Does a selective 5-hydroxytryptamine antagonist (ICI 169, 369) lower blood pressure in hypertensive patients?

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- 1 The effect of single doses (10, 30 and 50 mg) of a selective 5-HT₂ receptor antagonist, ICI 169, 369, on blood pressure, heart rate and the electrocardiogram was studied using a double-blind, placebo-controlled, within subject design in hypertensive patients.
- 2 ICI 169, 369 did not reduce blood pressure or increase QT interval as has been reported with ketanserin. This suggests that it is the other properties of ketanserin which are responsible for its antihypertensive effect.
- 3 Plasma concentrations of AUC for ICI 169, 369 were low. This is consistent with low bioavailability due to extensive first pass metabolism.
- 4 ICI 169, 369 was well tolerated and none of the symptoms reported by the patients was thought to be drug related.

Keywords 5-hydroxytryptamine 5-HT antagonists ICI 169, 369 hypertension

Introduction

5-Hydroxytryptamine (5-HT) functions as a neurotransmitter in the peripheral and central nervous systems and has been suggested to have a role in the regulation of blood pressure (Vanhoutte, 1987). Ketanserin, which has 5-HT receptor antagonist effects lowers blood pressure but has other properties that may be responsible for its antihypertensive action (Donnelly *et al.*, 1987). Ketanserin also increases QT interval (Donnelly *et al.*, 1987) and reduces heart rate (Persson *et al.*, 1983). The mechanism for these changes is uncertain resulting in debate as to whether a specific 5-HT receptor antagonist lowers blood pressure.

ICI 169, 369 [2-(2-dimethylaminoethylthio)-3-phenylquinoline hydrochloride] is a 5-HT receptor antagonist with selectivity for the 5-HT₂ and 5-HT_{1C} receptor subtypes (Blackburn *et al.*, 1987a, 1988). Unlike ketanserin, it has no demonstrable effect on other receptors, including α -adrenoceptors (Blackburn *et al.*, 1987b, 1988).

The aim of this study was to investigate the effects of single doses of ICI 169, 369 on blood pressure, heart rate and the electrocardiogram in patients with sustained hypertension.

Methods

Patient selection

Twelve patients (seven male) with sustained mild to moderate hypertension (untreated supine diastolic pressure 95–115 mm Hg, phase 5, using a Hawksley random zero sphygmomanometer, after 5 min rest on two separate occasions in the 2 week run-in period) were selected for study. The patients were aged 32–69 years (mean 55 years) and weighed 56.2–99.8 kg (mean 78.0 kg). All patients were in good general health at the time of the study with normal renal and hepatic function. Ten patients were taking no regular medication, one patient was euthyroid on thyroxine for hypothyroidism and one patient was taking ranitidine because of a past history of peptic ulceration.

Ethical approval was obtained from Grampian Health Board/Aberdeen University Joint Ethics Committee and written consent was obtained from all subjects.

Study design

Three single doses (10, 30 and 50 mg) of ICI 169, 369 and placebo were compared in a randomised

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(Latin square design) double-blind, within patient trial. There was an interval of 1 week between each study day. With 12 patients in a four period cross-over design an 80% chance was calculated of obtaining a statistically significant result at the 5% level (double sided) if the true difference between any two treatments was 13.2 mm Hg for systolic and 6.5 mm Hg for diastolic blood pressure (supine).

Heart rate and blood pressure (supine, 5 min rest; standing, 2 min) were measured using a 'Copal' UA 251 semi-automated sphygmomanometer at -30 min, -15 min pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h post-dose. ECG recordings for measurement of PR, RR and QT intervals were made pre-dose and at 2, 4 and 8 h post-dose. Rhythm strips were recorded at 50 mm s⁻¹ and the mean of four successive intervals (PR, RR, QT) was calculated. QT intervals were corrected for heart rate (QT_C) by the method of Bazett (1920).

Venous blood samples were collected pre-dose and at 2, 4, 6 and 8 h post-dose for measurement of whole blood ICI 169, 369 concentrations using a validated capillary gas chromatography method. Samples of blood (1 ml) were extracted with 1.5% (v/v) amyl alcohol in hexane using a forward-back-forward extraction sequence. The final extracts were evaporated to dryness and the residues redissolved in 1% ethanol in octanol. Chromatography was carried out using a Hewlett-Packard gas chromatograph fitted with a specific nitrogen detector. Separation of ICI 169, 369

and an internal standard (*N*-diethyl analogue of 169, 369) was achieved using a 5% methyl-phenyl silicone column (0.52 µ film thickness; 25 m × 0.31 mm i.d.) and a temperature programme from 190° C to 270° C. Concentrations of ICI 169, 369 were calculated from peak area ratios by reference to a standard calibration curve. The lower limit of detection was 4 ng ml⁻¹. Coefficient of variation was 8% at the concentrations found in this study.

AUC to 8 h was calculated by the trapezoidal rule. Statistical analysis was by analysis of variance unless otherwise stated.

Results

Ten patients completed the study. One was withdrawn because of transient weakness of his left hand 3 days after the first study day and one withdrew because of home circumstances.

The blood pressure recordings are shown in Tables 1 and 2. Statistically significant differences ($P < 0.05$) were noted for supine, systolic pressure (reduction) between placebo and 30 mg ICI 169, 369 at 30 min post dose and for standing systolic pressure (increase) between placebo and 50 mg at 2 h post dose. Copal monitors occasionally record spuriously high diastolic pressures. Only one such reading occurred in this study. This value (192 mm Hg) was rejected because it was clearly very much higher than all other recorded values on that study day.

Table 1 Supine blood pressure (mm Hg) following administration of single doses of ICI 169, 369 or placebo (mean ± s.d.). Pre-dose value is the mean of the -30 and -15 min recordings. * $P < 0.05$ compared with placebo

	Pre-dose	30 min	1h	2h	3h	4h	5h	6h	7h	8h
Placebo	179/101 ±23/11	177/102 ±26/10	174/99 ±30/11	174/100 ±28/13	174/103 ±30/9	183/103 ±24/10	169/95 ±24/6	166/95 ±25/8	177/100 ±27/8	182/100 ±24/11
10 mg	178/102 ±20/8	170/98 ±28/11	171/99 ±27/11	174/100 ±26/9	181/106 ±28/11	177/101 ±26/8	172/91 ±24/8	165/92 ±23/8	171/94 ±33/10	181/101 ±24/7
30 mg	176/101 ±26/9	*166/97 ±20/14	171/97 ±31/10	179/100 ±28/12	181/102 ±28/7	184/101 ±28/9	173/95 ±31/11	169/92 ±23/8	172/99 ±26/10	178/100 ±27/10
50 mg	171/96 ±26/10	171/99 ±27/8	166/100 ±27/9	170/101 ±28/8	174/100 ±27/9	175/109 ±27/9	169/93 ±28/8	164/97 ±26/8	171/97 ±30/11	174/102 ±27/6

Table 2 Standing blood pressure (mm Hg) following administration of single doses of ICI 169, 369 or placebo (mean ± s.d.). Pre-dose value is the mean of the -30 and -15 min recordings. * $P \leq 0.05$ compared with placebo

	Pre-dose	30 min	1h	2h	3h	4h	5h	6h	7h	8h
Placebo	163/102 ±15/15	160/99 ±23/10	161/102 ±23/13	158/102 ±17/10	163/100 ±19/11	165/104 ±23/11	160/93 ±16/11	160/98 ±19/10	168/103 ±17/10	164/100 ±21/12
10 mg	165/101 ±17/7	163/102 ±14/8	160/100 ±15/9	167/101 ±21/8	170/102 ±20/14	160/100 ±24/10	159/92 ±25/11	161/95 ±18/12	163/99 ±24/16	166/102 ±20/12
30 mg	164/99 ±13/11	153/92 ±16/16	160/98 ±21/11	162/101 ±10/11	166/102 ±15/11	161/99 ±14/14	158/90 ±14/11	155/92 ±20/8	159/97 ±20/14	167/100 ±20/8
50 mg	158/98 ±20/11	159/100 ±22/7	159/96 ±22/9	*164/101 ±19/8	159/98 ±22/9	161/102 ±15/8	161/94 ±17/7	151/99 ±14/11	162/98 ±28/8	162/100 ±20/9

Table 3 The effect of single doses of ICI 169, 369 on heart rate (beats min⁻¹; mean $\pm$ s.d.) **P* $\leq$ 0.05 compared with placebo

	-15 min	1h	2h	4h	8h
Placebo – supine	80 $\pm$ 16	72 $\pm$ 12	67 $\pm$ 15	66 $\pm$ 15	69 $\pm$ 11
– standing	93 $\pm$ 15	82 $\pm$ 15	79 $\pm$ 15	82 $\pm$ 14	78 $\pm$ 11
10 mg – supine	76 $\pm$ 13	68 $\pm$ 14	68 $\pm$ 12	66 $\pm$ 13	67 $\pm$ 11
– standing	85 $\pm$ 13	77 $\pm$ 11	78 $\pm$ 16	77 $\pm$ 17	75 $\pm$ 14
30 mg – supine	76 $\pm$ 15	69 $\pm$ 13	69 $\pm$ 13	66 $\pm$ 14	66 $\pm$ 12
– standing	87 $\pm$ 15	79 $\pm$ 12	78 $\pm$ 12	75 $\pm$ 14	74 $\pm$ 11
50 mg – supine	75 $\pm$ 11	68 $\pm$ 14	66 $\pm$ 13	64 $\pm$ 13	67 $\pm$ 12
– standing	88 $\pm$ 10	77 $\pm$ 13	75 $\pm$ 13	74 $\pm$ 14*	74 $\pm$ 11

Table 4 The effect of single doses of ICI 169, 369 on PR interval and the QT_C (ms) (mean $\pm$ s.d.). **P* $\leq$ 0.05 compared with placebo

	-15 min		2h		4h		8h	
	PR	QT _C	PR	QT _C	PR	QT _C	PR	QT _C
Placebo	182 $\pm$ 26	393 $\pm$ 27	182 $\pm$ 26	391 $\pm$ 35	184 $\pm$ 25	395 $\pm$ 29	182 $\pm$ 26	386 $\pm$ 23
10 mg	172 $\pm$ 25	403 $\pm$ 27	173 $\pm$ 26*	396 $\pm$ 34	172 $\pm$ 21*	397 $\pm$ 30	178 $\pm$ 20	399 $\pm$ 28
30 mg	174 $\pm$ 19	394 $\pm$ 20	172 $\pm$ 24*	396 $\pm$ 30	173 $\pm$ 22*	393 $\pm$ 21	172 $\pm$ 23*	392 $\pm$ 27
50 mg	180 $\pm$ 18	404 $\pm$ 30	181 $\pm$ 19	396 $\pm$ 27	183 $\pm$ 24	398 $\pm$ 27	182 $\pm$ 26	394 $\pm$ 32

The effect of ICI 169, 369 on heart rate is shown in Table 3. No overall effect was seen although there was one significant difference for standing heart rate, between placebo and 50 mg at 4 h.

ECG interval changes are shown in Table 4. There were significant differences in PR intervals between placebo and 10 mg at 2 and 4 h post-dose and between placebo and 30 mg at 2, 4 and 8 h post-dose. There were no significant differences in QT interval or in QT_C.

Blood pressure and QT_C data are further

illustrated in Table 5 which shows the mean differences (with confidence intervals) between placebo and each dose of ICI 169, 369 around the time of the peak plasma concentration (2, 3 and 4 h post dose).

AUC₀₋₈ values (mean $\pm$ s.d.) were 68 $\pm$ 28, 291 $\pm$ 87 and 595 $\pm$ 227 ng ml⁻¹ h for the 10, 30 and 50 mg doses respectively. The median peak plasma concentrations were 11.5 (range 7.1–35.5), 55.4 (29.9–127.7) and 103.9 (63.5–228.2) ng ml⁻¹ for the 10, 30 and 50 mg doses respectively.

Table 5 Differences between placebo and each dose of ICI 169, 369 for blood pressure (mm Hg) and QT_C (ms) at times around the peak plasma concentration: mean differences with 95% confidence intervals

		10 mg		30 mg		50 mg	
		Mean	C.I.	Mean	C.I.	Mean	C.I.
2 h	Supine SBP	-0.4	-11.2 to 10.4	-2.3	-9.8 to 5.2	0.3	-8.5 to 9.1
	Supine DBP	0.3	-5.7 to 6.3	0.6	-7.2 to 8.4	-1.1	-7.4 to 5.2
	Erect SBP	-9.5	-25.2 to 6.2	-3.3	-14.1 to 7.5	-10.3	-24.0 to 3.4
	Erect DBP	1.0	-4.0 to 6.0	-1.9	-7.5 to 3.7	-1.3	-10.4 to 7.8
	QT _C	-5	-21 to 11	-5	-25 to 15	-5	-16 to 6
3 h	Supine SBP	-5.9	-17.5 to 5.7	-1.3	-10.9 to 8.3	-2.5	-15.9 to 10.9
	Supine DBP	-3.3	-7.7 to 1.1	1.5	-4.9 to 7.9	1.2	-3.9 to 6.3
	Erect SBP	-7.2	-18.0 to 3.6	-3.1	-13.1 to 6.9	0.9	-11.1 to 12.9
4 h	Erect DBP	-1.6	-14.5 to 11.3	-1.1	-9.7 to 7.5	0.6	-7.5 to 8.7
	Supine SBP	5.9	-7.5 to 19.3	2.6	-6.9 to 12.1	5.1	-2.1 to 12.3
	Supine DBP	0.1	-7.1 to 7.3	1.8	-6.4 to 10.0	-2.1	-7.8 to 3.6
	Erect SBP	5.4	-16.1 to 26.9	3.5	-16.8 to 23.8	0.7	-15.3 to 16.7
	Erect DBP	3.9	-5.3 to 13.1	5.7	-8.5 to 19.9	0.7	-4.9 to 6.3
	QT _C	-4	-20 to 12	2	-16 to 20	-3	-21 to 15

No intravenous study was done but the concentrations achieved are consistent with low bioavailability.

No major adverse drug effects were observed and there was no change in haematology values, renal function or hepatic enzymes during the study. One patient experienced mild tremor and vomiting with the 50 mg dose and one patient complained of headache, nausea and dyspepsia with the 10 mg dose. These occurred 14 and 24 h post dose respectively and are unlikely to have been due to the drug. However, serum bilirubin concentration (eight patients – mean $\pm$ s.d.) was $10 \pm 1 \mu\text{mol l}^{-1}$ before and $7 \pm 1 \mu\text{mol l}^{-1}$ after the drug period ($P < 0.01$ – paired *t*-test).

Discussion

The selective 5-HT₂-receptor antagonist ICI 169, 369 had no consistent effect on blood pressure, pulse or ECG when compared with baseline and placebo results. The two significant differences in blood pressure found in this study (one increase, one decrease) probably occurred by chance. The differences in PR interval were thought to be due to the lower baseline with the 10 mg and 30 mg doses. The lack of an effect at the 50 mg dose supports the view that this was not a real drug effect. This is in contrast to the results obtained with ketanserin (Donnelly *et al.*, 1987). The present study suggests that a selective 5-HT₂-receptor antagonist without other receptor blocking properties does not have a useful hypotensive action in single doses. The lack of effect raises doubt as to the role of 5-HT in blood pressure reduction in hypertensive patients. This is supported by a recently published study using ritanserin which also had no effect on blood pressure (Stott *et al.*, 1988). However, ritanserin did prolong the QT_C interval.

The doses of ICI 169, 369 used in this study were selected on the basis of animal studies and effects on human platelet 5-HT receptors. However, it is difficult to establish reliably 5HT₂-receptor blockade in man because of a lack of suitable compounds with a clear pharmacological profile. The higher doses used (30 and 50 mg) and plasma concentrations achieved,

were considered sufficient to produce a significant inhibition of 5-HT₂ receptors though further studies are necessary. As designed, the power of the study was adequate to show a clinically important fall in blood pressure though the power was reduced because of two drop outs. The majority of mean values at different time points were remarkably similar when the drug was compared with placebo as shown in Table 5. A false negative (type 2 error) result for effect on blood pressure is thus unlikely.

A full pharmacokinetic analysis was not attempted in this study. The blood concentrations obtained suggested low bioavailability consistent with extensive first pass metabolism as has been demonstrated in animal studies. Insufficient data points were collected to allow accurate measurement of elimination half-life or AUC_∞.

The fall in bilirubin concentration was an unexpected observation. All the samples were taken at the same time of day under the same conditions. Analysis was by the routine hospital laboratory using a S.M.A.C. system. The small change in bilirubin concentration was of the same magnitude as has been shown with hepatic enzyme induction (Scott *et al.*, 1976) and hyperthyroidism (Scott *et al.*, 1984). This raises the possibility that ICI 169, 369 could be inducing bilirubin glucuronyl transferase. Large doses of ICI 169, 369 do induce enzymes in animals but the drug had no effect on antipyrine clearance or 6 β -hydroxycortisol excretion in human volunteers (unpublished data). Examination of data from other studies has not confirmed the effect on bilirubin which suggests that the present result may have occurred by chance (probability 1 in 100). The effect of acute and chronic dosing with ICI 169, 369 on serum bilirubin concentration is being investigated in further prospective studies.

ICI 169, 369 and other selective 5-HT₂ receptor antagonists may not be useful in the reduction of elevated blood pressure unless they have other ancillary actions. However, the present results using single doses require confirmation in a chronic dosing study. Further studies are necessary to examine the properties of drugs such as ketanserin which are effective in lowering blood pressure.

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