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A model for evaluation of thiazide-induced hypotension

The clinical efficacy of thiazide treatment alone or in combination with hypotensive drugs has long been recognized. Patients respond to chronic thiazide administration with a gradual decrease in blood pressure and a maximum response within 3–4 weeks after initial treatment. When the treatment is terminated an elevated pressure is resumed within 1–2 weeks. The hypotensive activity of the thiazides has been postulated to reside in the apparent decrease in body sodium and plasma volume (Dustan, Cummings & others, 1959; Friedman, Nakashima & Friedman, 1960). It is interesting to note, however, that thiazide treatment does not result in blood pressure lowering in rats with reno-vascular occlusive hypertension, which has been shown to be accompanied by a larger than normal amount of tissue sodium (Tobian & Coffee, 1964; Redleaf & Tobian, 1958). Hypertension induced by deoxycortone acetate and NaCl is also accompanied by an elevated tissue sodium (Tobian & Redleaf, 1957). I have made experiments to determine if production and maintenance of steroid and salt hypertension can be inhibited with chronic thiazide administration. These results have been compared with the clinical situation.

Hypertension was produced in two groups (A and B) of weanling (21 days) Sprague-Dawley rats by implanting two 25 mg pellets of deoxycortone acetate subcutaneously in the dorsal neck region. The animals were fed a Purina Laboratory diet containing 8% NaCl for the following 10 weeks and then regular Purina Laboratory diet was resumed. Animals in Group A received a placebo suspension subcutaneously for 16 weeks and animals in Group B a 10 mg/kg cyclothiazide suspension.

A sham operation was made on Group C and cyclothiazide was administered in an acacia suspension (10 mg/kg, s.c.) daily for the following 16 weeks. These animals were not fed the salt diet.

Group D was made hypertensive in a manner similar to A and B, however thiazide treatment (10 mg/kg, s.c.) was not started until 13 weeks after initial induction of hypertension. Thiazide administration was continued for 14 weeks and the animals were maintained throughout on the 8% NaCl diet.

Blood pressures were measured by an indirect method each week (Willard, Powell & Henderson, 1964). Where applicable Student's *t*-values were accepted as significant at $P < 0{\cdot}05$.

As in previous experiments with this technique, hypertension developed after 3–6 weeks treatment with the steroid and salt (Fig. 1). The concomitant treatment with cyclothiazide did not alter the time for production or degree of hypertension. Since there is no difference in blood pressure between Groups A and B during the production of hypertension, it may be that the elevation in pressure is due to a "sodium load",

which the dose of cyclothiazide fails to reduce sufficiently. When the animals were returned to normal diet (14 weeks) the blood pressure fell in both groups of rats, but the fall was greater in animals treated with cyclothiazide (Fig. 1). At 16 weeks a significant difference (40 mm Hg, $P < 0{\cdot}05$) between Groups A and B to thiazide treatment became evident.

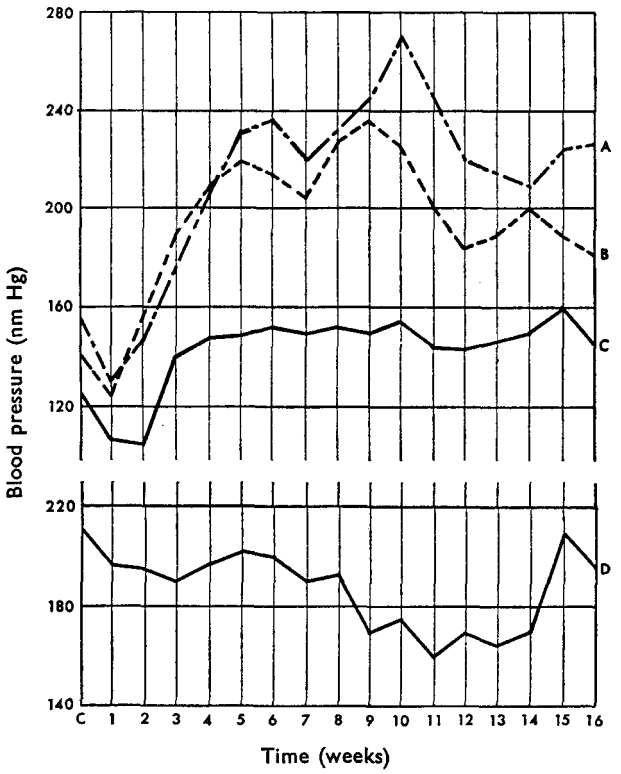

FIG. 1. Deoxycortone acetate-hypertensive rats in Groups A and B. Normotensive animals in Group C. Group A was the hypertensive control and Groups B and C received cyclothiazide 10 mg/kg daily for 16 weeks.

Group D was composed of animals with established deoxycortone acetate hypertension and was treated with cyclothiazide for the first 14 weeks.

The delayed response in Groups A and B with cyclothiazide suggested that long-term administration of drug might be necessary to produce hypotension. In other studies involving rats with reno-vascular occlusion (Tobian & Coffee, 1964; Tobian, Janacek & others, 1962; Renzi, Chart & Gaunt, 1959), the thiazide was probably administered for too short a duration to produce blood pressure lowering. Group D had been hypertensive for 13 weeks when the thiazide treatment was started. The 14 week treatment resulted in a gradual fall in blood pressure (Fig. 1). After 14 weeks when the treatment was stopped the blood pressure resumed the original hypertensive level. The contrast between the slow hypotensive response and relative fast recovery of hypertension corresponds to results obtained clinically. Since the animals were maintained continuously on 8% NaCl during the entire 16 weeks, the factor affected by cyclothiazide, possibly body sodium, is slow to respond. However, orthodox knowledge implies that the decrease in sodium and in expanded extracellular fluid should change within a few days after the start of thiazide treatment.

It is known that normotensive animals respond to thiazide treatment with NaCl excretion and diuresis (Renzi & others, 1959). However, the thiazide-treated normotensive animals in Group C did not have a blood pressure lower than has been observed in previous studies which employed the indirect technique for blood pressure measurement (Willard & others, 1964). Thiazide treatment also has little blood pressure lowering activity in normotensive patients.

These experiments demonstrate a similarity between clinical results and the animal model.

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