THE EFFECT OF INDORAMIN ON PERIPHERAL BLOOD FLOW

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- 1 The effect of indoramin, a new hypotensive agent, on peripheral blood flows of six normal subjects was determined and compared to placebo in a double-blind, randomized study.
- 2 Indoramin (0.25 mg/kg), administered intravenously, resulted in an increased forearm muscle volume as measured by strain gauge plethysmography and an increase in the skin temperature of the hand but not to the skin of the chest.
- 3 It is concluded that these effects are the result of α -adrenoceptor blockade.

Introduction

Indoramin (Wy 21901; 3-(2-(4-benzamidopiperidyl)ethyl) indole hydrochloride) is a new anti-hypertensive agent which has been shown in animals to possess antihistamine, local anaesthetic and competitive α -adrenoceptor blocking properties (Alps, Hill, Johnson & Wilson, 1972). Investigations in human subjects have confirmed its competitive α -adrenoceptor blocking activities by demonstrating a shift to the right of the pressor dose-response curve to noradrenaline following intravenous indoramin (Coltart, Lockhart, Royds & Turner, 1971; Boakes, Prichard & Teoh, 1972) and also by antagonism of phenylephrine induced mydriasis (Coltart *et al.*, 1971).

α -blocking agents have well documented effects upon peripheral blood flow which have been put to use in the treatment of peripheral arterial insufficiency, particularly of those conditions comprising relatively large components of adrenergic vasoconstriction. It was decided, therefore, to investigate the effects of intravenously administered indoramin on peripheral blood flow by determining changes in skin temperature and forearm volume and compare them to those following placebo using a double-blind cross-over technique. Alterations of skin temperature have been widely used as an indirect index of changes in cutaneous circulation whilst muscle blood flow in the forearm can be estimated accurately by plethysmography (Whitney, 1953).

A brief report of this investigation was presented at the Fifth International Congress of Pharmacology, San Francisco, in July, 1972.

Methods

Six healthy adults (four female, two male), aged 21-26 years and weighing 54-73.3 kg, were observed resting over a period of 3 h on two mornings during which either indoramin 0.25 mg/kg (4 mg/ml in 5% dextrose) or an identical quantity of 5% dextrose was administered intravenously as a bolus dose in random order and double-blind fashion. Total doses varied between 13.5 mg and 18.7 mg indoramin.

All the investigations were carried out at the same time of day under identical conditions in the same room which was air conditioned, temperature $19^{\circ} \pm 1^{\circ}\text{C}$. The subject lay supine on an examination couch for the whole period. Half an hour was allowed for the subject to adjust to the environment. This was followed by a further period of half an hour during which control observations were carried out. Indoramin or placebo was then injected into the right antecubital vein and observations continued for 2 hours.

Skin temperatures were measured by means of two thermistors (Light Laboratories Ltd.), one applied over the sterno-clavicular joint and the other on the dorsum of the right hand attached to an electric thermometer from which the temperatures were read directly. Temperature changes of

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Fig. 1 Mean effect of indoramin (Δ) and placebo ($\bullet$) on skin temperature of the chest and hand. * values significantly different from those after placebo ($P < 0.05$).

0.05°C within the range 25°-40°C were detectable.

Observations were carried out at 5 min intervals during the control period and subsequently at 2 min intervals for the first 30 min after injection, 5 min intervals for the next 30 min and 10 min intervals for the final hour. Heart rates were counted over 1 min at the same intervals.

Forearm blood flow was measured in the left arm using a mercury-in-rubber strain gauge plethysmograph as described by Whitney (1953) and recorded on paper by an ink recorder. Two tracings were obtained on each occasion; their results were averaged and expressed as ml blood/100 ml forearm volume/minute. Measurements were made at intervals of 5 min during the control period and for the first hour after injection, and at 10 min intervals for the final hour. ECG recordings (lead II) were obtained at similar intervals.

Results

Skin temperatures

Mean temperatures recorded from the skin of the hand and the chest are illustrated in Figure 1. No difference between chest temperatures in the placebo or indoramin groups is evident before or after injection. Hand temperatures of both groups decline during the control period but 6 min after indoramin there is a rapid rise to a peak occurring at between 20-26 min whilst little change is noticed after placebo. The difference between the two groups is statistically significant ($P < 0.05$;

paired 't' test) from 14-24 min after injection whilst the maximum mean difference amounts to 1.8°C at 22 minutes. One subject showed an increase of 4.95°C following indoramin.

Heart rate

Mean heart rates for both groups are illustrated in Figure 2. No change is seen following indoramin and there is no significant difference between the treatments.

Forearm blood flow

Results of mean values ($\pm$ S.E.M.) obtained are shown in Table 1. In general the figures demonstrate lower values in the indoramin group during both the control period and later in the experiment, from about 30 min onwards. An increase in blood flow occurred from 10-20 min following indoramin which, although maximum at 20 min was only statistically significant ($P < 0.05$; Student's 't' test) at 10 and 15 minutes. The influence of two subjects (forearm blood flows of 2.69 and 1.47) largely accounts for the peak at 20 minutes. Figure 3 illustrates these changes in forearm blood flow, results from each group being based on percentage changes from the mean of the control period values which were taken as 100%.

ECG

No alteration to ECG tracings were seen following either placebo or indoramin.

Fig. 2 Mean effect of indoramin (▲) and placebo (●) on supine heart rate. None of the differences is significant.

Table 1 The mean values ($\pm$ S.E.M.) of forearm blood flow after indoramin and placebo.

Time (min)	Forearm blood flow (ml blood/100 ml forearm volume)			
	Indoramin		Placebo	
	Mean	S.E.M.	Mean	S.E.M.
-30	0.70	0.09	0.87	0.13
-25	0.64	0.07	0.91	0.15
-20	0.66	0.09	0.88	0.15
-15	0.61	0.08	0.81	0.13
-10	0.58	0.05	0.84	0.11
-5	0.57	0.56	0.79	0.09
0	0.56	0.06	0.89	0.11
5	0.68	0.11	0.81	0.09
10	0.85	0.09	0.75	0.09
15	0.81	0.15	0.82	0.13
20	1.15	0.34	0.80	0.12
25	0.77	0.08	0.82	0.15
30	0.65	0.05	0.82	0.12
35	0.67	0.05	0.77	0.13
40	0.66	0.06	0.80	0.13
45	0.57	0.04	0.76	0.13
50	0.63	0.06	0.70	0.80
55	0.56	0.09	0.71	0.09
60	0.63	0.09	0.82	0.10
70	0.61	0.12	0.80	0.09
80	0.62	0.12	0.89	0.15
90	0.57	0.08	0.79	0.06
100	0.48	0.06	0.73	0.07
110	0.44	0.04	0.78	0.10
120	0.46	0.05	0.76	0.06

Side effects

Four subjects reported feeling a flushing of the face within a minute of injection of indoramin but not lasting for longer than 5 minutes.

Discussion

Cutaneous vasomotor control is thought to comprise of predominantly vasoconstrictor mechanisms in some areas of the body and vasodilator in others. Vasoconstrictor responses are determined by α -adrenotropic receptor activity (Moran, 1970) whilst the vasodilator responses are of cholinergic (Brody & Shaffer, 1970) and β -adrenoceptor origin (Harrison & Turner, 1969). Fox, Goldsmith & Kidd (1962) have shown that the vasodilator responses of the skin of the neck and upper chest are the result of active vasodilatation whereas others (Warren, Walter, Romano & Stead, 1942; Gaskell, 1956) have demonstrated that vasodilatation of the skin of the hand is the result of release of vasoconstrictor tone. Circulation in skeletal muscle is controlled by several mechanisms (Ross, 1971); in general, however, vasoconstriction is mediated by α -adrenotropic activity whilst vasodilatation is determined by cholinergic and β -adrenotropic activity.

In the experiments described here, indoramin was shown to increase forearm muscle blood flow and cutaneous blood flow of the hand whilst the cutaneous circulation of the chest was unaffected.

As vasoconstrictor α -adrenoceptors are present in both the hand and forearm but absent from the

Fig. 3 Mean effect of indoramin (Δ) and placebo ($\bullet$) on forearm blood flow expressed as % change from mean of controls (100%) for each group. * values significantly different from those after placebo ($P < 0.05$).

chest these effects would seem to result from the release of vasoconstrictor tone. Vasodilatation from a direct action on vascular smooth muscle or through cholinergic or β -adrenergic mechanisms may be discounted because of the lack of effect on cutaneous blood flow of the chest and also because pharmacological investigations of indoramin in animals and man have not demonstrated that it possesses any such activities. These considerations argue that the effects of indoramin on peripheral blood flow are the consequence of α -adrenoceptor blockade.

Most vasodilator drugs, including all α -adrenoceptor blockers, induce a reflex tachycardia in order to maintain blood pressure following a reduction in peripheral resistance. Animal experiments (Alps, Borrows, Johnson, Staniforth & Wilson, 1972) have demonstrated that indoramin possesses negative chronotropic and inotropic properties associated with hypotension and early studies in hypertensive patients (Royds, 1972) have tended to confirm these observations by demonstrating a reduction of blood pressure with-

out any alteration to heart rate, although Boakes *et al.* (1972) reported an increased heart rate on tilting following indoramin. In this study heart rate was not altered by indoramin, but it is probable that blood pressure was not significantly reduced in these subjects who were supine throughout the experiment.

However, the often troubling and dose limiting side effect of tachycardia experienced with vasodilator drugs in general might be avoided to advantage with indoramin, provided that an effective therapeutic dose level for adequate vasodilatation is achieved before significant hypotension occurs.

Indoramin might, therefore, offer a theoretically appropriate treatment for peripheral arterial insufficiency where the condition is largely the result of sympathetic vasoconstriction and further investigations in patients are indicated to determine its effects in such circumstances.

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