Hypotensive Action of Pronethalol

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Ahlquist (1948) proposed the division of the adrenergic sites of action into alpha and beta receptor groups. The beta receptors include the adrenergic effects on the heart and relaxation of bronchial muscle; the alpha group include the contraction of smooth muscle, such as vasoconstriction in certain vascular beds. Noradrenaline was found to have almost entirely alpha effects, isoprenaline almost purely beta actions; adrenaline has both. The classical adrenergic blocking drugs, such as phenoxybenzamine, block only the alpha receptors; hence they do not prevent the action of adrenaline on the heart. The first agent discovered which blocked the beta receptors was dichloroisoprenaline (Powell and Slater, 1958; Moran and Perkins, 1958); however, it was soon shown to have potent sympathomimetic effects of its own.

Pronethalol is an adrenergic beta-receptor-blocking agent which is free from any sympathomimetic activity. Its animal pharmacology was described by Black and Stephenson (1962). After its slow intravenous administration to anaesthetized cats they found a slight fall in blood-pressure associated with peripheral vasodilatation, while rapid injection gave a sharp fall in blood-pressure associated with myocardial depression. Dornhorst and Robinson (1962) found an increase in forearm blood-flow in man for the duration of an intra-arterial infusion of pronethalol but no consistent effect on blood-pressure after intravenous administration.

The effect of pronethalol on the blood-pressure is reported here in 15 patients taking the drug orally for three months, and in patients and normal subjects after a single intravenous injection: four normotensive patients were receiving pronethalol for angina pectoris; the remaining 11 were hypertensives.

Results

The effects of oral administration are summarized in the Table. The subjects have been divided into six groups as indicated. The mean fall in blood-pressure for all groups was: supine, 33/23 mm. Hg; standing, 27/16 mm. Hg. The dose of other hypotensive agents was not altered during pronethalol administration.

Effect of Oral Pronethalol on the Blood-pressure

Group	Mean of Last 3 B.P. Readings Prior to Pronethalol		B.P. Prior to Any Hypotensive Drugs	Fall in B.P. after Treatment with Pronethalol		Doses in mg./day; 2–4 Divided Doses
	Supine	Standing		Supine	Standing	
Hypertensives:						
1. No previous hypotensive drugs	207/110	200/108	—	10/14	8/10	800
	203/118	184/113	—	70/44	46/15	200
	195/104	177/103	—	55/22	37/15	1,600
2. On guanethidine	207/113	180/110	205/115	35/17	10/10	800
	195/115	166/114	300/130	55/27	58/24	400
	182/108	156/106	260/160	49/28	36/36	800
3. On bethanidine	213/140	179/138	245/160	22/21	25/28	1,600
4. On reserpine	193/108	193/112	200/125	38/32	53/22	800
	157/83	—	200/110	30/8	—	1,000
5. On chlorothiazide	207/110	193/112	290/140	12/25	3/22	400
	213/128	220/120	250/140	23/18	40/15	800
Normotensives	126/89	—	—	29/30	—	400
	148/93	137/80	—	10/18	17/6	600
	163/87	—	—	17/8	—	1,200
	120/68	120/70	—	36/28	36/10	1,000

Mean fall in blood-pressure: Supine: systolic 33 mm. Hg, S.E. ± 4·70, $P < 0.001$; diastolic 23 mm. Hg, S.E. ± 6·25, $P < 0.005$. Standing: systolic 27 mm. Hg, S.E. ± 5·37, $P < 0.001$; diastolic 16 mm. Hg, S.E. ± 5·23, $P < 0.01$.

During a double-blind trial of pronethalol in angina pectoris (unpublished data from Prichard, Dickinson, Alleyne, Hurst, Hill, Rosenheim, and Laurence, 1963) supine blood-pressure averaged 8.3/5.7 mm. Hg lower on pronethalol than on placebo ($P<0.05$). The mean standing diastolic pressure was reduced by 4.8 mm. Hg ($P<0.05$) and the mean standing systolic pressure by 6.5 mm. Hg ($P>0.05$). In each patient four readings were taken at weekly intervals on both pronethalol and placebo.

Five infusions of 100 mg. of pronethalol at 10 mg./min. in four normotensive volunteers produced no significant change in the blood-pressure, confirming the findings of Dornhorst and Robinson (1962). Eight infusions were given to five volunteer hypertensives. Five showed no change, but in three infusions (two patients) there was an increase in blood-pressure of between 15/15 and 60/35 mm. Hg.

On three occasions the effect of intravenous pronethalol on the response to Valsalva's manœuvre in hypertensives was studied. There appears to be a reduced reflex rise of blood-pressure and pulse rate during the effort and a reduced pulse-pressure in a diminished overshoot after release.

In four volunteer hypertensive patients—two on no other hypotensive therapy and two on guanethidine—there was no appreciable difference in the alteration of blood-pressure and pulse when they were tilted to 45 and 90 degrees, before and after intravenous pronethalol. Pronethalol produced no appreciable alteration of the effects of exercise, supine and erect.

Comment

In all of 11 hypertensive patients on pronethalol there has been a considerable fall in blood-pressure, with the absence of postural hypotension. Side-effects, chiefly tiredness, were avoided by carefully adjusting the dose. The slight hypotensive action seen in the double-blind trial in angina pectoris, where placebo and drug were given for two fortnightly periods in randomized order, may be due to the fact that longer administration is needed to produce maximal effect. The lack of hypotensive action after intravenous administration is in accord with this. The rise in blood-pressure seen after three infusions might be due to anxiety. Though the hypotensive action apparently takes some time to develop, pronethalol seems to have an immediate effect on cardiovascular reflexes, as shown by its modification of the response to Valsalva's manœuvre.

The hypotensive effect is probably due to block of the positive chronotropic and inotropic effects of the sympathetic nerves on the heart. Pronethalol does not block peripheral vasoconstrictor α effects.

It is well known that hypertensive patients may overact to many cardiovascular stimuli. Interference with the cardiac component of such responses might exert a useful effect in preventing the transient rises in blood-pressure that so readily occur in hypertensives, and so be valuable in therapy.

It does not seem likely that pronethalol exerts its hypotensive action by a peripheral effect on the blood-vessels, although Dornhorst and Robinson (1962) showed a vasodilatation during intra-arterial infusions in man, and blood-flows rapidly returned to control levels after the end of the infusion. This is an immediate effect, and intravenous pronethalol in the doses used does not produce any immediate fall in blood-pressure. In addition, an agent producing appreciable hypotension by peripheral vasodilatation would be expected to produce postural hypotension.

We have not further investigated the hypotensive action of pronethalol in view of its tumour-producing action in mice,

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even though this is absent in rats and dogs (Paget, 1963), and we therefore think it should be given over long periods only to patients with a poor life expectancy. However, when a non-carcinogenic beta-receptor-blocking drug is produced it would be worth trying in the treatment of hypertension.

SUMMARY

Pronethalol, an adrenergic beta-blocking drug, has been found to have a hypotensive action in man.

After intravenous administration no hypotensive effect is seen. After short-term oral administration in a double-blind trial in angina pectoris (Prichard *et al.*, 1963) there was a small but statistically significant hypotensive action.

After three months' use in 15 patients, 11 of whom were hypertensives, there was a mean fall in blood-pressure of 33/23 mm. Hg supine and 27/16 mm. Hg standing. This effect may be due to block of sympathetic nerves to the heart.

However, in view of its carcinogenic properties pronethalol should not be used in the treatment of hypertension.

I am indebted to I.C.I. Pharmaceuticals for the supply of pronethalol used in this study.

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Medical Memoranda

Hydatidiform Mole Misdiagnosed as Chorioncarcinoma

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In the field of malignant disease diagnostic mistakes are rare except in one condition—chorioncarcinoma. Out of 159 cases submitted as chorioncarcinoma to the Albert Mathieu Chorion-epithelioma Registry, Novak and Seah (1954b) found that 85 (53%) were benign conditions, among which were 61 cases of hydatidiform mole. Cytotoxic therapy is now thought to be indicated in the treatment of chorioncarcinoma (Hertz, Bergenstal, Lipsett, Price, and Hilbish, 1959; Bagshawe and McDonald, 1960; Chan, 1962; Bagshawe, 1963), but these papers also record the very severe side-effects of this therapy. This case of hydatidiform mole is reported because it was initially diagnosed as chorioncarcinoma, and the patient, after hysterectomy, was saved from massive cytotoxic therapy only by a fortuitous severe gingivitis.

It sounds a note of caution regarding the use of cytotoxic agents outside specialized centres and underlines the necessity for all similar cases to be transferred to such centres for diagnosis and treatment.

CASE REPORT

A married European woman aged 26, who had borne one child, was transferred to St. Thomas's Hospital on 24 March 1962 from another hospital with a diagnosis of chorioncarcinoma, the husband having been informed of the appalling prognosis. Her last menstrual period had taken place 12 weeks previously but she had been bleeding intermittently per vaginam for four weeks before admission. On examination she was pale and grossly dyspnoeic. The uterus was enlarged to the size of a 32-week pregnancy but no foetal parts could be felt and radiography disclosed no evidence of calcification. A Hogben test was positive to a dilution of 1:100 but negative in dilutions beyond this. The haemoglobin was 43%, and after transfusion of three pints of packed cells rose to 70% without clinical improvement. There was no evidence of pre-eclampsia. A radiograph of the chest showed diffuse miliary shadows suggestive of multiple secondary deposits. As a result of these findings it was decided to perform an examination under anaesthesia and laparotomy. Bimanual examination confirmed the previous findings but resulted in profuse uterine bleeding. A total hysterectomy was performed mainly to control this severe haemorrhage, but partly because chorioncarcinoma remained a likely diagnosis. Yellow cysts were present in both ovaries, on one of which a biopsy was carried out.

Pathological Findings.—The cavity of the uterus contained typical molar vesicles but there was no macroscopic evidence that the mole had penetrated to the outer surface of the uterus. Histological sections showed numerous avascular hydropic villi with areas of trophoblastic hyperplasia. The myometrium was infiltrated by hyperplastic trophoblast and in some areas there were malignant-looking pleomorphic cells destroying muscle fibres (Fig. 1). Numerous vascular channels in the myometrium contained similar pleomorphic cells (Fig. 2). These findings were reported as: "A partly necrotic hydatidiform mole showing apparently malignant features." The ovarian biopsy showed theca lutein cysts.

Post-operative Course.—In view of the chest radiograph and the histological report it was decided that cytotoxic therapy should be started immediately, but owing to a severe post-operative gingivitis this had to be withheld. The patient's recovery was dramatic, with a spontaneous clearing of the lungs that was radiologically complete by the third post-operative week. She was discharged on 9 May 1962 and was last seen on 8 November 1963, 20 months after

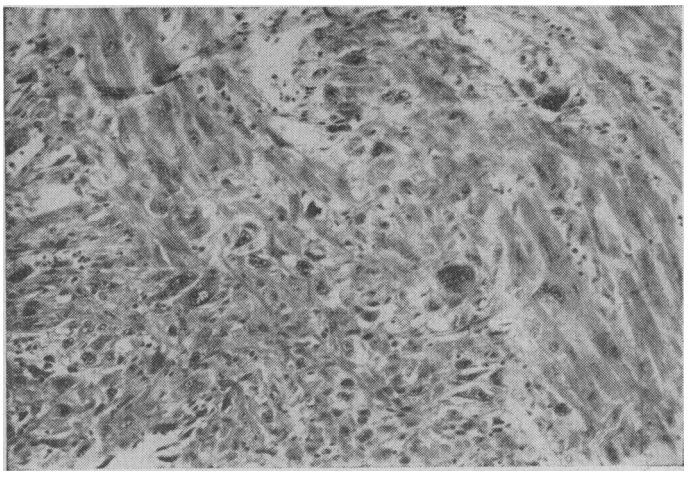

FIG. 1.—Photomicrograph showing malignant-looking cells infiltrating and destroying myometrium. (×90.)