Effect of Various Adrenal Steroids on the Electrocardiogram of Adrenalectomized Dogs

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Numerous studies of the electrocardiogram (ECG) of adrenalectomized dogs\textsuperscript{1-3} and Addisonian patients\textsuperscript{4-7} have been made. These investigations have been primarily concerned with the relation between plasma levels of K, Mg and other ions to alterations in the electrocardiogram.\textsuperscript{8} The present communication is concerned with the possibility that adrenal steroids possessing chiefly mineralocorticoid activity, such as aldosterone and desoxycorticosterone, have effects on the electrocardiogram of adrenalectomized (adx) dogs different from those elicited by high potency glucocorticoids, such as several of the recently synthesized analogs of hydrocortisone.

Methods

These studies were made on healthy, vigorous, mongrel dogs without adrenal glands for periods ranging from 1 to 3 years and had been repeatedly observed through cycles of insufficiency and recovery on various types of substitution therapy. In the interim between experiments, the animals were adequately maintained by daily intramuscular injections of 0.5 to 0.7 mg of desoxyeorticosterone in oil (DCA) plus a daily NaCl supplement of 1 to 2 grams in the food. The dogs usually received an injection of 50 mg of solubilized hydrocortisone once every 30 days when not under experimentation. DCA and salt were discontinued the day previous to starting an experiment and no animal was used that had received gluco-corticoid within a period less than 25 days previously. Methods employed for determining arterial pressure, plasma volume and electrolytes have been described elsewhere.\textsuperscript{9,10} The compounds used for intravenous injections were free alcohols of the steroids and the method used for solubilizing them was reported earlier.\textsuperscript{9}

More than 400 electrocardiograms were taken on 24 adrenalectomized dogs over a 2-year period with a Sanborn V 150 Cardiette, Model 52. Three standard limb leads were used routinely but the examples shown are from standard lead II. The electrocardiograms were taken with the dogs lying on their backs on a V-shaped operating board with both fore and hind limbs restrained, thereby establishing relative constancy of the position of the heart from day to day. These precautions seem to lessen variability of the T wave in those animals which may have what Lepeschkin\textsuperscript{11} refers to as vertical hearts and loose mediastina. Anesthesia was never employed. In all cases the dogs were subjected to a control period, usually lasting several days, during which the blood pressure, blood constituents and electrocardiograms were checked to ascertain whether or not the animals were adequately maintained.

Characteristic electrocardiogram changes occurring in representative cases of adrenal insufficiency are shown in figure 1 (A and B). The maintenance dose of DCA was withdrawn from dog A on 11/21/58. The dog slowly developed symptoms with elevation of plasma K and Mg. The more common electrocardiographic alterations encountered in adrenal insufficiency are diphasic or inverted T with gradual lowering of the P wave until it disappears. A specific example of this is shown in figure 1 (A) from a record taken on 12/16/57. These changes can be reversed over a period of a few days by intravenous injections of a gluco-corticoid such as 2-methyl-9a-fluorohydrocortisone (2-methyl FF), which in this particular animal began on the morning of 12/16. The P wave reappears promptly but correction of the T wave is a relatively slow process. Return of activity, vigor and appetite are much more rapid than return to normal of the electrocardiographic changes. A less common pattern, i.e., a small R and a large S wave which occurs in about 10 per cent of dogs presenting symptoms of adrenal insufficiency is shown in figure 1 (B).

Results

Mineralo-corticoids

Desoxycorticosterone

It has been our experience that the abnormal electrocardiographic changes appearing in adrenalectomized dogs exhibiting insuffi-
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Figure 1
(A) Most common type of electrocardiographic changes seen in adrenalectomized dogs exhibiting insufficiency. (B) Small R and large S type seen in less than 10 per cent of such animals.

ciency while maintained solely on mineralocorticoids are not promptly corrected by either intravenous injections of solubilized desoxycorticosterone (DOC), or intramuscular injections of DCA, unless the dogs receive large amounts of salt by stomach tube or by vein and are adequately fed. Furthermore, adrenalectomized dogs, while maintained in normal health, may frequently develop an inverted T when given an overdose of a mineralo-corticoid. Figure 2 shows development of an inverted T of an adrenalectomized dog free from symptoms given 4 mg./day for 3 days of an oil solution of DCA. A fasted animal presenting symptoms of insufficiency with an inverted T received 100 mg. of solubilized DOC by vein over a 48-hour period, but showed no correction of the T wave until injections of the potent gluco-corticoid 2-methyl-9a-fluorohydrocortisone (2-methyl FF) were given.

Aldosterone

Figure 3 shows the ineffectiveness of synthetic dL-aldosterone for restoring to normal the electrocardiogram of a fasted adrenalectomized dog in adrenal insufficiency. The T wave became more deeply inverted even when the steroid was injected in doses of 20 mg. within 48 hours. The plasma electrolytes showed an apparent rise presumably due to further contraction of the plasma volume (p.v.), since aldosterone is incapable of raising the plasma volume of an adrenalectomized dog deprived of exogenous sources of food and water. Fasted adrenalectomized dogs receiving aldosterone therapy during episodes of insufficiency require a gluco-corticoid to correct the inverted T wave. It has been observed repeatedly that T inversion deepens following excessive DOC or aldosterone therapy if the animal is starved during the period over which the injections are given. A rapid reversal of the inverted T occurs within 4 to 5 days in the aldosterone-treated dogs when they are also injected with gluco-corticoid and fed their normal daily ration of food.

Glucocorticoid Possessing Potent Mineralo-corticoid Activity

2-methyl-9a-fluorohydrocortisone (2-methyl FF)

A vigorous male dog with intact adrenals was given subcutaneously 3 mg./Kg. of this potent steroid for 26 days (fig. 4A). Definite electrocardiographic deviations from the normal appeared, apparently associated with

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plasma hypokalemia. The changes from normal consisted of broadening and lowering of the T wave. One adrenalectomized dog in normal health and with a normal electrocardiogram was given the same amount of steroid with similar effect. The T wave developed a flat top as the plasma K was reduced (fig. 4B). When 2-methyl FF was discontinued, the electrocardiogram returned to normal. The plasma K of one other dog was reduced to 2.19 mEq./L, but the animal did not survive the experiment.

Glucocorticoids Predominately Natriuretic in Their Action

Prednisolone (1-dehydrohydrocortisone or 1-dehydro F)

Seven adrenalectomized dogs free from symptoms received 5 to 10 mg./day of this steroid subcutaneously for periods ranging from 16 to 51 days. All developed a diabetes insipidus-like syndrome and after prolonged treatment, a marked lowering of the plasma Na. However, the plasma volume remained within the normal range. Four animals developed a diphasic T, which eventually was found to be typical of mineralo-corticoid deficiency. An example is shown in figure 5. Three dogs exhibited various changes which, in our experience, apparently are associated with deficiency of both mineralo- and glucocorticoids. Two of these developed an rS type of electrocardiographic deformity which apparently occurs in about 10 per cent of dogs suffering from severe adrenal insufficiency, as noted in figure 1(B). The other animal presented a church steeple T said to be characteristic of hyperkalemia, but showed no marked evidence of any disability. All dogs receiving 10 mg./day had 0.5 to 1.0 mm. depression below the base line of the P-Q interval. This was followed by a depressed or, in some cases, a sloping S-T and a small downward deflection, then an almost vertical rise, followed by a gradual resumption of the base line. Prednisolone lacks mineralo-corticoid activity and is strongly natriuretic and, hence, is unable to maintain the normal plasma electrolyte pattern even at a dose level of 10 mg./day. However, the plasma volume remained within the normal range and the animal retained his normal activity and vigor for long periods. Chronic administration of large doses of prednisolone to adrenalectomized dogs leads to severe depletion of plasma Na and eventually to lassitude, refusal of food, weakness and spasticity. The abnormal electrocardiograms are readily restored to normal after discontinuing the drug, by daily intramuscular injections of DCA either with or without cortisone supplements. Salt had been continued in the diet of the animals during the experiment.

Triamcinolone (1-dehydro-16a-hydroxy-9a-fluorohydrocortisone)

Two adrenalectomized dogs were given large doses of triamcinolone (Aristocort, Lederle):
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Changes in the electrocardiogram in adrenalectomized dogs after prolonged treatment with triamcinolone (Aristocort).

one dog received 10 mg./day, the other, 5 mg. Both developed a depression of the P-Q and low T waves. The electrocardiogram of the prednisolone-injected dogs also showed similar changes although of less magnitude. Two other dogs given a smaller quantity of the drug showed less P-Q depression, but later developed mild symptoms somewhat resembling those of adrenal insufficiency, with T inversion occurring in one animal and a diphasic T in the other (fig. 6). During the period they were showing symptoms which we attribute to overdosage, they exhibited mild acidosis as shown by lowering of the plasma bicarbonate and some elevation of plasma K. All 4 of these animals seemed to require both mineralo- and gluco-corticoids for correction of the electrocardiogram and return of the dog to normal health and vigor.

Dexamethasone (1-dehydro-16α-methyl-9α-fluorohydrocortisone)

Two adrenalectomized dogs given diminishing amounts of this potent gluco-corticoid (Merck) to determine the minimum maintenance dosage requirements developed a downward slope of the P-Q and also S-T depression. When the daily dose was reduced to a point where evidence of mild adrenal insufficiency appeared, the T wave became diphasic. This was corrected by DCA plus cortisone given intramuscularly. Two other adrenalectomized dogs were given 5 mg. of dexamethasone per day for 27 days; they developed a severe diabetes insipidus-like syndrome with fluid intake and output of over 4,000 cc. per 24 hours.

Their P-Q became depressed but with the continued large dose the S-T became elevated. The health of these dogs remained good, but at the end of 27 days they showed symptoms of overdosage with obvious signs of gluco- and mineralo-corticoid imbalance as indicated by severe polydipsia and polyuria, some increase in plasma K, and the appearance of a diphasic T wave (fig. 7). Considerable improvement in the electrocardiogram followed repeated doses of DCA but a cortisone supplement of 50 mg. hastened recovery.

Discussion

These experiments indicate that in adrenalectomized dogs presenting symptoms of insufficiency the electrocardiogram may be employed to determine whether the deficiency is due to gluco- and mineralo-corticoid. However, it must be admitted there is little specificity in the relation of the electrocardiogram to many of the electrolyte derangements, presumably because there are so many factors influencing the metabolism during depolarization and especially during repolarization that can alter the direction of the action current or lower the potential. In adrenalectomized dogs, regardless of the corticoid given, any degree of adrenal corticoid imbalance that occurs shows up in about 90 per cent of the electrocardiographic patterns, viz., (1) excess of gluco-corticoids is characterized by a diphasic T; and (2) excess of mineralo-corticoids is associated with an inverted T wave. Prednisolone, triamcinolone and dexamethasone are similar in basic chemical structure since they are analogs of hydrocortisone. All 3 compounds produce a depression in the P-Q
interval varying from 0.5 to 2.0 mm. soon after the dogs are injected with the drugs. The significance of this is questionable, since no great importance has been attached to it in clinical studies of electrocardiographic alterations in health and disease.

A balance between mineralo- and glucocorticoids is essential for long-term maintenance of health and vigor of adrenalectomized dogs and the difference in the S-T and T-wave configuration of the electrocardiogram makes it possible to predict, with a fair degree of accuracy, which type of steroid is needed by the dog lacking adrenals. If a strong mineralocorticoid is required, S-T is often depressed and the T is diphasic; this regularly occurs with prolonged use of prednisolone, triamcinolone and dexamethasone. On the other hand, if glucocorticoids are deficient, the T is inverted.

Summary

The effects of large amounts of various adrenal steroids on the electrocardiogram of the adrenalectomized dog are described. The changes which occurred most frequently fell into 2 major groups: (1) those following excess of mineralo-corticoids, e.g., desoxycorticosterone and aldosterone, and (2) those appearing after glucocorticoid administration. A characteristic type of diphasic T wave frequently followed treatment with hydrocortisone and its analogs, and its correction was hastened by substituting mineralo-corticoid therapy.

The 3 analogs of hydrocortisone (dexamethasone, prednisolone and triamcinolone) induce similar electrocardiographic patterns and after prolonged administration alter the P-Q interval in varying degrees, but more frequently produce a diphasic T. Dexamethasone preserves the normal pattern longer than the other steroids tested.

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