Endocrine Effects of p,p'Diaminochalcone. (28853)

ROY HERTZ AND WILLIAM W. TULLNER
Endocrinology Branch, National Cancer Institute, NIH, Bethesda, Md.

Since the initial demonstration of the inhibitory effects of amphenone on adrenal cortical steroid secretion in numerous species(1, 2,3), there have been subsequent reports of other inhibitors of adrenal cortical steroid production(4,5). In further studies we have investigated the endocrine effects of a series of chalcones, a class of compounds distinctly different from those previously reported. Experiments described here show that p,p'diaminochalcone (Fig. 1), like amphenone, inhibited corticosteroid secretion in dogs although this compound failed to produce certain endocrine effects observed in ovariectomized rats and in estrogen-primed female rabbits following amphenone treatment.

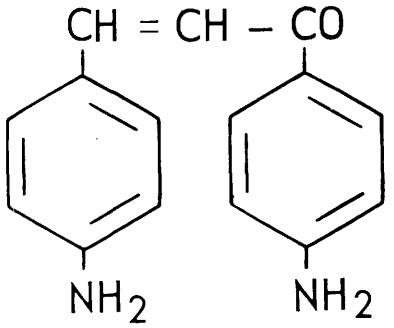

FIG. 1. Structural formula of p,p'-diaminochalcone.

Materials and methods. Aqueous solutions of p,p'diaminochalcone dihydrochloride were given except in the case of the rats in which propylene glycol suspension of p,p'diaminochalcone was used.

In dog studies adult male and female mongrels were used. Body weights ranged from 10-15 kg. Intravenous p,p'diaminochalcone solutions were administered rapidly. Procedures for adrenal vein cannulation and 17-hydroxycorticoid determination (Porter-Silber) have been described(6). In 2 of the dogs, chromatograms of adrenal vein plasma extracts were run in the Bush (B-4) system for qualitative detection of cortisol(7).

In studies on the rat, Sprague-Dawley strain females were ovariectomized at 70 days of age. Treatment was started 7 weeks later. The compound was administered daily by gavage in 0.5 ml solution. Animals were killed with chloroform and body and organ weights were recorded.

A modified Clauberg assay was used to assess progestational activity(8). Rabbits were given subcutaneous injections of test compounds.

Results and discussion. Dog adrenal corticoids. A reduction in output of 17-hydroxycorticoids occurred 5 minutes after rapid intravenous administration of p,p'diaminochalcone in each of 6 dogs. Doses of 25, 65 and 75 mg/kg were used. At a dose level of 25 mg/kg, corticosteroid output returned to normal in 30 minutes. In a dog at the highest dose (75 mg/kg), corticosteroid secretion returned to a normal level after 120 minutes (Fig. 2). Arterial blood pressure and adrenal vein blood flow were unaltered by drug treatment. The degree of suppression of 17-hydroxycorticoids (Porter-Silber chromogens) by p,p'diaminochalcone was similar to that of amphenone at comparable doses(6). In 2 dogs, adrenal vein blood samples were collected just prior to and 5 minutes after di-

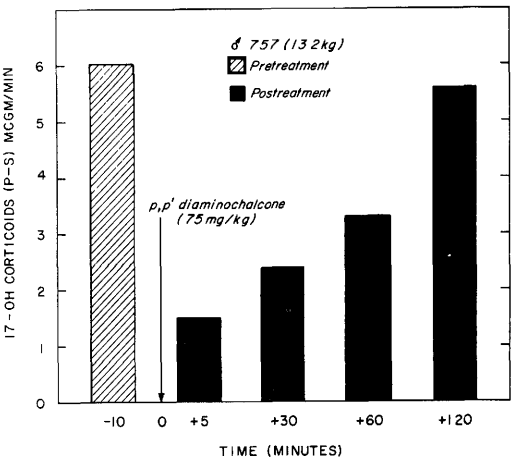

FIG. 2. Effects of treatment with p,p'-diaminochalcone on 17-hydroxyeorticoid output in the intact dog.

TABLE I. Effect of p,p'Diaminochalcone in Castrated Female Rats.

Treatment	Total dose, mg	Body, g	Adrenals, mg	Uterus, mg	Thyroids, mg
Chalcone*	250	281 ± 16	85 ± 9	70 ± 9	15 ± 3
None	—	278 ± 17	61 ± 4	68 ± 4	11 ± 2

* Free base suspended in propylene glycol given orally in 0.5 cc daily for 5 days. 5 rats per group. Weights given are mean and standard deviation.

aminochalcone administration. In chromatograms of these plasma extracts, cortisol content was found to be greatly diminished after drug treatment.

Endocrine organs, ovariectomized rats. Effects of p,p'diaminochalcone on adrenal, uterine, and thyroid weights of ovariectomized rats were tested in several series of animals. Table I summarizes data from such an experiment. In this series in which p,p'diaminochalcone (free base) was administered orally at 250 mg total dose, there was a significant increase in adrenal weight, ($p<.01$) and the enlarged adrenals exhibited the characteristic yellowish discoloration seen after amphenone administration. Thyroid and uterus weights, however, were unchanged. Treatment with p,p'diaminochalcone dihydrochloride did not alter weights of these tissues in comparable groups of rats. Slower absorption of the free base might account for the adrenal effect.

Rabbit assay for progesterone. Estrogen-primed, immature female New Zealand white rabbits (3 animals per group) were given 5 daily subcutaneous injections as follows: Group I, p,p'diaminochalcone dihydrochloride, 200 mg; Group II, progesterone, 0.1 mg. There was no endometrial response to diaminochalcone. Progesterone produced a maximum endometrial proliferation (+4). It was also noted that intravenous infusion of the chalcone (200 mg/kg) induced anesthesia in the rabbit. Doses of 400 mg/kg caused respiratory arrest.

On the basis of these results, it is apparent that inhibitory effects on adrenal steroid output in dogs, adrenal enlargement and discoloration in rats, and anesthetic action in rabbits are common to both p,p'diaminochalcone and amphenone.

Summary. The compound p,p'diaminochalcone inhibited cortisol production in intact dogs, increased adrenal weight and induced a yellowish discoloration of the adrenals in ovariectomized rats, and possessed anesthetic action in rabbits. Unlike amphenone, this compound did not elicit uterine and thyroid weight increases in the ovariectomized rat nor did it induce progestational effects in rabbits.

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