Antiarrhythmic Activity of Various Steroidal Spirolactones in Dogs. (26074)

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The steroidal spirolactones have been of recent interest because of their ability to inhibit the urinary electrolyte effects of aldosterone and desoxycorticosterone (DOC) in laboratory studies(1-3) and in man(4-6). In addition, one compound in the series, SC-8109, appears to possess quinidine-like activity in isolated rabbit atria(7,8), and positive inotropic action on ventricular muscle(9). These observations prompted further studies on cardiac effects of steroidal spirolactones. The present report is concerned with antiarrhythmic properties of 3 aldosterone blocking agents, SC-8109, SC-5233 and Aldactone,* as determined by tests in anesthetized dogs. Three structurally related compounds with poor DOC-blocking properties were also chosen for cardiac tests, to assess the relationship of DOC-blocking and antiarrhythmic activities.

Materials and methods. Atrial arrhythmias were established in anesthetized adult mongrel dogs by crushing a portion of the atrium and stimulating electrically(10). This procedure usually resulted in atrial flutter with 2:1 A-V block. After a brief control period, compounds were given intravenously at 1 mg/kg/minute until a total dose of 20 mg/kg was administered, or until restoration of normal sinus rhythm(11). Spontaneous reversion to sinus rhythm occasionally occurred, but could be differentiated from drug action by reestablishment of flutter with immediate restimulation. If stimulation flutter could not be produced initially, local application of 0.05% solution of aconitine nitrate on the atrium produced atrial fibrillation(12). All compounds were given as 1.5 to 3.0% solutions in propylene glycol. The atrial electrogram, lead II electrocardiogram, and femoral artery blood pressure were recorded simultaneously. Typical reversions of each type of arrhythmia are shown in Fig. 1. The following compounds were tested: 3-(3-oxo-17β - hydroxy-19-nor-4-androsten-17α-yl)propanoic acid lactone, or SC-8109; 3-(3-oxo-17β - hydroxy-4-androsten-17α-yl)propanoic acid lactone, or SC-5233; 3-(3-oxo-7α-acetylthio - 17β - hydroxy - 4-androsten-17α-yl)-propanoic acid lactone, or Aldactone; 3-(3-oxo - 17β-hydroxy-4-androsten-17α-yl)acrylic acid lactone, or SC-4988; 3-(3-oxo-17β- hydroxy-19-nor-4-androsten-17α-yl)acrylic acid lactone, or SC-8288; and 3-oxo-17β-hydroxy-4-androsten-17α-yl propiolic acid, or SC-5314. Chemistry for most of these compounds has been reported(13-15).

Results and discussion. Table I summarizes results of our study in terms of mean effective dose (MED) for reversal of induced atrial arrhythmias in dogs. In our experience, the injury-stimulation arrhythmias are generally more difficult to correct than the aconitine type. That is, a compound with relatively weak antiarrhythmic potency may cause reversion of the aconitine fibrillation but may not appreciably affect a stimulation flutter. In view of the observed difference, results of the 2 tests are listed separately in Table I. Data on a standard antiarrhythmic drug, quinidine sulfate, are included in the table. It is noteworthy that aconitine arrhythmias responded to treatment with SC-8109, SC-5233 and Aldactone. SC-4988, a close structural derivative of SC-5233 with an unsaturated lactone group, also corrected aconitine arrhythmias in 4 dogs at a mean dose of 14.8 mg/kg. Comparison of MED in pairs by Wilcoxon Rank-sum test(16) revealed no significant differences among the 4 active compounds ($P>0.1$). In contrast, only SC-8109, the 19-nor compound, was effective against stimulation flutter; Aldactone, SC-5233 and SC-4988 were ineffective at 20 mg/kg. Three of the active spirolactones were also potent DOC-blocking agents, as shown in last column of table. The propiolic acid derivative (SC-5314) and unsaturated

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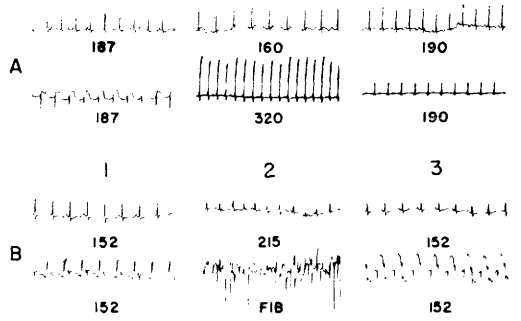

FIG. 1. (A) Stimulation flutter treated with DOC: 1. Control, before stimulation; 2. atrial flutter with 2:1 A-V block; 3. after 3 mg/kg DOC intrav. (B) Aconitine fibrillation treated with SC-8109: 1. Control, before aconitine application; 2. atrial fibrillation; 3. after 4 mg/kg SC-8109 intrav. Upper line in each record is lead II electrocardiogram and lower line is atrial electrogram. Number below tracing indicates ventricular or atrial rate in each case.

lactone in the 19-nor series (SC-8288), both with weak activity as anti-DOC agents, were without effect at 20 mg kg. These last data could be interpreted as indicating some association between antiarrhythmic and DOC-blocking properties in steroidal spirolactones, but the relationship does not appear to be a strict one.

Additional comments may be made from the results of our study. The 19-nor modification is present in SC-8109 and SC-8288, but only the former was effective in correcting aconitine fibrillation. In addition, SC-5233 and Aldactone, which are members of the normal series, were approximately as effective as SC-8109. These observations indicate that antiarrhythmic activity is not directly dependent on 19-nor modification.

In the present study, DOC also reverses the atrial flutter resulting from electrical and aconitine stimulation (Table I), and shows, therefore, an effect similar to that of the spirolactones. This observation is in contrast to the antagonistic effects of these 2 types of compound with regard to kidney function. On the other hand, the data appear consistent with the results of *in vitro* experiments, in which spirolactones appear to act qualitatively like mineralocorticoids. Aldosterone, DOC, SC-5233 and SC-8109 were able to potentiate epinephrine-produced contractions of rabbit aortic smooth muscle(17). Quinidine, DOC and SC-8109 had similar effects on functional refractory period and trans-membrane potassium flux in isolated rabbit atria (7,8). Isolated papillary muscles from cat hearts gave positive inotropic responses when bathed with solutions of SC-8109 and DOC (9). These considerations suggest that the fundamental receptors affected by the 2 types of steroids may be identical in extra-renal tissues as well as in the kidney.

Summary. The effects of SC-8109, or 3-(3 - oxo - 17β - hydroxy - 19 - nor - 4 - androsten-17α-yl)propanoic acid lactone, and 5 structurally related compounds on atrial arrhythmias were investigated in anesthetized dogs. SC-8109 and 3 other steroidal spirolac-

TABLE I. Comparison of Anti-DOC and Antiarrhythmic Effects of SC-8109 and Some Structurally Related Compounds.

	Atrial arrhythmias				
	Stimulation flutter		Aconitine fibrillation		Anti-DOC
Compound*	MED† (mg/kg)	Response‡	MED† (mg/kg)	Response‡	potency§
SC-8109	14.5	2/2	8.3 ± 3.6‖	5/5	100
Aldactone	>20	0/2	10.2 ± 5.4	5/5	27
SC-5233	"	0/2	15.0 ± 4.6	5/5	41
SC-4988	"	0/3	14.8 ± 5.0	4/4	<4
SC-8288	"	0/1	>20	0/4	"
SC-5314	"	0/2	"	0/2	"
DOC	6	1/2	4.5	2/2	—
Quinidine sulfate	8.7 ± 5.8‖	8/8	8.6 ± 4.2	14/14	—

* Propylene glycol, the solvent used for all compounds, was inactive in 6 arrhythmic dogs at 12 ml/dog.
† MED = Mean effective dose.
‡ Response = Ratio, No. of reversions : No. of dogs tested.
§ Relative parenteral potency calculated from data supplied by Dr. C. M. Kagawa.
‖ ± stand. dev.

tones (SC-5233, Aldactone and SC-4988) were approximately equipotent in correcting aconitine-induced arrhythmias. Of these compounds, only SC-4988 did not possess significant DOC-blocking activity in the mammalian kidney. The other 2 compounds in the series, similarly weak as DOC-blockers, were inactive as antiarrhythmic agents. SC-8109 alone reversed the arrhythmia induced by electrical stimulation. DOC and quinidine sulfate were effective against both types of flutter. The relationships of structure-antiarrhythmic activity and of DOC blocking-antiarrhythmic activities of the steroidal spirolactones are discussed.

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Influence of Hair Growth Cycle on Lipid Composition of Mouse Epidermis and Dermis.* (26075)

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Recent evidence indicates that the hair growth cycle in the mouse not only influences the thickness and morphology of the entire skin, but also has some effect on its chemical composition. Changes in chemical composition of skin as related to hair follicle activity (1,2,3) are mainly obtained from histochemical procedures(4). Little is known concerning alterations in lipids in skin during the hair growth cycle. Although the adipose layer of skin doubles in thickness during periods of active hair growth, total fat content is not significantly increased over that in skin containing quiescent hair follicles(3). Lipid composition of epidermis and dermis including adipose and muscle layers for skin in growing (anagen VI) and quiescent (telogen) hair follicles(5) is given in this report.

Methods. Hair growth was initiated in adult Swiss mice by plucking of quiescent (telogen) hair from the entire dorsum of each mouse(5). Skin samples were obtained from mice killed by cervical dislocation on the 12th (anagen VI) and 22-23rd (telogen) days following plucking(5). Fat below the panniculus carnosus was carefully removed after which the epidermis was separated from the dermis at 50°C by the procedure of Baumberger *et al.*(6). Dermal specimens included the adipose layer and panniculus carnosus. The variation in dermal preparations produced by scraping of these layers from

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