Comparison of propranolol and Ro 3-3528 in hyperthyroid tachycardia and dysrhythmias

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Summary

Ro 3-3528, a non-selective β -adrenoceptor blocking drug which lacks intrinsic activity, produces a dose-response effect in hyperthyroid tachycardia, and shows no dysrhythmic properties. In hyperthyroid patients, β -blocking drugs of this nature are preferable to those possessing intrinsic sympathomimetic activity, which may have dysrhythmic properties in this condition.

Introduction

Ro 3-3528 is a nonselective competitive β -adrenoceptor blocker, which, in normal volunteers, is five to six times more potent than propranolol given intravenously (Haefely, Hürlimann & Thoenen, 1967; Hicks & Phillips, 1972). It is known to lack intrinsic sympathomimetic activity in reserpinized rats (Parkes & Parks, personal communication).

The hyperthyroid state is associated with enhanced responses to exogenous catecholamines (Schneekloth, Kurland & Freedberg, 1953), while adrenergic-neurone-blocking drugs may diminish the peripheral manifestations of hyperthyroidism (Canary *et al.*, 1957; Goldstein & Killip, 1965). Wilson, Theilen & Fletcher (1964) found that the β -adrenoceptor-blocking drug pronethalol failed to reduce the peripheral cardiovascular signs of spontaneous and experimental hyperthyroidism, and this drug has marked intrinsic sympathomimetic activity (Black, Duncan & Shanks, 1965). In contrast, a dose-response inhibitory effect on hyperthyroid tachycardia was shown for propranolol, a compound which has no significant intrinsic activity before metabolism (Turner & Hill, 1968). Studies on other β -adrenoceptor-blocking agents in this condition have since shown that those drugs possessing intrinsic activity fail to produce dose-response inhibitory effects (alprenolol, oxprenolol, practolol, prinodolol) whereas sotalol, lacking in intrinsic activity, does so (Turner & Hill, 1968; Turner, 1970; Ekue, Lowe &

Shanks, 1970; Arbab & Turner, 1971). Moreover, dysrhythmias may occur following drugs possessing intrinsic activity, presumably due to the enhanced responsiveness to agonist activity in the hyperthyroid state (Turner & Hill, 1968).

The present paper compares the inhibitory effect on hyperthyroid tachycardia of propranolol and Ro 3-3528 in two comparable intravenous doses with that of a saline placebo, observes the incidence of spontaneous ectopic arrhythmias before and after injection and measures the plasma levels of both drugs obtained after injection.

Subjects

Six patients of proven hyperthyroid status were studied prior to treatment. Two men and four women aged 26-58 were admitted to either St Bartholomew's Hospital or to the North Middlesex Hospital for 5 days. All were free from cardiac disease, bronchial asthma, hepatic and renal disease, and from diabetes mellitus. Full blood count, blood urea and electrolytes, serum proteins, alkaline phosphatase, and serum glutamic oxaloacetic transaminase and hydroxybutyric dehydrogenase were normal. Urinalysis was normal. Electrocardiographs were normal apart from the presence of spontaneous supraventricular or ventricular ectopic beats in five patients. Informed consent was obtained from each patient.

Procedure

At 24-hr intervals patients received saline placebo, low or high doses of propranolol, or comparable doses of Ro 3-3528 intravenously under double-blind conditions (Table 1). The order of treatments was random, but low doses were planned to be given before high doses. In spite of this precaution, two patients showed such a drop in heart rate during days 1-3 (of the order of 20/min for subject BP and

TABLE 1. Plasma levels of propranolol and Ro 3-3528 obtained at 10 min after intravenous injection in low and high doses in six hyperthyroid patients, and incidence of spontaneous ectopic beats observed for 5 min before and 17.5 min after beginning of injection

	Patient											
	BP		BB		EM		EH		DN		JA	
Sex	F		M		F		F		F		M	
Age	26		37		51		37		47		58	
Intravenous doses (mg)												
Propranolol low	1.25		1.0		1.0		1.0		0.5		1.0	
Propranolol high	2.5		2.0		2.0		2.0		1.0		2.0	
Ro 3-3528 low	6.0		6.0		6.0		6.0		3.0		6.0	
Ro 3-3528 high	12.0		12.0		12.0		12.0		6.0		12.0	
Plasma levels (ng/ml) 10 min after injection												
Propranolol low	4.4		4.8		4.4		3.2		< 1.0		4.9	
Propranolol high	11.6		8.9		10.5		5.4		3.5		8.6	
Ro 3-3528 low	14.5		15.1		18.4		10.0		6.5		6.8	
Ro 3-3528 high	24.6		56.5		37.4		37.0		19.8		17.2	
Ectopic beats*												
Saline	0	0	3V	2V	0	3S	0	0	0	0	1V	0
Propranolol low	0	0	2V	0	0	2S	0	0	1V	2V	1V	0
Propranolol high	2V	0	0	0	0	2S	0	0	0	0	0	0
Ro 3-3528 low	0	2V	0	0	0	0	0	0	0	0	1V	0
Ro 3-3528 high	0	2V, 1S	0	0	0	0	0	0	1V	1V	2V	1V
Relation to injection	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After

*V, ventricular; S, supraventricular.

13/min for subject DN) that, rather than double the doses on days 4 and 5, the doses were halved.

At the start of each study, patients rested for 5 min on the bed. Heart rate was then recorded electrocardiographically every minute for 5 min, following which an intravenous injection was given over 7.5 min. Ectopic beats were noted and counted for 5 min before injection, during injection and for 10 min after injection. Heart rate was recorded every minute for 5 min after cessation of injection, and at 7.5 and 10 min. Immediately after the last heart rate recording, 10 ml of blood were obtained by venepuncture in the contralateral arm to the injection for estimation of plasma level of drug. Blood was collected in heparinized tubes, and plasma was separated by centrifugation at 3000 rpm for 10 min. Samples were deep-frozen and estimated up to 2 weeks after collection. No deterioration of fluorescence occurred in standard solutions kept under the same conditions for at least 8 weeks.

Estimation of propranolol was by the method first described by Black, Duncan & Shanks (1965), and modified by Shand, Nuckolls & Oates (1970).

Plasma levels of Ro 3-3528 were estimated fluorimetrically by the method of Long & Francis (personal communication) and modified by Phillips & Hicks (1972).

Drugs

Placebo used as normal saline.

Propranolol as the hydrochloride, 1 and 10 mg/ml (Inderal, ICI)

Ro 3-3528 (racemic 6,7-dimethyl- α [(isopropylamino) methyl]-2-benzofuranmethanol hydrochloride: synthesized by Dr O3bond, Roche Products Ltd) was used as 8 mg/ml solution in normal saline. All doses were diluted in normal saline to give a final volume of 2 ml.

Results

No patient experienced side-effects, but four volunteered on days in which they received active drugs that they noticed a suppression of palpitation for 2-4 hr after injection. No patient noted improvement on saline days.

Ectopic supraventricular and ventricular beats were noted in five patients (Table 1). They occurred before and after injections of both β -adrenoceptor-blocking agents and of saline. There was no evidence that either drug was associated with the production of dysrhythmias.

Pooled results from the six patients were submitted to analysis by Student's 't' test. There was a significant difference between mean heart rates before and after injection of each drug in both doses ($P < 0.001$), whereas the change in mean heart rate on saline days was insignificant (Fig. 1 and Table 2). There was no significant difference between the drop in heart rates obtained after the low dose of propranolol and the low dose of Ro 3-3528; but a significant difference in changes in heart rate occurred between the high doses of both drugs ($P < 0.02$).

There was a highly significant difference between

FIG. 1. Mean resting heart rates in six untreated hyperthyroid patients before and after intravenous saline (— — —), or low or high doses of propranolol and Ro 3-3528 (— — —). Diagonally hatched areas, injection over 7.5 min.

TABLE 2. Mean resting heart rates in six hyperthyroid patients before and after intravenous injection of normal saline, propranolol or Ro 3-3528 in low and high doses

Drug	Number of observations (n)	Mean resting heart rate	SD	Variance	t	P
Saline						
Before injection	30	101.7	10.5	111.3		
After injection	40	99.5	14.60	214.7	2.171	< 0.05
Propranolol						
Low dose						
Before injection	30	105.6	13.50	182.4		
After injection	40	95.0	10.40	109.1	11.54	< 0.001
High dose						
Before injection	30	106.1	11.7	137.4		
After injection	40	92.1	11.9	142.3	15.25	< 0.001
Ro 3-3528						
Low dose						
Before injection	30	104.0	12.5	157.4		
After injection	40	93.2	11.5	133.0	11.63	< 0.001
High dose						
Before injection	30	107.1	9.5	89.9		
After injection	40	90.6	8.2	68.4	24.16	<< 0.001

Differences tested between pre-injection and postinjection heart rates using Student's 't' test with 68 degrees of freedom. (Five observations were made on each of six patients before injection; seven observations were made on each of five patients, and five observations on the sixth patient after injection; the last observations being lost due to ECG failure.)

the mean changes in heart rate following low and high doses of Ro 3-3528 ($P < 0.001$); the difference between mean heart rate changes after low and high doses of propranolol, although in the appropriate direction, did not reach as high a level of significance ($P \doteq 0.05$; Table 3, and Fig. 2).

Table 1 and Fig. 3 compare the plasma levels and effects of both drugs: a relationship is apparent between the mean log plasma level of both agents and their therapeutic effect.

Discussion

Ro 3-3528 and propranolol show a mean dose-response effect on inhibition of hyperthyroid tachycardia, and this effect is related to the plasma level of the drug in each case. It is of interest that all six patients demonstrate a clear dose-response effect with Ro 3-3528: four out of the six show a similar response with propranolol, whereas two subjects (BP and EM, Table 1 and Fig. 2) showed less inhibition with the higher than with the lower dose of propranolol. Fitzgerald & O'Donnell (1971) have shown in reserpinized animals that the active metabolite of propranolol, 4-hydroxypropranolol, exhibits intrinsic sympathomimetic activity. However, the metabolite is not formed following intravenous injection, thus obviating this explanation for our anomalous results. If 4-hydroxypropranolol exerts intrinsic activity in man, such a factor might be important when considering treatment of hyperthyroid patients with oral propranolol, since its active metabolite would then be formed, countermanding to some extent the effect of the parent compound (Coltart & Shand, 1970). Ro 3-3528 has no known active metabolites in man (Hornby,

FIG. 2. Change in resting heart rate in six hyperthyroid patients following intravenous saline, propranolol or Ro 3-3528 in low or high doses.

(Heart rates are corrected to a common pre-injection rate for each subject).

1969). On this basis, it is possible that sotalol or Ro 3-3528 might be preferable to propranolol in the management of hyperthyroid states by oral therapy. We found that the intravenous administration

TABLE 3. Mean changes in heart rate in six hyperthyroid patients over 5 min following intravenous injection of normal saline, propranolol or Ro 3-3528 in low and high doses

Drug	Mean change in heart rate	SD	Variance	<i>t</i>	<i>P</i>	
Saline	-2.5	6.58	43.29			
Propranolol						
Low dose	-11.3	5.97	35.60	5.337	< 0.001	Mean drug response vs mean saline response
High dose	-14.2	5.41	29.03	7.410	< 0.001	
Ro 3-3528						
Low dose	-11.5	4.19	17.57	6.211	< 0.001	
High dose	-17.8	4.91	24.14	10.032	< 0.001	
Low dose propranolol vs high dose propranolol:				1.942	$\doteq 0.05$	
Low dose Ro 3-3528 vs high dose Ro 3-3528:				5.254	< 0.001	
Low dose propranolol vs low dose Ro 3-3528:				0.147	NS	
High dose propranolol vs high dose Ro 3-3528:				2.659	< 0.02	

Differences tested with Student's '*t*' test with 58 degrees of freedom. $n = 30$.

FIG. 3. Mean fall in resting heart rate (---) and mean plasma levels of β -adrenoceptor blocker (—) in six untreated hyperthyroid patients following intravenous saline, propranolol or Ro 3-3528 in low and high doses.

of neither propranolol nor Ro 3-3528 was associated with an increase in spontaneous ventricular or supraventricular ectopic beats; this would support our conclusion that β -adrenoceptor-blocking drugs without intrinsic activity have consistent inhibitory effects on hyperthyroid tachycardia without dysrhythmic effect, whereas those agents possessing intrinsic sympathomimetic activity do not predictably inhibit such a tachycardia, and may even be associated with the induction of arrhythmias. The cardioselective β -adrenolytic agent practolol, although perhaps preferred on the grounds of receptor selectivity, falls into the latter category.

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