Species Differences in Lipid and Endocrine Gland Responses to a Stilbene Derivative

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A stilbene derivative, α-(*o*-anisyl)-β,β-diphenylacrylic acid, administered to healthy male adults did not affect, as it did in certain experimental animals, food intake, body weight, serum lipid levels, thyroid activity, adrenocortical function, or the other endocrine indices tested.

A DERIVATIVE of the stilbenes, α-(*o*-anisyl)-β,β-diphenylacrylic acid,[1] at dosages of 10 mg./Kg./day or higher, exerts a hypocholesterolemic effect in the mouse, rat, and dog, but not in the monkey (1). Studies in experimental animals have also demonstrated that ingestion of the compound is accompanied by an absolute or relative decrease in seminal vesicle and prostate weights and increases in pituitary, thyroid, and adrenal size. The adrenomegaly in such animals is associated with decreased adrenocortical function, judging from a delayed excretion of a water load, decreased tolerance to cold stress, and diminished corticogenesis *in vitro* in adrenals from rats pretreated with this derivative. Estrogenic effects have also been observed during such therapy and in the rat the compound has been found to inhibit the ovarian hypertrophy which follows unilateral ovariectomy. This derivative exerted a profound anorexigenic effect in the mouse, adult rat, and rabbit resulting in a marked loss of weight, but this was not evidenced in the dog or monkey. It has been suggested that the hypocholesterolemic effect in animals may be related to decreased food intake and that the compound probably exerts antithyroid, antiadrenocortical, and antigonadotropic actions (1).

The studies reported here indicate that in healthy adult males comparable dosages, up to 800 and 1600 mg./day for 1 month or longer, neither affected body weight, serum cholesterol, triglycerides, or other solutes, nor did it produce changes in indices of the thyroid, adrenocortical, adrenomedullary, or other endocrine gland function.

MATERIALS AND METHODS

The derivative of stilbene was administered *per os* to 14 healthy adult male prisoners in increasing dosages: 50 mg. daily for 3 weeks, followed by 100 mg. daily for 3 weeks, 200 mg. daily for 3 weeks, 400 mg. daily for 4 weeks, and 800 mg. daily for 4 weeks. In another group of four men 1600 mg. was administered daily for 4 weeks.

Blood and serum solutes (venous blood sugar and NPN) and serum CO_2, Cl, Na, K, albumin, globulin, calcium, inorganic phosphorus, uric acid (2), creatinine (3), total and α- and β-lipoprotein cholesterol and triglycerides (4–7), NEFA (8), and protein bound iodine (9) were measured in samples obtained at 6:30 to 7:00 a.m. during the fasting state on two occasions 1 week apart prior to therapy. The same studies were repeated at the end of each dosage period.

Urinary 17-ketosteroids (10), Porter-Silber chromogens (11), 11-desoxycortisol metabolites (12), pressor materials as measured by aortic strip assay (13), and gonadotropins (14) were determined in 24-hr. refrigerated specimens of urine prior to and during the administration of 400, 800, and 1600 mg. per day.

Plasma 17(OH) corticosteroids (15) were measured at weekly intervals prior to and during therapy in samples of venous blood obtained between 6:30 and 7:00 a.m.

The response of plasma 17(OH) corticosteroids to exogenous ACTH [80 units (Parke-Davis) in 500 ml. of 5% dextrose in water] administered by intravenous infusion during a 6-hr. period was examined before and during therapy with the compound at 400 mg./day for 4 weeks and 1600 mg./day for 4 weeks. The plasma corticosteroid levels were measured in samples of blood obtained just before the infusion and just at the end of the infusion.

The effects of intravenously administered rapidly acting insulin (0.1 unit/Kg. of body weight injected intravenously) upon venous blood sugar and serum inorganic phosphorus levels, were assessed prior to and during the 12th week of therapy when the dosage had reached 400 mg./day.

Certain hepatic indices (serum bilirubin, cephalin flocculation, thymol turbidity, alkaline phosphatase in addition to serum albumin, globulin, and lipids already cited) were obtained before and during therapy. Renal status was evaluated by means of routine urine analyses and creatinine clearance on two occasions prior to and two others during therapy. The hemoglobin and relative blood cell volume (hematocrit) were also measured on the above schedule.

RESULTS

The drug was taken without evoking any symptoms or signs. Body weights were of the same order of magnitude prior to and during therapy. Therapy

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[1] Supplied by Smith Kline & French Laboratories, Philadelphia, Pa., as SK&F 16046.

was not associated with any change in the venous blood sugar or NPN or the serum CO_2, Cl, Na, K, Ca, inorganic phosphorus, albumin, globulin, and uric acid. The serum total cholesterol and triglycerides and their respective α and β lipoprotein fractions remained unchanged. Serum PBI levels were not altered during therapy. The excretion of urinary 17-ketosteroids, Porter-Silber chromogens, and 11-desoxycortisol metabolites expressed in mg./day/1.0 Gm. of creatinine was essentially the same before and during ingestion of this compound. During therapy the fasting a.m. levels of plasma 17(OH) corticosteroids did not differ significantly from the values recorded during the control period.

The plasma 17(OH) corticosteroid responses to intravenous ACTH prior to and during administration of the compound were of the same order of magnitude. Therapy for 12 weeks was not accompanied by significant alteration in the hypoglycemic or hypophosphatemic effects of intravenously administered rapidly acting insulin. The urinary excretion of gonadotropins, urinary pressor activity (aortic strip assay), serum creatinine, and creatine clearances and routine urine analysis were unchanged at the end of the treatment period. Hepatic indices and the hematocrit and hemoglobin remained within the pretherapy range during ingestion of this agent.

DISCUSSION

None of the effects of this derivative of the stilbenes, variously observed in some but not all species of experimental animals tested (1), could be discerned in the trials in healthy male adults described here. Thus, anorexia, weight loss, and hypocholesterolemia (perhaps related to decreased food intake) did not occur. Also indices of pituitary, thyroid, adrenocortical, adrenomedullary, and gonadotropic and other endocrine gland function were not affected. Blood sugar responses to intravenous insulin were not changed. The compound did not alter the hepatic indices tested. In other words, effects of this stilbene derivative, observed in certain species of experimental animals, were not evident in healthy male adults receiving this compound in comparable dosages.

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Effects of Certain Preservatives on the Aging Characteristics of Acacia

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The rheological characteristics of acacia solutions of various concentrations were examined. Based on the results, a series of 25 per cent acacia solutions using five different preservatives and two combinations of preservatives were studied for a period of 1 year. Rheological, pH, and organoleptic data were obtained in order to describe the aging characteristics of the solutions. In each case, the results showed a reduction in pH and viscosity, which was most pronounced in the unpreserved control solution. Possible reasons for the decrease, as well as for the rate at which it occurred, are discussed.

ACACIA HAS been in use for at least 4000 years and yet comparatively little quantitative research appears in the literature (1). Curiously, in spite of the popularity enjoyed by this polysaccharide as a protective colloid and emulsifier in numerous pharmaceutical preparations, only a handful of findings pertaining to its aging characteristics are reported.

Taft and Malm (2) found that bacterial growth appeared in dilute solutions of gum arabic 36–48 hr. after preparation. Osborne and Lee (3) carried out experiments to establish the effect of aging upon preserved and unpreserved acacia mucilages. The preservative used was 0.2% benzoic acid. These investigators reported an initial rise and an eventual decrease in the viscosity of the mucilages. They further observed a considerably greater decrease in the viscosity of the unpreserved mucilage than of the preserved one. Joslin and Sperandio (4) reported that acacia mucilages prepared with boiling water exhibited a reduction in viscosity over a period of 8 weeks. However, the authors stated that this decrease in viscosity was less pronounced than the reduction occurring in those mucilages prepared with water at room temperature. They further noted that the acacia mucilages became slightly more acidic during the aging period.

Recently, Ory and Steiger-Trippi (5) reported the changes in viscosity observed after 1 month's

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