Hemodynamic effects of methylprednisolone acetate administration in cats

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Objective—To investigate the mechanisms by which corticosteroid administration may predispose cats to congestive heart failure (CHF).

Animals—12 cats receiving methylprednisolone acetate (MPA) for the treatment of dermatologic disorders.

Procedure—The study was conducted as a repeated-measures design. Various baseline variables were measured, after which MPA (5 mg/kg, IM) was administered. The same variables were then measured at 3 to 6 days and at 16 to 24 days after MPA administration. Evaluations included physical examination, systolic blood pressure measurement, hemodynamic analysis, serum biochemical analysis, thoracic radiography, echocardiography, and total body water and plasma volume determination.

Results—MPA resulted in a substantial increase in serum glucose concentration at 3 to 6 days after administration. Concurrently, RBC count, Hct, and hemoglobin concentration as well as serum concentrations of the major extracellular electrolytes, sodium and chloride, decreased. Plasma volume increased by 13.4% (40% in 3 cats), whereas total body water and body weight slightly decreased. All variables returned to baseline by 16 to 24 days after MPA administration.

Conclusions and Clinical Relevance—These data suggest that MPA administration in cats causes plasma volume expansion as a result of an intra-to extracellular fluid shift secondary to glucocorticoid-mediated extracellular hyperglycemia. This mechanism is analogous to the plasma volume expansion that accompanies uncontrolled diabetes mellitus in humans. Any cardiovascular disorders that impair the normal compensatory mechanisms for increased plasma volume may predispose cats to CHF following MPA administration. (Am J Vet Res 2006;67:583-587)

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total body water. Informed consent was obtained from all cat owners after the purpose, nature, and potential risks and benefits of the study were reviewed. The Institutional Animal Care and Use Committee of the University of Minnesota approved the study.

**Study design**—The study was conducted as a repeated-measures design. At the first time point, various baseline clinical and laboratory variables were measured, after which MPA (5 mg/kg) was administered by IM injection and the cat was returned to the care of its owner. The same variables were then measured at 2 subsequent time points (ie, at 3 to 6 days and 16 to 24 days after MPA administration). Cats received no food for 12 hours prior to sample and data collection at each time point, but water was allowed ad libitum. All cats received regular commercial cat food prior to and throughout the study period.

Physical examination and systolic blood pressure—Physical examinations and systolic blood pressure measurements were performed in a quiet examination room. Systolic blood pressure was measured from the right forelimb by the same experienced technician at each time point by use of a standard noninvasive Doppler method as described by Henik et al. Weight was measured at each time point by use of the same electronic digital scale.

Hematologic and serum biochemical analyses—Blood samples were collected by jugular venipuncture. Samples were submitted to the Clinical Pathology Laboratory at the University of Minnesota Veterinary Medical Center for hematologic and serum biochemical analysis.

Thoracic radiography and echocardiography—Right lateral and dorsoventral thoracic radiographic views were taken and subjectively evaluated for cardiac silhouette shape and size relative to the thorax as well as for any pulmonary infiltrates or pleural effusions to suggest the presence of CHF. Vertebral heart size was calculated by use of measurements made from the right lateral radiographic view. Two-dimensional and M-mode echocardiography was performed by use of a 7- to 4-MHz multifrequency phased array transducer and harmonic imaging. Doppler echocardiography was performed in any cats in which murmurs were detected during physical examination. A veterinarian (AHT) who was board-certified in cardiology performed the echocardiographic examinations.

Total body water determination and change in plasma volume—Total body water was determined by bioimpedance analysis. At least 7 measurements of impedance and phase angle were obtained. Data were then fitted to the Cole-Cole model and Xitron mixture equation to determine total body water. Only data that had excellent or good fits to the model were used to determine total body water. Change in plasma volume (%ΔPV) was determined by the following equation:

\[
\%\Delta PV = \left( \frac{Hb_{before}}{Hb_{after}} \right) \times \left( \frac{1-Hct_{after}}{1-Hct_{before}} -1 \right) \times 100
\]

where Hb is hemoglobin.

Statistical analysis—Data that were not normally distributed on the basis of Shapiro-Wilk W test results are reported as median and range values. All other data are reported as mean ± SD values. Variables measured at each of the 3 time points were compared by 1-way repeated-measures ANOVA, with a value of P < 0.05 designated as the threshold for significance. A Greenhouse-Geisser adjusted P value was used to account for violations of the assumption of compound symmetry that invariably accompany this experimental design. Multiple comparisons were performed by use of the Dunnett test to compare baseline data with data from the 2 time points after MPA administration. All analyses were performed by use of commercial software.

**Results**

**Study population**—The study was curtailed after 12 cats had been enrolled because changes in all key variables necessary to distinguish between the 4 proposed mechanisms had attained significance. Ten of the cats were mixed breeds (9 domestic short hairs and 1 domestic medium hair), 1 was a Persian, and 1 was a Siamese. Mean age among the 12 cats was 5.9 ± 3.6 years; 6 were spayed females, and 6 were castrated males.

Physical examination findings were unremarkable except for the dermatologic conditions (eosinophilic granuloma complex [n = 7], allergic dermatitis [4], and inflammatory skin disorder [1]) and the presence of soft parasternal systolic heart murmurs of similar intensity on left and right sides in 3 cats. Doppler echocardiography disclosed minor and hemodynamically benign abnormalities (trivial tricuspid regurgitation [n = 2] and mild dynamic right ventricular outflow obstruction [1]).

Physical examination and systolic blood pressure—No adverse clinical effects attributable to MPA administration were observed either by the owners or during the reviews of the history and physical examinations performed at the 2 time points after MPA administration. Systolic blood pressure and heart rate had no significant change from baseline at either of the 2 time points after MPA administration. However, body weight was slightly decreased at 3 to 6 days after MPA administration and returned to baseline by 16 to 24 days after MPA administration (Table 1).

Hematologic and serum biochemical analyses—Serum glucose concentration was significantly increased 3 to 6 days after MPA administration. Serum glucose concentrations were above reference range in 9 cats and above the reported renal threshold of 180 to 220 mg/dL in 6 cats. Concurrently, several key variables decreased significantly from baseline. These included RBC count, Hct, hemoglobin concentration, and serum concentrations of sodium and chloride. All of these variables returned to baseline at 16 to 24 days after MPA administration (Table 1).

Thoracic radiography and echocardiography—Results of thoracic radiography revealed no changes to indicate CHF (ie, no pulmonary infiltrates or pleural effusions) in any of the cats at any time point. Further, vertebral heart size was not significantly different from baseline at either time point after MPA administration. Results of 2-dimensional and Doppler echocardiography were similarly unchanged from baseline following MPA administration. However, M-mode echocardiography disclosed a small increase in interventricular septal thickness in diastole at 16 to 24 days after MPA administration (Table 1). Other wall thickness and chamber dimension measurements were not significantly different from baseline at either time point after MPA administration.

Total body water and plasma volume—Bioimpedance analysis was technically challenging in fully conscious cats. It was not possible to restrain and calm
and not significantly different from baseline.

Change in plasma volume from baseline was calculated for only 3 to 6 days after MPA administration because the variables used in the equation to determine the percent change in plasma volume (ie, hemoglobin and Hct) were significantly different from baseline at 3 to 6 days after MPA administration. By 16 to 24 days after MPA administration, total body water was 2.21 ± 0.77 L and not significantly different from baseline. References 3 to 6, 16 to 24 range Before days days

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference range values</th>
<th>MPA administration</th>
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</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>NA</td>
<td>5.79 ± 1.12</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>50–150</td>
<td>136 ± 46</td>
</tr>
<tr>
<td>RBC count (X 10^6/mL)</td>
<td>5.74–10.50</td>
<td>8.07 ± 1.09</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>26.1–46.7</td>
<td>34.9 (22.4–42.3)</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>8.8–16.0</td>
<td>12.4 ± 1.8</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>149–158</td>
<td>152 ± 2</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>117–128</td>
<td>122 (120–131)</td>
</tr>
<tr>
<td>Interventricular septal thickness in diastole (mm)</td>
<td>≤ 6.0</td>
<td>4.3 ± 1.3</td>
</tr>
</tbody>
</table>

*Data that are not normally distributed are reported as median (range) values; all other data are reported as mean ± SD values. †Significantly different from baseline value.

Discussion

One potential mechanism by which corticosteroids could induce CHF is via fluid retention caused by a mineralocorticoid effect. Mineralocorticoids stimulate active reabsorption of sodium from renal tubular fluid into the nearby capillaries and stimulate renal excretion of potassium. Water is passively reabsorbed with sodium, and consequently, little or no increase in serum sodium concentration occurs. However, total body sodium and water retention lead to an increase in extracellular fluid volume and an associated increase in body weight. Increased excretion of potassium results in a decrease in serum potassium concentration.

Most synthetic corticosteroids that are administered for their anti-inflammatory effect have little or no mineralocorticoid action. For example, in comparison with cortisol, betamethasone and dexamethasone have relative anti-inflammatory potencies of 25, whereas their relative sodium retaining potencies are 0. In comparison with cortisol, MPA has a relative anti-inflammatory potency of 4 and a relative sodium-retaining potency of 0.5. We consequently considered it unlikely that MPA could cause sodium and fluid retention in cats. Among the 12 cats in our study, plasma volume increased by a median of 13.4%, but this was not associated with any increase in total body water or body weight. Rather, these 2 variables had a small decrease at 3 to 6 days after MPA administration before returning to baseline at 16 to 24 days after MPA administration. Further, no change was found in serum potassium concentration at either time point after MPA administration. Thus, administration of MPA in cats does result in a transient increase in plasma volume. However, this is not the result of a mineralocorticoid effect because neither an associated increase in total body water and body weight nor a decrease in serum potassium concentration was found.

An alternate mechanism by which plasma volume expansion may occur following MPA administration is by a fluid shift from the intra- to extracellular space. This would result in plasma volume expansion without any increase in body weight or total body water. Plasma volume expansion by this mechanism has been documented in humans with uncontrolled diabetes mellitus and results from the osmotic effect of extracellular hyperglycemia.

Corticosteroids with a predominantly glucocorticoid effect cause transient extracellular hyperglycemia or glucose intolerance by promoting hepatic gluconeogenesis and antagonizing the effect of insulin, thereby reducing cellular uptake of glucose and its use by peripheral tissues. Transient glucose intolerance caused by exogenous corticosteroids is well described in cats and serum glucose concentration among the cats in our study had a clinically important and significant increase 3 to 6 days after MPA administration before returning to baseline at 16 to 24 days after MPA administration. Coincident with the increase in serum glucose concentration were the following: 1) decreases in RBC count, Hct, and hemoglobin concentration; 2) decreases in serum concentrations of the major extracellular electrolytes, sodium and chloride; and 3) plasma volume expansion in each of our study cats. All of these variables returned to baseline by 16 to 24 days after MPA administration.

Although hemodilution is 1 explanation for the transient decrease in RBC variables following MPA administration, other possibilities exist. These hemogram changes could also be the result of hemolysis or blood loss, especially considering the ulcerogenic potential of...
exogenous corticosteroids. However, MPA administration has not been reported to cause hemolysis in any species, and none of the cats had any laboratory evidence of hemolysis (ie, no hemoglobinemia) or physical evidence of hemorrhage (ie, cavity effusions or melena) despite fairly substantial decreases in hemogram values in some cats. Further, no laboratory indication of RBC regeneration was found at either time point after MPA administration, as would be expected with either hemolysis or blood loss. Transient suppression of erythropoiesis could also explain the decrease in RBC variables observed in our study cats. However, no data were found to indicate that MPA, or any other corticosteroid, causes transient suppression of erythropoiesis in cats. Consequently, plasma volume expansion and hemodilution are the most likely explanation for the observed decreases in RBC count, Hct, and hemoglobin concentration, especially considering the concurrent decreases in serum concentrations of sodium and chloride.

There seems little doubt that the determined extent of plasma volume expansion (median, 13.4% and > 40% in 3 study cats) has the potential to induce CHF, especially in cats with cardiovascular compromise. However, none of our study cats developed clinical or radiographic signs of CHF. This presumably reflects a variety of compensatory mechanisms that accommodate plasma volume expansion, such as increased vascular capacitance. However, any impairment of these mechanisms may predispose cats to CHF when plasma volume expands following MPA administration.

Data from our study disclosed a small but steady increase in interventricular septal thickness in diastole, and this variable was significantly different from baseline at 16 to 24 days after MPA administration. This change in cardiac morphology, although significant, was small and of doubtful clinical importance. Further research is necessary to determine whether corticosteroids have any direct myocardial effect that could predispose some cats to CHF.

Increased ventricular pre- and afterload could result in CHF secondary to increased cardiac workload, reduced cardiac output, left ventricular hypertrophy, and progression of cardiac pump failure.10 Whereas increased afterload caused by systemic hypertension is a rare cause of CHF in cats, it is one of the most important risk factors for CHF in humans.31 Increased venous and arterial reactivity leading to systemic hypertension is recognized in many humans with hyperadrenocorticism.32 However, in our study, no change was found from baseline in systolic blood pressure at either time point after MPA administration. Consequently, our data disclosed no evidence that MPA administration changes vascular reactivity. The absence of any detected increase in systolic blood pressure, despite plasma volume expansion, probably reflects compensatory mechanisms that accommodate for gradual shifts in body fluid.

In addition to evaluating the 4 potential mechanisms by which corticosteroids may predispose cats to CHF, additional features of the data warrant further discussion. Total body water decreased in 6 of the 7 cats in which it was measured at 3 to 6 days after MPA administration. Consistent with this finding was a small decrease in body weight. The cause or causes for the decrease in total body water and body weight after MPA administration warrant further investigation and may include the following: 1) hyperglycemia exceeding the renal threshold15 and resulting in osmotic diuresis; 2) plasma volume expansion resulting in increased glomerular filtration rate and increased urine output; and 3) polyuria caused by antagonism of the release and action of antidiuretic hormone by MPA, similar to the polyuria that occurs in cats with hyperadrenocorticism.33 A limitation of our study was the difficulty in performing bioimpedance analyses in fully conscious study cats. The technique accurately measures total body water in anesthetized laboratory cats.34 However, its use in awake, client-owned cats is challenging and investigational at present. To our knowledge, this is the first time that the results of total body water determined by bioimpedance analysis have been reported for fully conscious cats. Consequently, the absolute values for total body water reported in our study should be regarded with care. On the other hand, the observed changes in total body water appear reliable because the bioimpedance analysis measurements disclosed a decrease in total body water at 3 to 6 days following MPA administration, after which it returned to baseline. In addition, changes in total body water were corroborated by appropriate directional changes in body weight.

In conclusion, results of our study suggest that the pathophysiologic mechanisms by which MPA administration may predispise cats to CHF is via plasma volume expansion caused by glucocorticoid-induced extracellular hyperglycemia with a shift of fluid from the intracellular to extracellular space. This mechanism is directly analogous to the intracellular to extracellular shift of fluid that occurs in humans with uncontrolled diabetes mellitus.3 A mineralocorticoid effect and an increase in ventricular afterload were excluded because MPA administration caused neither total body water retention nor any increase in systolic blood pressure. The increase in interventricular septal thickness in diastole at 16 to 24 days following MPA administration was small and probably clinically unimportant but warrants further investigation. Despite a substantial increase in plasma volume in some of our study cats following MPA administration, CHF did not occur presumably because normal compensatory mechanisms accommodate the changes in body fluid distribution. However, cardiovascular disorders that impair these compensatory mechanisms could predispose cats to developing CHF following MPA administration.

References


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