

## Response of Metacorticoid Hypertension to Bistrium, Apresoline, Veriloid and Serpentina. (20554)

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Metacorticoid, or post-DCA, hypertension is a self-sustaining cardiovascular disease attained in rats approximately 2 months after the implantation of a desoxycorticosterone acetate (DCA) pellet and the substitution of saline for drinking water(1-4). In many respects this type of hypertension appears similar to essential hypertension in man(1,5); as a consequence, it should prove useful for screening compounds of possible value in the treatment of humans. To test this hypothesis, we have investigated the activity of several agents known to have some effect in essential hypertension: Bistrium (hexamethonium iodide, Squibb), Apresoline (1-hydrazinophthalazine, Ciba), Veriloid (a purified alkaloidal fraction of *Veratrum viride*, Riker), and Serpentina (powdered roots of *Rawwolfia serpentina*, Penick).

**Materials and methods.** Acute experiments: Groups of male Sprague-Dawley rats were used which had received a single 20 mg pellet of DCA 3 to 6 months previously, and had been maintained on 0.86% NaCl solution and Rockland Rat Diet *ad libitum*. The systolic blood pressures of treated rats were estimated with a photoelectric tensometer(6) immediately before and 2, 4½, 6½ and 25 hours after treatment, and were compared to simultaneous readings from saline-injected controls. The mean blood pressure of over 400 normal rats has been determined by the tensometer method as 120 mm Hg, with a standard deviation of 10. Pressure readings on individual rats were made in ignorance of the treatment the rat had received and of the previous pressure reading. Each test was completed by one person on the same tensometer in a darkened room at constant temperature. The rats were trained for at least 3 months before testing, and were deprived of food and saline from the first pressure reading until after the 6½-hour reading. Saline solutions of

Bistrium, Apresoline, and Veriloid were administered by stomach tube or subcutaneous injection at several dose levels (Table I). Although the *t*-tests for significance(7) utilized data from single control experiments, these data are averaged in Table I for brevity. Chronic experiment: Wilkins and Judson(8) reported that the response of hypertensive patients to *Rawwolfia serpentina* usually is not seen until after 3 to 6 days of administration. Accordingly, for 10 days 6 hypertensive rats (mean weight = 440 g) were offered *ad libitum* ground Rockland Rat Diet containing 5% powdered *R. serpentina* roots. Six hypertensive controls of similar body weight received Rat Diet only; both groups were offered 0.86% NaCl solution to drink. Blood pressures were taken as above, immediately before, and after 3, 5, 7, and 10 days of treatment (Table I).

**Results and discussion.** Single injections of Bistrium, Apresoline, and Veriloid significantly reduced blood pressures below simultaneous control readings, although when normotension was achieved, it was not generally maintained over the 25-hour period. On a dosage basis, Veriloid appeared to be the most active of the 3 compounds tested acutely. On the other hand, Bistrium and Apresoline, in the doses employed, seemed to have a greater duration of effect.

Serpentina was effective when administered in the food over a several day period. Assuming a food consumption of 80 g/kg/day (unpublished data), these rats were receiving approximately 4 g of root/kg/day.

Metacorticoid hypertension is not ameliorated by removal of the adrenals, thyroid, parathyroids or gonads, nor by drastic dietary restriction of Na or K(1). Hypophysectomy (2) and nephrectomy(3) abolish the hypertension, while Dibenzamine(1) and certain 11,17 derivatives of 4-androsten-3-one(9) lower the blood pressure temporarily. The

TABLE I. Therapy of Metacorticoid Hypertension.

| Treatment  | Dose,<br>mg/kg | Route* | No.<br>rats | Mean blood pressure of treated rats, mm Hg |            |           |           |            |
|------------|----------------|--------|-------------|--------------------------------------------|------------|-----------|-----------|------------|
|            |                |        |             | Before<br>inj.                             | 2 hr†      | 4½ hr     | 6½ hr     | 25 hr      |
| Apresoline | 5              | SC     | 3           | 193                                        | 175        | 179       | 183       | 180‡       |
|            | 10             | "      | 8           | 192                                        | 154‡       | 157       | 167       | 180        |
|            | 25             | "      | 4           | 189                                        | 162§       | 150§      | 146§      | 152§       |
|            | 200            | ST     | 3           | 189                                        | 170‡       | 176       | 198       | —          |
| Control    |                |        | 20          | 192                                        | 192        | 187       | 189       | 191        |
| Bistrium   | 32             | SC     | 8           | 188                                        | 185        | 157§      | 148§      | 166§       |
|            | 40             | "      | 8           | 189                                        | 145§       | 148§      | 158§      | 181‡       |
|            | 20             | ST     | 4           | 189                                        | 185        | 184       | 181       | 192        |
|            | 320            | "      | 4           | 198                                        | 138§       | 181       | 167       | 156§       |
| Control    |                |        | 24          | 192                                        | 190        | 188       | 190       | 193        |
| Veriloid   | .05            | SC     | 4           | 200                                        | 203        | 188       | 190       | 194        |
|            | .10            | "      | 4           | 200                                        | 190‡       | 186§      | 178§      | 188        |
| Control    |                |        | 8           | 200                                        | 198        | 199       | 202       | 198        |
|            |                |        |             | Before<br>inj.                             | 3<br>days† | 5<br>days | 7<br>days | 10<br>days |
| Serpentina | 5% in food     |        | 6           | 177                                        | 142§       | 146‡      | 139‡      | 144‡       |
| Control    |                |        | 6           | 178                                        | 183        | 168       | 166       | 170        |

\* SC = subcut.; ST = by stomach tube.  
 ‡ P < .05 that treat mean = control mean.

† Indicates hr or days after inj.  
 § P < .01 that treat mean = control mean.

present data do not contradict the thesis that metacorticoid hypertension closely resembles those cases of essential hypertension in which the maintenance of elevated blood pressure does not involve adrenocortical participation(1).

**Summary.** Single injections of Bistrium, Apresoline, and Veriloid induced significant temporary reductions in the blood pressure of rats with metacorticoid (post-DCA) hypertension. Similar rats treated chronically with Serpentina root exhibited a sustained depression of blood pressure.

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