CLINICAL PHARMACOLOGY SECTION

Log dose-response curve to assess the effects of propranolol in angina pectoris

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When propranolol was first used in angina some investigators used small doses (Scrivastava, Dewar & Newell, 1964; Keelan, 1965), others larger doses (Gillam & Prichard, 1965), and it was not immediately clear that larger doses were needed for maximum effect.

In the present study a dose-response curve for the effect of propranolol in angina pectoris has been plotted. The dose of propranolol was adjusted in each individual patient; it was increased until resting supine heart rate was 55–60/min or a side effect prevented any further dose increment. This was defined as full dose (average 417 mg/day; range, 80–1,280 mg/day). Full dose, half dose, quarter dose, and one eighth dose, besides placebo were each given for 2 weeks in random order and the cycle of treatment was repeated three times, that is 6 weeks on each dose. There was a straight line relationship from one eighth dose to full dose in terms of the parameters measured, a progressive reduction in angina attacks, a reduction in heart rate supine and standing.

Because even at full dose, as defined above, the dose/response relationship was still linear, it can be concluded that a larger dose would have a still greater effect.

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Hypotensive action from combination of propranolol and other hypotensive drugs

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Propranolol is an effective hypotensive drug when used in adequate doses in man (Prichard & Gillam, 1969), an effect that was not predicted from animal experiments. The antihypertensive action of hydrallazine, guanethidine and methyldopa was antagonized by propranolol in renal hypertensive rats (Bein & Brunner, 1966). Grewal & Kaul (1970) have recently discussed the antagonism of the hypotensive action of guanethidine by propranolol that they also observed. Our initial observations suggested that propranolol exerted an additive effect with a variety of hypotensive agents —including bethanidine, guanethidine, methyldopa, hydrallazine—and diuretics (Prichard & Gillam, 1969).

Hypertensive patients have been observed over a period of change of treatment from bethanidine, or methyldopa to propranolol. Blood pressures were taken under standard conditions supine after 1 min resting, supine after 3 min (this reading used in assessment), standing after 1 min and after ascending and descending eighteen stairs. Blood pressures were recorded by the London School of Hygiene and Tropical Medicine sphygmomanometer (Rose, Holland & Crowley, 1964), a device that ensures the observer is unaware of the actual pressure when he auscultates. Evidence for

interaction of propranolol with bethanidine and methyldopa has been sought from patients who received the combination at one time of methyldopa (or bethanidine) at a dose of approximately 50% (range 30–70%) of their last dose used by itself to control the blood pressure and propranolol at approximately 50% (range 30–70%) of the dose first used to control the blood pressure.

The total of these percentages of doses of propranolol and methyldopa (or bethanidine) used in combination was kept in the range 90–110%.

Table 1 shows that blood pressures on the combination of drugs tended to be lower than on methyldopa, bethanidine and propranolol. When blood pressure was lowered by propranolol there was no postural or exercise hypotension (Prichard & Gillam, 1969; Prichard, Gillam & Graham, 1971) in contrast to the effect seen with bethanidine, guanethidine and methyldopa. The ratios, derived from Table I, of erect/supine, or post-exercise/supine show that blood pressure in the presence of a mixture of propranolol with methyldopa or bethanidine shows a response to posture and exercise intermediate between propranolol alone and methyldopa or guanethidine alone.

TABLE 1. *Mean blood pressure (diastolic pressure plus 1/3 pulse pressure) in mmHg*†

	Supine	Erect	After exercise
Bethanidine (B) $n=5$	145	123	111
	$P<0.025$	$P<0.025$	N.S.
B+P	125	104	96
	N.S.	$P<0.05$	$P<0.05$
Propranolol (P)	128	124	129
Methyldopa (M) $n=7$	115	104	98
	$P<0.05$	N.S.	N.S.
M+P	103	102	99
	$P<0.01$	$P<0.001$	$P<0.001$
Propranolol (P)	112	118	119
Previous therapy $n=12$	128	112	102
(B = 5, +M = 7)	$P<0.005$	$P<0.10$	N.S.
Previous+P	112	103	98
	$P<0.005$	$P<0.001$	$P<0.005$
Propranolol (P)	119	121	123

N.S.=$P<0.10$. (P (single tail) calculated from differences in logarithms of pairs.) † 1 mmHg≡ 1·333 mbar.

The animal experiments referred to above were of short duration and this may explain the differences from the results in man. In view of the postural and exercise hypotension on the effects of the combination of propranolol with methyldopa or bethanidine it appears preferable to use propranolol alone, rather than in combination, to treat hypertension.

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