by gas-liquid chromatographic techniques. The pH of 2 ml samples of plasma was adjusted to 10 with sodium hydroxide (0·75 N) and the drug extracted into ether. 20 μl of acetone and acetic anhydride were added to the separated ether layer which was then evaporated to dryness, using a stream of nitrogen, on a sand bath. The residue was redissolved in 2 μl of acetone, 1 μl of which was injected into the gas chromatograph (Perkin Elmer F 11) equipped with a flame ionization detector. Methylamphetamine was used as an internal standard.

To determine the pharmacokinetics and clinical effects of the drug, 100 mg boluses of Kö 1173 were administered to six patients who had stable premature beats. The patients rested in a quiet room for 30 min after insertion of an indwelling catheter and were then given 10 ml of saline intravenously. Kö 1173 was injected over a 2 min period. Blood for drug level measurements was taken at 5 min intervals for 1 h together with 60 s e.c.g. rhythm strips. For all six patients under study, a semilogarithmic plot of blood level concentration against time suggested that the drug has a biphasic half-life. The first half-life was very similar in all cases with a mean of $12{\cdot}3 \pm 0{\cdot}53$ min (mean $\pm$ S.E.). The second half-life was more prolonged and variable for each study, the results ranging from 53 min to 170 minutes. In 4 patients the frequency of premature beats was significantly suppressed. One patient only had a transient suppression and another showed no response. The steady plasma levels after the initial fall were similar, irrespective of their clinical response. In one oral study of drug absorption, the patient received Kö 1173 in a dose of 7 mg/kg body weight. The peak blood level occurred at 3 h with a half-life of 160 min which was similar to that of the second phase half-life after intravenous administration.

Myocardial function was assessed using the duration of aortic ball valve travel time as an index of myocardial depression after increasing intravenous doses of Kö 1173. The measurements were repeated on a separate occasion using lignocaine. Kö 1173 caused minimal myocardial depression equal to that found with lignocaine. Depression of contractility was dose related and was apparent immediately following administration.

Kö 1173 is an effective antidysrhythmic drug with an apparent biphasic half-life within the duration of this investigation. Its action has a rapid onset and persists in spite of a rapid fall in blood levels during tissue distribution.

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Interaction between debrisoquine and phenylephrine in man

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Phenylephrine has been used to study human baroceptor reflexes; the intravenous method (Bristow, Honour, Pickering, Sleight & Smyth, 1969) was modified to enable oral phenylephrine and cuff blood pressure measurements to be used (Aminu, 1972). Some exaggerated blood pressure responses were then observed in hypertensive subjects taking debrisoquine (3,4-dihydro-2 (1H) isoquinoline carboxamidine sulphate) (Aminu, D'Mello & Vere, 1970).

Four normal subjects, two females and two males, took debrisoquine (0·5–0·75 [mg/kg]/day) in capsules as divided doses, increasing the dose until sufficient was taken to cause measurable changes in the cardiovascular response to a passive tilt of 80°. Syrup, with or without phenylephrine (0·75 mg/kg) was taken before debrisoquine, and

on the third day of effective debrisoquine treatment and this was repeated on the third day after debrisoquine had been withdrawn.

Blood pressures measured during the first phenylephrine experiment were significantly higher, and their elevation more prolonged in three of the four subjects than in the

TABLE 1. *Changes (△B.P.) in blood pressure (mmHg) in four normal subjects, induced by oral phenylephrine before and during debrisoquine treatment. All results are means±S.E. of 3 readings. C represents results within 95% confidence limits for the control means. Parentheses enclose single readings*

		Control observations—phenylephrine alone				First phenylephrine experiment, with debrisoquine			
		Supine		Tilted		Supine		Tilted	
Subject	△ B.P.	Peak effect	At 90 min	Peak effect	At 90 min	Peak effect	At 90 min	Peak effect	At 90 min
A.S.	△ Syst.	14±6	C	20±3	C	24±2	17±1	44±4	44±4
	△ Dias.	15±0·3	C	19±1	C	35±4	25±2	34±0·3	34±0'3
C.D.	△ Syst.	25±3	C	16±3	C	(62)	17±2	46±4	25±1
	△ Dias.	22±4	C	9±5	C	(30)	6±5	43±10	16±4
T.B.	△ Syst.	6·6±3	C	8·7±6	C	18·3±8	—	35±5	—
	△ Dias.	3·2±1	C	9·7±3	C	24±2	—	29±1	—
W.A.	△ Syst.	12±3	C	15±4	C	7±2	C	16±4	C
	△ Dias.	8±4	C	10±5	C	15±3	C	11±1	C

control observations made before debrisoquine (Table 1). In one subject phentolamine was given when blood pressure exceeded the prearranged limit of 180/120 mmHg. The effect was not seen in the experiment after debrisoquine withdrawal.

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The pharmacology of human isolated pulmonary vascular tissue

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The pharmacological actions of human isolated pulmonary arterial and venous tissues have been studied. Spirals of muscle were cut from vessels dissected after lobectomy or

TABLE 1. *Responses of human isolated pulmonary vascular tissues to some pharmacological agonists*

Agonist	n	Artery Response	n	Vein Response	Dose range
Acetylcholine	17	+/−/0 (6) (7) (4)	25	+/0 (19) (6)	100 ng/ml– 10 μg/ml
Noradrenaline	50	+++ (50)	40	+++ (40)	5 ng/ml– 2 μg/ml
Adrenaline	2	+++ (2)	4	+++ (4)	50 ng/ml–400 ng/ml
Phenylephrine	2	+ (2)	2	+ (2)	50 ng/ml–800 ng/ml
Isoprenaline	22	++/−/0/biphasic* (4) (13) (3) (2)	29	++/−/0 (7) (15) (7)	50 ng/ml– 32 μg/ml
Histamine	15	+++ (13)	13	+++ (13)	0·5 μg/ml–128 μg/ml
5-Hydroxytryptamine	10	+++ (10)	9	+++ (9)	250 ng/ml– 1 μg/ml
Nicotine	14	+ (8)	14	+ (11)	1 μg/ml– 50 μg/ml

0=No response to agonist although tissue shown to be alive in response to other agonists.
+Contraction, −Relaxation } Numbers of symbols for each agonist give an approximate comparison of height of maximal contraction between agonists.
n=Number of tissues.
*In these two tissues initial relaxation (slight) was followed by contraction at higher doses.