$ 3.4†	79.5 $\pm$ 4.0
48	98.4 $\pm$ 3.5	91.9 $\pm$ 3.4	94.3 $\pm$ 3.7	90.0 $\pm$ 5.5	91.5 $\pm$ 4.7	88.6 $\pm$ 2.6	86.8 $\pm$ 2.6	86.3 $\pm$ 4.1

† $P < 0.05$ compared to placebo**Table 3** Mean ($\pm$ s.e. mean) ($n = 8$) exercise heart rate after placebo, atenolol (25, 50 and 100 mg) Ro31-1118 (40, 80, 160 and 320 mg ($n = 7$))

Time from receiving treatment (h)	Placebo	Atenolol 25 mg	Atenolol 50 mg	Atenolol 100 mg	Ro31-1118 40 mg	Ro31-1118 80 mg	Ro31-1118 160 mg	Ro31-1118 320 mg
0	164.5 $\pm$ 2.6	166.0 $\pm$ 4.7	161.6 $\pm$ 4.1	160.9 $\pm$ 4.4	167.6 $\pm$ 4.9	161.5 $\pm$ 4.0	168.4 $\pm$ 3.9	164.7 $\pm$ 4.2
2	162.6 $\pm$ 5.7	137.3 $\pm$ 4.0†	124.1 $\pm$ 3.5†	114.1 $\pm$ 2.3†	140.9 $\pm$ 4.3†	137.5 $\pm$ 2.9†	131.3 $\pm$ 2.4†	126.6 $\pm$ 2.5†
4	167.3 $\pm$ 3.6	137.1 $\pm$ 3.3†	127.1 $\pm$ 3.6†	116.4 $\pm$ 2.5†	141.4 $\pm$ 3.9†	136.5 $\pm$ 2.1†	133.1 $\pm$ 2.6†	126.4 $\pm$ 2.3†
6	167.3 $\pm$ 3.6	140.8 $\pm$ 3.2†	131.1 $\pm$ 2.7†	125.1 $\pm$ 3.6†	142.4 $\pm$ 4.6†	138.0 $\pm$ 3.0†	133.8 $\pm$ 1.8†	130.4 $\pm$ 3.7†
8	166.6 $\pm$ 4.4	146.0 $\pm$ 3.9†	136.9 $\pm$ 3.4†	127.1 $\pm$ 4.1†	142.0 $\pm$ 4.5†	139.1 $\pm$ 2.8†	132.5 $\pm$ 3.2†	127.0 $\pm$ 2.4†
24	164.4 $\pm$ 4.7	155.1 $\pm$ 4.7	148.1 $\pm$ 3.7†	142.8 $\pm$ 3.2†	146.5 $\pm$ 5.0†	142.1 $\pm$ 2.9†	140.6 $\pm$ 6.1†	129.0 $\pm$ 2.1†
32	162.3 $\pm$ 5.3	160.8 $\pm$ 4.4	154.6 $\pm$ 5.3	151.3 $\pm$ 5.3	149.5 $\pm$ 5.0	148.9 $\pm$ 3.4	141.3 $\pm$ 3.4†	132.7 $\pm$ 1.7†
48	164.1 $\pm$ 4.9	160.0 $\pm$ 3.9	157.6 $\pm$ 4.1	155.6 $\pm$ 4.1	154.9 $\pm$ 4.1	147.0 $\pm$ 4.7†	141.8 $\pm$ 2.9†	134.7 $\pm$ 2.2†

† $P < 0.05$ compared to placebo

1.25% (Figure 3) while the largest reduction after Ro31-1118 was $23.13 \pm 0.7\%$. At 24 h the percentage reduction ($21.5 \pm 1.7\%$) after Ro31-1118 (320 mg) had hardly changed, while the corresponding value for atenolol had decreased to $11.1 \pm 1.6\%$. Apart from a significant reduction in systolic blood pressure after 100 mg atenolol at 2 h no other dose of either drug had any effect on exercise blood pressure values.

Study 4 In the study of three volunteers who received placebo, Ro 31-1118 160 mg and atenolol 50 mg, Ro31-1118 and atenolol had different effects on resting parameters 3 h after drug administration (Table 4). Heart rate, forearm blood flow and systolic blood pressure were decreased by atenolol but not by Ro31-1118. Atenolol had little effect on resting finger tremor, but after Ro31-1118 there was an approximate three fold increase in tremor which precluded a comparison of the effects of atenolol and Ro31-1118 on isoprenaline mediated tremor. The isoprenaline heart rate dose-response curve (Figure 4) was shifted to

the right in a parallel manner by both drugs. Ro31-1118 shifted the dose-response curve further than atenolol. The increase in systolic blood pressure produced by isoprenaline was reduced to a greater extent by Ro31-1118 than atenolol. The increase in forearm blood flow induced by isoprenaline was decreased by atenolol more than Ro31-1118 (Figure 5).

Adverse effects

Apart from one subject with nausea after atenolol 100 mg there were no other adverse effects reported by the subjects who received this drug. Adverse reactions were frequent with 160 and 320 mg of Ro31-1118. Tremor was complained of by four out of eight subjects after 160 mg and by six out of seven subjects after 320 mg of Ro31-1118. Visual disturbances were reported by subjects after Ro31-1118, while no visual phenomena were described after atenolol or placebo. These consisted of tailing of lights, persistence of after-images, haloes and a flickering visual effect usually described as visual flicker. After 160 mg of

Figure 3 Mean ($\pm$ s.e. mean) ($n = 8$) percentage maximum inhibition ($\bullet$ — $\bullet$) of an exercise tachycardia after oral doses of Ro31-1118 (40, 80, 160 and 320 mg ($n = 7$)) and atenolol (25, 50 and 100 mg). Percentage inhibition of an exercise tachycardia ($\bullet$ --- $\bullet$) 24 h after oral doses of Ro31-1118 and atenolol.

Table 4 Mean ($\pm$ s.e. mean) ($n = 3$) changes in resting variables recorded during saline infusion, after oral administration of placebo, atenolol 50 mg and Ro31-1118 160 mg

	Placebo	Atenolol	Ro31-1118
Heart rate (beats/min)	66.7 $\pm$ 1.5	56.7 $\pm$ 2.8	72.0 $\pm$ 4.0
Systolic pressure (mm Hg)	115.2 $\pm$ 3.3	102.2 $\pm$ 1.9	122.2 $\pm$ 3.9
Diastolic pressure (mm Hg)	71.8 $\pm$ 2.7	68.3 $\pm$ 3.3	67.7 $\pm$ 3.2
Finger tremor	82.7 $\pm$ 11.4	60.3 $\pm$ 15.6	269.5 $\pm$ 100.2
Forearm blood flow (ml 100 ml ⁻¹ min ⁻¹)	5.21 $\pm$ 1.09	2.43 $\pm$ 0.06	5.90 $\pm$ 0.81

Figure 4 Mean ($\pm$ s.e. mean) ($n = 3$) heart rate increase during isoprenaline infusion of 8 min duration following placebo (●—●), atenolol 50 mg (●---●) and Ro31-1118 160 mg (▲—▲). **Figure 5** Mean ($\pm$ s.e. mean) ($n = 3$) increase in forearm blood flow during isoprenaline infusion of 8 min duration following placebo (●—●), atenolol 50 mg (●---●) and Ro31-1118 160 mg (▲—▲).

Ro31-1118 four out of eight subjects complained of visual disturbances while six out of seven subjects reported similar experiences after 320 mg of Ro31-1118. The visual side-effects never persisted for longer than 18 h after administration.

Discussion

The bioavailability of β -adrenoceptor antagonists varies widely from drug to drug due mainly to first-pass metabolism, which is greatest for alprenolol (von Bahr *et al.*, 1974) and propranolol (Routledge & Shand, 1979) which

despite complete absorption have an oral bioavailability of 10–30%. First pass metabolism also decreases the bioavailability of metoprolol, oxprenolol, pindolol and timolol but to a lesser extent (Shand, 1974, 1978; Tocco *et al.*, 1975; Vermeij *et al.*, 1978; Regårdh *et al.*, 1984). Only for practolol and sotalol is bioavailability 100% since these drugs are completely absorbed essentially unmetabolised (Bodem & Chidsey, 1973; Anttila *et al.*, 1976). Ro31-1118 has about 50% bioavailability and is therefore roughly in the middle of the known range for β -adrenoceptor antagonists. The finding of radio-labelled metabolites within a short time of oral dosing is in keeping with a significant first-pass metabolism of Ro31-1118.

The mode of elimination of β -adrenoceptor antagonists is related to their lipid solubility (Shand, 1978). Alprenolol and propranolol which are highly lipid soluble are eliminated by metabolism, whereas, atenolol, practolol and sotalol which are poorly lipid soluble are eliminated unchanged by the kidneys. The findings that Ro31-1118 is extensively metabolised is in keeping with its high lipid solubility (R. J. Francis, unpublished observations). The pharmacokinetics of Ro31-1118 are linear, and intersubject variation is small. The results also demonstrate that the first-pass effect of Ro31-1118 cannot be saturated even at high dose levels.

The increase in heart rate produced by moderate to severe exercise results largely from an increase in sympathetic drive to the heart (Carruthers *et al.*, 1976). Reduction in an exercise tachycardia has been shown to be a sensitive and reproducible method for assessing the effects of β -adrenoceptor antagonists in man (McDevitt, 1979). The studies reported here have established that Ro31-1118 is an effective β -adrenoceptor antagonist in man, with a long duration of effect. The long duration of action of Ro31-1118 should ensure that, with once daily dosing a high degree of blockade of cardiac β -adrenoceptors is maintained throughout the 24 h period. When the inhibition of maximal exercise tachycardia produced by Ro31-1118 is related to the concentration of the drug in the plasma it appears that an effect becomes evident at 15 ng/ml and was maximal at 100 ng/ml. Higher concentrations than this do not produce significantly greater blockade. This flattening of the exercise heart rate dose response curve with Ro31-1118 occurs with β -adrenoceptor blocking drugs with PAA (Carruthers *et al.*, 1974; Brick *et al.*, 1968).

β -adrenoceptor antagonists with PAA reduce resting heart rate less than drugs devoid of PAA (Finch *et al.*, 1983; Svendsen *et al.*, 1981; Gugler *et al.*, 1980). The lack of effect of Ro31-1118 on resting supine heart rate, which was

reduced by atenolol, is suggestive of PAA, which animal studies have shown is a feature of Ro31-1118 pharmacology (Blaber *et al.*, 1983). Atenolol had a greater inhibitory effect on standing heart rate than did Ro31-1118 which again is indicative of Ro31-1118 possessing PAA. The flatter exercise heart rate dose response curve with Ro31-1118 also indicates the presence of PAA. The lack of effect of Ro31-1118 on resting forearm blood flow compared to atenolol which produced a marked decrease could be due to PAA. However, atenolol reduced resting heart rate (and presumably cardiac output) by 15% and mean arterial pressure. These effects of atenolol may elicit reflex reductions in forearm blood flow which would be absent with Ro31-1118 as it had no effect on heart rate or blood pressure. Thus the difference in the effects of the two drugs on forearm blood flow might not necessarily be due to their effects on β -adrenoceptors in the vasculature of the forearm. The differences in the cardiovascular profile of the two drugs may result from the PAA of Ro31-1118. The large increases in resting finger tremor produced by Ro31-1118 could be caused by PAA effects on the peripheral β_2 -adrenoceptors. Pindolol, a β -adrenoceptor antagonist with PAA can increase resting tremor (Hod *et al.*, 1980). In normal subjects, Ro31-1118 attenuated the heart rate and systolic blood pressure responses to isoprenaline to a greater extent than atenolol. However, the effects of Ro31-1118 on isoprenaline induced changes in forearm blood flow were less than with atenolol. These results indicate that Ro31-1118 is at least as cardio-selective as atenolol.

In the present study the visual adverse effects of Ro31-1118 were unexpected. Similar visual effects were described following infusion of pronethalol (Dornhorst & Robinson, 1962), but have not been described after oral administration of β -adrenoceptor antagonists. The mechanism of production of the visual adverse effects due to Ro31-1118 is unknown.

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