β-adrenoceptor-blocking agent pindolol (Visken, LB 46) is excreted up to 80% in the urine, of which about 40% is unchanged. As it is used in the treatment of hypertension, we were interested in testing the 'intact nephron hypothesis' in the case of unchanged pindolol, in order to find the appropriate individual dose schedule for patients with renal impairment.

Twenty-five patients with different degrees of renal impairment, endogenous creatinine clearance ranged from 0–125 ml/min, were given 3 mg pindolol I.V. The concentrations of pindolol in the plasma and urine were measured by a fluorimetric method (Pacha, 1969). From these measurements, the 'overall' (k_e), the renal (k_r) and the extrarenal (k_m) elimination rate constants for each individual patient were calculated on the basis of a first order one compartment open model. At the same time, endogenous creatinine clearance ($\dot{V}_{cr}$) was estimated.

No linear correlation according to the equation $k_e = k_m + a \cdot \dot{V}_{cr}$ could be calculated between the elimination constant and the endogenous creatinine clearance. Using the method of 'the least squares of errors', the following equation was calculated: $k_e = 0{\cdot}185 - 0{\cdot}00023 \cdot \dot{V}_{cr}$; $r = 0{\cdot}17$; $s_{y/x} = \pm 0{\cdot}056$; $P > 0{\cdot}05$. This means that the calculated line is parallel to the abscissa and that no change in the elimination rate constant or the half-life, respectively, of unchanged pindolol takes place in patients with renal impairment. According to the equation $k_e = k_m + a \cdot \dot{V}_{cr}$, k_r gets lower with decreasing endogenous creatinine clearance and accordingly k_m increases. From this fact it must be concluded that in patients with renal impairment a much increased metabolism of the substance occurs. Explanations for this increased metabolism are not known.

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Isoprenaline antagonism and duration of action in exercise induced tachycardia of three β-adrenoceptor blocking drugs: pindolol, LF 17-895 and propranolol

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Orally administered pindolol (Visken, LB 46, 1-(indol-4-yloxy)-3-(isopropylamino)-2-propanol) has been shown to be between 20 and 40 times as potent as propranolol in antagonizing tachycardia due to isoprenaline inhalation (Hill & Turner, 1969). In this study the 2-methyl derivative of pindolol (LF 17-895, 1-(isopropylamino)-3-(2-methylindol-4-yloxy)-2-propanol) has been compared with pindolol and propranolol in healthy volunteers for their antagonism to isoprenaline induced tachycardia. In addition the duration of action of all three drugs has been investigated using the model of exercise induced tachycardia.

Subjects rested supine and isoprenaline hydrochloride was infused into a left antecubital vein. Starting with 2 μg/min, the dose was doubled every 5 min until a heart rate of above 130 beats/min was reached. The infusions were repeated 2 h after pindolol (1 mg, 2·5 mg, 5 mg), LF 17-895 (0·5 mg, 1·25 mg, 2·5 mg), propranolol (40 mg, 80 mg) and placebo administered to all three volunteers orally in random sequence. From isoprenaline dose response curves the dose of isoprenaline required to increase heart rate to 120 beats/min was extrapolated for each dose of the three drugs and placebo (Table 1). These results indicate that orally administered LF 17-895 was 2·5 times more potent in this test than pindolol, which showed, in accordance with Hill & Turner (1969), about 40 times the activity of propranolol.

Five other volunteers exercised on a cycle ergometer (150 watts for 3 min) before and 1, 2, 4, 6 and 8 h after the oral application of pindolol (5 mg), LF 17-895 (2·5 mg) and propranolol (100 mg) administered in random order. These doses of the three drugs reduced exercise tachycardia to about the same extent with a maximum after two hours. The reductions after 4, 6 and 8 h were expressed as % of the effect at 2 h (Table 1). The duration of action of pindolol (5 mg) and LF 17-895 (2·5 mg) is significantly longer in this test than that of propranolol (100 mg).

TABLE 1

A. Isoprenaline antagonism
Dose of isoprenaline (μg/min) required to increase heart rate to 120 beats/min. (2 h after oral application of the drug) (n=3).

Placebo	Pindolol			LF 17895			Propranolol	
	1·0 mg	2·5 mg	5·0 mg	0·5 mg	1·25 mg	2·5 mg	40 mg	80 mg
3·9±0·8	66±11	169±48	279±50	80±13	220±61	486±103	83±21	126±24

B. Duration of action (exercise induced tachycardia) (n=5)

		Reduction of 'end of exercise heart rate' (beats/min) 2 h	(% of reduction at 2 h) 4 h	6 h	8 h
Pindolol	5 mg	41·7±1·9	89·8±2·6	87·0±4.8	84·3±4·8*
LF 17895	2·5 mg	37·3±3·7	90·3±0·9	86·4±2·0*	80·8±2·9*
Propranolol	100 mg	40·8±2·3	89·8±1·9	74·6±4·2	66·9±4·4

* Significant difference to propranolol ($P<0·05$, paired t-test)

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Clinical pharmacological studies of Kö 1173—a new antiarrhythmic agent

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Kö 1173 1-(2, 6-dimethylphenoxy)-2-amino-propane has anticonvulsant properties and can suppress ventricular arrhythmias in experimental animals by reducing the maximal rate of ventricular depolarization (Allene, Kofi Ekue, Shanks & Zaidi, 1970; Singh & Vaughan Williams, 1972).

Kö 1173, given intravenously or orally, successfully controlled ventricular arrhythmias in 35 of 47 patients. Plasma concentrations of the drug were measured by gas-liquid chromatography in 38 patients.

In acute ventricular arrhythmias the mean minimum effective plasma concentration of Kö 1173 was 1·6 μg/ml (range 0·8 to 2·9 μg/ml) whereas the corresponding value in stable ventricular arrhythmias was 0·7 μg/ml (range 0·5 to 1·3 μg/ml). Central nervous and cardiovascular toxicity was often observed with concentrations above 3·0 μg/ml.

Following intravenous injection the drug disappeared quickly from the plasma and high rates of infusion were required initially to maintain adequate plasma concentrations. An initial intravenous bolus of 150–200 mg is followed by an infusion at the rate of 250 mg in 30 min, 250 mg in the next 2·5 h and 500 mg in the subsequent 8 h. For maintenance therapy 500 mg is infused every 12 h.

After intravenous infusions lasting 24–72 h were discontinued, the mean plasma half-life in 11 patients with myocardial infarction was 18·6 h (range 10–26 h). The long half-life may result in cumulation and late toxicity. The apparent volume of distribution was in the range 200–400 l.

Kö 1173 was well absorbed when given orally to 11 patients. A loading dose of 600 mg produced peak plasma concentrations of 1·6 to 2·8 μg/ml in 3 h and effective concentrations were maintained with 450 to 1,050 mg daily.

In 6 healthy volunteers peak plasma concentrations of 0·3 to 0·5 μg/ml occurred 1–4 h after ingestion of 3 mg/kg of Kö 1173 in solution. The mean plasma half-life was 11·5 h