VENTILATORY AND CARDIOVASCULAR EFFECTS OF BHT 933 IN VOLUNTEERS

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In 12 healthy volunteers BHT 933 in doses of 5 and 10 mg had minimal effects on ventilation, a small fall in total volume occurred with the highest dose. BHT 933 (5 mg) reduced both systolic and diastolic blood pressure, but had little effect on autonomic reactivity tests, whereas the 10 mg dose reduced the response to these tests. Both doses of BHT 933 caused marked sedation. It is concluded that 5 mg BHT 933 orally presents the most suitable profile of activity for further studies into its usefulness as an anti-tussive and antihypertensive.

Introduction

BHT 933, is an oxazolo-azepine which has significant anti-tussive activity in both animals and man. In the cat BHT 933 intravenously produces a biphasic effect on respiratory frequency and tidal flow, an initial increase followed by decrease. BHT 933 has much less effect upon respiratory indices in the cat than equally anti-tussive doses of thebacon hydrochloride (Boehringer Ingelheim, unpublished data).

Uncontrolled studies in man have shown that 3 to 15 mg BHT 933 daily caused no important changes in blood gas estimations, minute volume or vital capacity.

BHT 933 possesses hypotensive properties which have been classified as 'clonidine-like' (Kobinger & Pichler, 1977). Volunteer studies with a low dose of BHT 933 (4.5 mg) have demonstrated that, although the drug causes a significant fall in systolic blood pressure when compared with placebo, its effects on autonomic function are minimal (Redpath & Pleuvry, 1981).

The present study was designed to determine the effects of two doses of BHT 933 (5 and 10 mg orally) on the ventilatory response to carbon dioxide in volunteers. In addition, some tests of autonomic function were examined before drug and at 2 h post ingestion. This time interval coincides with the maximum effects of 4.5 mg BHT 933 on these tests (Redpath & Pleuvry, 1981).

Methods

Twelve healthy males aged 22 to 39 (mean 28) years and weighing between 60 and 85 (mean 68.5) kg were studied. None of the subjects smoked tobacco and all the subjects consumed alcohol. Three drank alcohol

occasionally and the remainder were regular drinkers of moderate amounts of alcohol. Written informed consent was obtained. The subjects were fasted from 22.00 h the previous evening and only fruit juice or water was allowed prior to the trial. No fluids were allowed during the 2 h prior to the trial, but 2 h after ingestion of the tablets a light breakfast was served. Four hours after the tablets, meals and fluids were permitted *ad libitum* with the exception of caffeine or alcohol containing drinks.

Each volunteer was required to attend on three occasions at least 1 week elapsing between treatments. Placebo, 5 mg BHT 933 and 10 mg BHT 933 were administered using a double-blind protocol in a random order. Ventilation and ventilatory response to carbon dioxide (CO₂) was measured by the method previously described by Redpath & Pleuvry (1982).

These measurements were made prior to drug administration and then at 0.5, 1.5, 2.5, 3.5 and 6 h post drug administration. Blood pressure was measured using an electronic sphygmomanometer (BE 237R) and a continuous record of heart rate was obtained using a Tektronic ECG monitor (412) connected to a pen recorder. The same arm was used for all blood pressure recordings and preliminary experiments, using both the electronic sphygmomanometer and a stethoscope indicated that the apparatus recorded diastolic blood pressure at stage 5.

Sitting heart rate and blood pressure were assessed just prior to each assessment of ventilation and ventilatory response to CO₂ as was sedation score. Sedation was assessed using a visual analogue 100 mm scale marked at one end 'Wide awake' and at the other end 'Nearly asleep'.

Tests of autonomic reactivity similar to those described by Redpath & Pleuvry (1981) were carried

out prior to drug administration and 2 h post drug administration. Pupil size was measured using a pupil gauge based on an entoptic phenomenon (Duke-Elder, 1971). Unless otherwise stated results are expressed as mean values $\pm$ s.e. mean.

Significance between treatments was assessed using analysis of variance and significance between means was assessed using Duncan's test.

Results

BHT 933 had minimal effects on ventilation. A significant difference between treatments was seen for tidal volume 1.5 h after drug administration ($F = 5.16$; d.f. 2, 33; $P < 0.05$). Subjects given 10 mg BHT 933 produced a mean fall in tidal volume ($\pm$ s.e. mean) of 0.13 ± 0.051 compared with a rise in tidal volume of 0.06 ± 0.041 in subjects given placebo. The tidal volume change was associated with a diminution of the slope of ventilatory response to carbon dioxide (Table 1) which was not significant in the number of subjects tested. No other important changes in ventilation were observed.

Both doses of BHT 933 caused significant falls in sitting systolic and diastolic blood pressure (Table 2). The effects upon systolic blood pressure were more profound and longer lasting than those on diastolic blood pressure. Significant differences between treatments were also demonstrated with respect to sitting heart rate 2.5 and 3.5 h after drug administration ($F = 4.67$ and $F = 3.43$ respectively, $P < 0.05$). The higher dose of BHT 933 caused a fall in heart rate of -16.2 ± 3.5 beats min^{-1} and -12.4 ± 4.3 beats min^{-1} at these two time intervals compared with placebo falls of -7.5 ± 1.6 beats min^{-1} and -1.4 ± 2.7 beats min^{-1} .

The sedation score results indicate that both doses of BHT 933 caused marked and prolonged sedation (Table 2).

The additional tests carried out pre drug and 2 h post drug administration illustrated the dose dependence of the effects of BHT 933. Saliva weight

collected for 2 min at 2 h was 2.23 ± 0.49 g in placebo treated subjects, 0.97 ± 0.36 g in 5 mg BHT 933 treated subjects and 0.52 ± 0.12 g in subjects given 10 mg BHT 933 ($F = 6.1$, $P < 0.01$). The heart rate response to standing was increased to $+23.4 \pm 3.6$ and $+22.25 \pm 2.7$ by 5 and 10 mg BHT 933 respectively compared with placebo changes of 14.2 ± 2.9 beats min^{-1} . The increase in diastolic pressure of 15 to 20 mm Hg was unaffected by BHT 933, but on standing the systolic blood pressure was extremely variable and generally less well maintained in subjects given 10 mg BHT 933; there being a fall of 8.8 ± 4.7 mm Hg compared with a rise of 2.3 ± 2.2 mm Hg in placebo treated subjects. The systolic overshoot after the Valsalva manoeuvre was reduced in a dose dependent manner by BHT 933 ($F = 4.32$; $P < 0.05$), but only the 10 mg dose produced less post blow bradycardia, -5.7 ± 2.2 beats min^{-1} compared with -11.3 ± 1.9 beats min^{-1} for placebo treated subjects. The 5 mg dose of BHT 933 produced slightly enhanced bradycardia (-14.2 ± 2.2) despite the reduction in systolic overshoot. BHT 933 reduced the increase in diastolic blood pressure produced by the cold pressor test, although the increase in systolic pressure remained unchanged. Pupil size was also reduced in subjects given BHT 933, the mean change in subjects given 10 mg was -0.9 ± 0.2 mm; -0.6 ± 0.1 mm in subjects given 5 mg and -0.1 mm in subjects given placebo.

Discussion

Respiratory depression is an unwanted side effect of anti-tussive agents (Eddy *et al.*, 1970) and the present study has shown that BHT 933 has only minimal effects on ventilation and ventilatory response to carbon dioxide in a dose as high as 10 mg orally. However, in single doses the drug causes marked sedation which could limit its daytime use as an anti-tussive. The sedative effects of BHT 933 were predictable from its 'clonidine-like' antihypertensive action (Kobinger & Pichler, 1977). BHT 933 differs from

Table 1 Effect of placebo, 5 mg BHT 933 and 10 mg BHT 933 on the slope of the ventilatory response to carbon dioxide (l kPa^{-1})

Treatment	Change from pre-drug records					
	Pre-drug	30 min	90 min	150 min	210 min	360 min
Placebo	18.91 ± 3.22	$+2.10 \pm 2.26$	$+3.11 \pm 2.90$	$+1.95 \pm 2.00$	$+2.66 \pm 1.69$	$+4.86 \pm 2.56$
5 mg BHT 933	18.55 ± 3.16	$+0.76 \pm 1.67$	-0.13 ± 2.18	$+2.37 \pm 1.52$	$+1.60 \pm 2.12$	$+3.28 \pm 2.46$
10 mg BHT 933	19.70 ± 2.82	-3.46 ± 1.05	-4.26 ± 1.31	-1.75 ± 1.43	-0.76 ± 1.19	$+3.97 \pm 2.05$
<i>F</i>	0.34	2.71	2.55	1.51	0.75	0.11

Results are means $\pm$ s.e. mean ($n = 12$)

Table 2 Effect of placebo 5 mg BHT 933 and 10 mg BHT 933 on sitting blood pressure (mm Hg) and sedation score (mm on analogue scale)

	Pre-drug	Change from pre-drug				
		30 min	90 min	150 min	210 min	360 min
<i>Blood pressure systolic</i>						
Placebo	118 ± 3	-3.1 ± 2.3	-3.3 ± 3.0	-2.7 ± 1.8	-0.0 ± 2.7	+2.8 ± 2.4
5 mg BHT	119 ± 4	-8.2 ± 3.2	-19.0 ± 4.0**	-17.4 ± 3.1**	-15.5 ± 3.6**	-8.0 ± 3.0*
10 mg BHT	118 ± 5	-10.1 ± 4.2	26.5 ± 4.4**	-22.6 ± 4.4**	-27.0 ± 3.8**	-16.2 ± 5.2*
F	0.009	2.40	9.24	14.5	15.6	6.45
<i>Blood pressure diastolic</i>						
Placebo	71 ± 3	-0.2 ± 2.4	0.1 ± 1.8	3.5 ± 2.6	-6.1 ± 2.7	-10.8 ± 2.6
5 mg BHT	74 ± 3	-3.3 ± 2.4	-9.4 ± 2.6*	-6.5 ± 3.5*	-10.8 ± 3.1	-12.1 ± 2.6
10 mg BHT	76 ± 4	-1.8 ± 2.1	-11.5 ± 3.2*	-12.2 ± 3.2*	-15.3 ± 2.5	-18.9 ± 3.0
F	0.58	0.44	5.72	6.35	2.75	2.75
<i>Sedation score</i>						
Placebo	14 ± 3	-0.7 ± 3.2	-2.1 ± 3.1	-2.5 ± 3.7	-3.8 ± 4.4	-1.0 ± 5.0
5 mg BHT	14 ± 3	3.4 ± 3.4	39.3 ± 10.0**	25.6 ± 6.8**	38.1 ± 6.5**	25.6 ± 11.3*
10 mg BHT	14 ± 3	6.7 ± 4.7	60.5 ± 9.1**	45.0 ± 7.2**	57.2 ± 8.0**	30.2 ± 8.0*
F	0.004	0.94	15.91	15.53	21.73	4.3

Results are means ± s.e. mean ($n = 12$) ** $P < 0.01$, * $P < 0.05$ significance compared with placebo

clonidine in that it is reported to have greater selectivity for α_2 -adrenoceptors (Timmermans & van Zwieten, 1980). Clough & Hatton (1981) examined a series of centrally acting hypotensive agents with varying selectivity for α_1 - and α_2 -adrenoceptors. Although there were exceptions, Clough & Hatton (1981) concluded that hypotensive activity was associated with α_1 selectivity whilst sedation was more associated with α_2 selectivity. Our results would support this view as relatively high doses of BHT 933 are necessary to produce hypotension and this is associated with marked sedation.

The hypotension produced by BHT 933 was dose dependent and the 10 mg dose of BHT 933 reduced the responses to the tests of autonomic reactivity. Even the response to the cold pressor test was reduced and our volunteers reported that this was not

due to any analgesic action of the drug. One volunteer given 10 mg BHT 933 felt nauseous and his sitting blood pressure was 62 mm Hg systolic and 44 mm Hg diastolic. These observations together with the tendency for systolic blood pressure to fall on standing, suggest that 10 mg BHT 933 might be above the optimum therapeutic dose.

The minimal effects of 5 mg BHT 933 on responses to autonomic tests together with its lack of effects on ventilation suggest the suitability of this oral dosage for further study with respect to both anti-tussive and antihypertensive activity.

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