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# Effect of spironolactone on diuresis and urine sodium and potassium excretion in healthy dogs

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**Abstract** *Objectives:* To document the diuretic effect of different oral doses of spironolactone (SP) in healthy dogs.
*Background:* SP is currently mentioned as a diuretic agent in the dog. However, the recommended doses were empirically defined and their corresponding diuretic effect has never been documented in dogs.
*Animals, materials and methods:* Eight adult Beagle dogs were used for two separate 2 * 2 cross-over designs. In the first cross-over, 4 dogs received SP orally for 8 days at 1 and 2 mg/kg per day. In the second cross-over the 4 other dogs received SP similarly, but at 4 and 8 mg/kg per day. Dogs were weighed on the first and last day of each period. Plasma SP and canrenone (the main active metabolite of SP) were assayed by high performance liquid chromatography (HPLC). Daily water consumption, urine weight, urine specific gravity, and urine excretion of sodium and potassium were measured during the SP treatment.
*Results:* Two hours after SP administration, SP was metabolized into canrenone. A significant 14 and 22% decrease in urine potassium excretion was observed at 1 and 2 mg/kg, respectively, but not at the two other dose levels. Daily water consumption, urine weight, urine specific gravity, and urine excretion of sodium were not significantly altered by the SP treatment regardless of dose.
*Conclusions:* Repeated oral administration of SP at 1, 2, 4 or 8 mg/kg for 8 days had no effect on water and sodium diuresis in healthy dogs.


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## Introduction

Spironolactone (SP) is a competitive inhibitor of aldosterone acting at the distal tubular level. Its main effects are to increase sodium and water excretion, and decrease potassium excretion. SP has been widely used for approximately 50 years in human patients,[1] alone or in combination with furosemide or hydrochlorothiazide, for the treatment of hypertension, primary hyperaldosteronism, and edematous conditions (i.e., in heart failure, cirrhosis, and nephrotic syndrome).[2] However, aldosterone antagonists only exhibit demonstrable pharmacological activity in healthy human volunteers when mineralocorticoid excess is induced either by administration of exogenous mineralocorticoids or by stimulation of endogenous mineralocorticoids (by salt restriction and/or diuretic administration).[3] The use of SP has also been recommended in veterinary medicine alone or in conjunction with additional diuretics for the treatment of patients with congestive heart failure that do not respond to furosemide and ACE inhibitors, or in those which develop hypokalemia while receiving other diuretics.[4] Spironolactone may also be effective in treating ascites, especially in hepatic failure.[5,6] The doses recommended for such indications in the dog are 1—2 mg/kg every 12 h per os in hepatic failure,[5] and 2—4 mg/kg per day[4] in heart failure. However, these dosage regimens were defined empirically and no titration study has been reported in the literature. Therefore, the objective of the present study was to determine the diuretic effect of SP administered for 8 consecutive days at 4 different doses (1, 2, 4 and 8 mg/kg) in healthy dogs.

## Animals, materials, and methods

### Animals

Eight, 2 year old (±3 months) male beagle dogs weighing between 12.8 and 15.7 kg (14.0 ± 0.90 kg) were used. All animals were considered healthy based on a complete physical examination and plasma biochemistry. They were placed in individual cages in an air-conditioned room (21 ± 1 °C). A commercial diet[c] containing 0.31% of sodium was offered (about 250 ± 5 g/day) once daily at 12.00 AM throughout the study. Water was given ad libitum for 12 h (from 8:00 AM to 8:00 PM). The dogs were acclimatized to the experimental conditions for 2 weeks before the beginning of the study. The study was performed according to the National Institutes of Health Guide for Care and Use of Laboratory Animals.

### Study design

Two separate 2 * 2 cross-over designs were used for the study, each involving 4 dogs. The first 4 dogs received SP at doses of 1 and 2 mg/kg, and the other 4 dogs received 4 and 8 mg/kg. The duration of each study period was 11 days and the 2 consecutive cross-over periods were separated by a washout phase of at least 9 days. Urine was collected for 3 days prior to each treatment to determine pre-treatment values and then for 8 days once treatment was initiated.

### Spironolactone administration

Capsules of spironolactone[d] were orally administered by gavage once a day for 8 days at a dose of 1, 2, 4 or 8 mg/kg according to the cross-over design. The SP treatment was started after 3 days of pre-treatment urine collection.

### Urine collection

The dogs were placed in metabolism cages from the 1st—11th day of each period, and urine was collected daily in glass bottles kept at 4 °C on ice in polystyrene boxes. The bladder was completely emptied by catheterization just before the beginning of the collection period, at the end of the third day of collection (i.e., just before the first administration of the test article), and at the end of the 11th day (i.e., 24 h after the last administration). The urine collected by catheter was pooled with the urine collected in the metabolism cage for the corresponding period.

### Blood collection

A 5 mL blood sample was taken on the second day of urine collection for use as a control. Five mL blood samples were then drawn from the jugular vein into heparinized tubes every day from the 3rd to 11th day, 2 h after SP administration. The blood was immediately centrifuged (3000 *g*, 4 °C) and the plasma stored at −20 °C until assay.

[c] Royal Canin M25, Aimargues, France.

[d] Spiroctan®, Laboratoires Ferlux, 63804 Cournon d'auvergne, France.