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Protective Effect of Digitoxin in Adrenal-Compression Hypertension[1] (39370)

S. AYACHI AND C. E. HALL

Department of Physiology and Biophysics, University of Texas Medical Branch, Galveston, Texas 77550

Digitalis and its derivatives are the drugs of choice in the treatment of congestive heart failure, although, despite the many studies on the pharmacology of this class of compounds, their mode of action is still unclear.

Their effect on blood pressure is reported to depend on the integrity of reflexogenic areas of the cardiovascular system (1) and the presence or absence of heart disease (2). Therefore, in response to glycoside administration, blood pressure may increase (3-5), decrease (6, 7), or not change (8).

Selye (9) reported that rats treated with digitoxin (in conjunction with disodium phosphate and corn oil) develop nonocclusive myocardial necrosis. This is apparently due to increased metabolic demand, which was prevented by simultaneous administration of various substances including spironolactone, an antimineralocorticoid that is believed to promote potassium-sparing. In this regard, potassium salts or potassium-sparing agents similarly protect the rat from the toxic effects of digitalis (10).

Preliminary studies performed in this laboratory on spontaneously hypertensive (SH) rats of the Okamoto-Aoki strain indicate that cardiac glycosides may exert a hypotensive effect (unpublished observations).

This is a report on the effect of digitoxin treatment on the course of hypertension induced by adrenal compression in rats (11, 12). The cause of this type of hypertension, like that of adrenal regeneration hypertension (ARH) (13), is uncertain, but presumed to be due to an excessive secretion of one or more mineralocorticoids.

Materials and methods. Thirty female Sprague-Dawley rats weighing 75-90 g were divided into three equal groups, right-nephrectomized, and given 1% saline solution to drink and laboratory chow *ad libitum*. In addition, groups 1 and 2 underwent bilateral adrenal compression for the induction of hypertension (11). Group 3 rats which served as controls had the adrenals explored but not compressed.

From the eighth day postoperatively, the earliest time at which hypertension could be expected to occur, until the twenty-sixth day, all rats were given 1 ml of 0.9% saline per 100 g body wt daily by gavage. In the case of group 2, each milliliter contained, suspended, 0.5 mg of digitoxin powder (Parke, Davis & Co., Detroit, Mich.).

Weekly systolic blood pressure, electrocardiogram (ECG), and heart rate recordings were obtained on unanesthetized animals using a Narco-Biosystems PE-300 Programmed Electrosphygmomanometer and appropriate modules attached to a DMP-4B Physiograph (Narco-Biosystems, Inc., Houston, Texas). Pressures in excess of 150 mm Hg were regarded as indicative of hypertension.

On Day 27, the rats were sacrificed with an overdose of ether and autopsied. Various organs were removed, examined for lesions, and placed in fixative (10% neutral formalin). The organs were subsequently weighed and the weights expressed as mg per 100 g of final body weight. The lesions were graded by modified established criteria (14) as follows: 0 indicates no abnormality; 1, few small nodules, hypertrophy; 2, moderately nodular with some mottling; 3, greater nodularity, mottled with red spots; 4, rough, mottled, and flea-bitten appearance. The average severity of lesions was obtained by dividing the total score by the number of rats in the group.

The two-tailed Student's *t* test was used to determine the significance of differences between group means. Confidence limit was set at the 5% level, a *P* value of 0.05 or less indicating significance.

Results. Blood pressure. Two rats in

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group 1 (compressed adrenals; not given digitoxin) died the first week; one of pneumonia, the other of hydronephrosis. Data on these are not reported here. In the survivors, systolic pressure rose rapidly so that by Day 15, five of eight rats had pressures ranging from 157–197 mm Hg. By Day 25, all animals had readings in excess of 150 mm Hg (164–230 mm Hg). The averages were significantly different ($P < 0.03$) from controls on all occasions after the first week.

In group 2 (digitoxin-treated), only one rat showed definite hypertension on all occasions and two others had pressures slightly above 150 mm Hg by Day 15. By Day 25, 8 of 10 animals were hypertensive (160–210 mm Hg). The rat which became hypertensive early became severely so (210 mm Hg). The averages for this group were higher than those of controls, but not significantly so on any occasion ($P > 0.07$). No ECG abnormalities such as T wave inversion or heart block were noted to occur.

Three of the 10 rats in group 3 became hypertensive (155–214 mm Hg). The blood pressures are depicted in Fig. 1.

Body weight. Rats treated with digitoxin showed a slightly depressed growth rate. Nevertheless, there was no difference in the final weight between adrenal-compressed rats receiving digitoxin and those given saline, because the latter became ill as a result of very severe hypertension. Neither group, however, differed significantly from control (Table I).

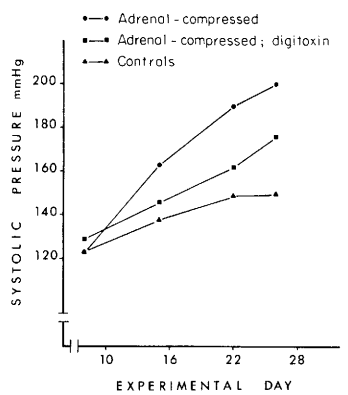

FIG. 1. Before treatment became effective (first estimation), there were no differences between the group average systolic pressures. Thereafter the pressures of untreated experimental rats were significantly higher than in controls on all occasions ($P < 0.03$), whereas those of digitoxin-treated rats occupied an intermediate range, and were not significantly higher on any occasion ($P > 0.07$).

Organ weights. Untreated rats with compressed adrenals had greatly enlarged hearts, kidneys and adrenals, atrophic thymus glands, and very severe renal lesions (Table I). In contrast, although there was slight cardiac hypertrophy in the digitoxin-treated group, kidney enlargement did not occur. Furthermore, except for two of the rats which developed moderately severe hypertension and nephrosclerosis, such organs from digitoxin rats were indistinguishable from controls and neither adrenal enlargement nor thymic atrophy occurred.

Discussion. Although digitoxin treatment instituted one week following adrenal compression did not entirely prevent the development of hypertension, it did nevertheless retard the process, ameliorate its severity, and reduce lesion formation (as observed macroscopically) in the kidneys. It remains to be seen whether or not digitoxin (at 0.5 mg/ml/100 g of body weight by gavage) would be more effective in abrogating adrenal-compression hypertension if treatment were started immediately following sensitization (adrenal compression, uninephrectomy and 1% NaCl feeding) rather than deferring treatment until hypertensive changes were expected to appear.

Digitoxin would presumably also be effective in other forms of adrenal injury hypertension (enucleation, puncture) and perhaps hypertension due to steroid overdosage.

The mechanism(s) by which digitoxin modulates the hypertensive process is(are) uncertain. The glycoside may exert its effect on baroreceptors (15) causing them to respond "effectively" in counteracting pressure elevations.

Another possibility is that, because of its structural similarities, digitoxin competes with the hypertensogenic steroid for mineralocorticoid receptors thereby normalizing electrolyte balance. Selye *et al.* (16) have reported that spironolactone antagonizes digitoxin-induced arrhythmias and prevents myocardial lesion formation. Other substances as well exhibit antagonistic effects to digitoxin and other digitalis drugs. For

TABLE I. PERTINENT FINDINGS IN RATS WITH COMPRESSED ADRENALS, WITH AND WITHOUT DIGITOXIN TREATMENT.

		Group 1 Compressed adrenals	Group 2 Compressed adrenals + digitoxin	Group 3 Controls
Number of animals	Initial	10	10	10
	Final	8	10	10
Body weight (g)	Initial	84 ± 2[a]	85 ± 1	85 ± 1
	Final	153 ± 9	153 ± 6	170 ± 7
Incidence of hypertension* (%)		100	80	30
Renal lesions	Incidence (%)	86	20	0
	Severity	2.4	0.5	0
Organ weights (mg%)	Heart	481 ± 28[b,c]	412 ± 16[b]	358 ± 13
	Kidney	893 ± 54[b,c]	719 ± 33	694 ± 21
	Thymus	81 ± 32[b,c]	154 ± 9	160 ± 14
	Adrenals	44.2 ± 4.6[b]	36.0 ± 2.7	32.7 ± 1.4

[a] Mean ± SE.
[b] Different from control group ($P < 0.05$).
[c] Different from other experimental group ($P < 0.05$).
* Systolic pressure 150 mm Hg or greater.

instance, whereas toxic doses of ouabain (97 mg/kg, ip) will kill the animals within 40–50 min, ATP (50 mg/kg, pH 7.2) injection immediately following administration of ouabain not only protects the rat from death, but also from any cardiac rhythm disturbances (17).

In terms of blood pressure response, there are reports that glycosides cause pressure elevation in anesthetized (3, 5) as well as conscious animals (18) and in both patients free of (19) and affected by cardiovascular disease (20). On the other hand, there is an indication that they exert both a hypotensive (6, 7) and other protective effects, thus reducing morbidity and mortality from cardiac failure due to aortic constriction (2) and shock (21, 22).

Of particular significance is the finding that in addition to antagonizing cardiac (2) and renal (*vide supra*) hypertrophy, digitoxin inhibited lesion formation in these organs, in spite of the moderate hypertension observed in this experiment. It also prevented the thymus involution and adrenal enlargement, changes associated with the stress state evoked by severe hypertension.

Summary. Bilateral compression of the adrenal glands combined in mononephrectomy and followed by the imposition of a high NaCl intake resulted in severe hypertension in all rats so treated. It was accompanied by enlargement of the heart, kidneys, and adrenal glands, atrophy of the thymus, and the occurrence of severe nephrosclerosis. Digitoxin treatment delayed the onset, reduced the incidence, and ameliorated the magnitude of the hypertensive response in such animals; it also reduced the degree of cardiac hypertrophy and the severity of nephrosclerosis and completely prevented enlargement of the adrenals and kidneys and atrophy of the thymus.

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