

Denosyl®

RESEARCH & USE FOR
HEPATIC SUPPORT



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Denosyl®

S-Adenosylmethionine Supplement Research and Use for Hepatic Support

Background

Denosyl, a nutritional supplement, is a stabilized bioavailable salt of S-Adenosylmethionine, for veterinary use only. S-Adenosylmethionine is made by all cells from methionine and adenosine triphosphate (ATP) and is important to normal liver function in several ways. It plays central roles in synthesis and metabolic reactions involving transmethylation, transsulfuration and aminopropylation pathways. It is abundantly produced by hepatocytes, as the liver is responsible for the significant portion of these reactions.

- Transmethylation is a part of many reactions, such as detoxification of compounds, carnitine and creatine synthesis in the liver, and stabilization of the phospholipid membranes of cells.
- Transsulfuration is the pathway by which compounds become sulfated. It is important for the formation of the potent antioxidant/detoxifying agent, glutathione, and the conjugation of waste products into water-soluble compounds for excretion.
- Aminopropylation leads to the formation of antioxidant polyamines that are important for cell growth and repair.

Under normal circumstances, the liver produces a rich supply of antioxidants, free radical scavengers and detoxifying agents as well as provides pathways to dispose of the waste products. When liver function is compromised, production of these antioxidants is reduced due to decreased production of S-Adenosylmethionine.¹ A study found that low liver glutathione concentrations are common in dogs and cats with compromised hepatobiliary function.² Lipid peroxidation, which is the oxidative fragmentation of lipid molecules in the cell membrane bi-layer leading to cell membrane damage, is now recognized as the basic mechanism of liver destruction.¹ Glutathione scavenges free radicals to inhibit this lipid peroxidation. Increasing glutathione levels in the face of compromised liver function would, therefore, be beneficial. Controlled veterinary studies have shown that administration

of Denosyl increases hepatocyte and erythrocyte intracellular glutathione levels in dogs and cats.^{3,4} No other nutritional supplements have been shown to do this in published veterinary clinical trials in dogs and cats. However, Denosyl goes far beyond just increasing hepatic glutathione levels. Denosyl improves cell membrane fluidity and decreases membrane fragility⁴ via the transmethylation pathway. Denosyl has been shown to protect hepatocytes from cell death.^{5,6} Denosyl is also useful for hepatocellular regeneration due to its activity in polyamine synthesis (aminopropylation pathway) and protein methylation (transmethylation pathway).¹ A study has also shown that it may improve bile flow in cats.⁷

Supplementing with Denosyl has been shown to be beneficial.^{1,3-8,12-15} Supplementing with the precursor methionine to animals with decreased liver function does not increase hepatic levels of S-Adenosylmethionine and may be toxic.¹ In compromised liver tissue, levels of S-Adenosylmethionine synthetase, the enzyme that converts methionine to S-Adenosylmethionine, are decreased, so the supplemented methionine cannot be converted to S-Adenosylmethionine.¹ Methionine is actually contraindicated in cases of portocaval shunts as it acts synergistically with elevated ammonia levels to induce hepatic coma.⁹

Total support for the liver is achieved by the use of agents with different supportive actions. Denosyl is used as a part of this complete support. S-Adenosylmethionine and tauroursodeoxycholic acid were actually shown to have an additive effect in reducing hepatocyte apoptosis caused by bile acids.¹⁰ Coadministration of Denosyl and prednisolone did not affect the bioavailability or pharmacokinetics of either substance.³

Safety

Denosyl demonstrates an exceptionally wide margin of safety. Oral acute toxicity studies in rats indicated an LD₅₀ greater than 4,640 mg/kg.¹ Clinically healthy dogs administered 20 mg/kg/day of Denosyl for 6 weeks and clinically healthy cats administered Denosyl at 2 times the recommend-

ed daily amount for 118 days remained healthy with no adverse effects from administration of Denosyl®.^{3,4}

Absorption

The presence of food decreases optimal absorption of S-Adenosylmethionine; it is, therefore, recommended to administer Denosyl on an empty stomach.¹ A pharmacokinetic study in fasted dogs administered Denosyl showed peak plasma levels in most dogs within 4 hours after administration.³ A pharmacokinetic study in fasted cats showed peak plasma levels at 2-4 hours.¹¹

Clinical Applications

For recommended applications, see “New Approach to Managing Hepatic Dysfunction, Part I,” Veterinary Forum, November 2000¹² and “New Approach to Managing Hepatic Dysfunction, Part II,” Veterinary Forum, December 2000.¹³ Also see “Liver Disease in Dogs and Cats”, Veterinary Forum, Volume 22(5A), 2005.¹³

Denosyl Studies

Evaluation of the influence of

S-Adenosylmethionine on systemic and hepatic effects of prednisolone in dogs.

Center SA, Warner K, Hoffman WE, et al.³

Results of a pilot study in dogs showed that bioavailability and pharmacokinetics of Denosyl and prednisolone were not affected by administering the two compounds together. Further evaluation in a double-blind, placebo-controlled, crossover study showed that Denosyl attenuated the loss of erythrocyte glutathione caused by administration of prednisolone. Hepatic glutathione levels were also improved in the Denosyl– prednisolone versus placebo-prednisolone group.

Influence of S-Adenosylmethionine on erythrocytes and liver tissue in healthy cats.

Center S, Randolph JF, Warner K, et al.⁴

Erythrocyte fragility and glutathione levels in erythrocytes and liver tissue improved in cats administered Denosyl for 118 days. As an incidental finding, portal inflammation was found on biopsy in 5 cats at the initiation of the study and resolved either partially or completely by the end of the study. TBARs (thiobarbituric acid-reactive substances), which are an index of lipid peroxidation, were decreased in erythrocytes. As expected, no signs of toxicity were noted.

S-Adenosylmethionine and cAMP confer differential cytoprotection against bile acid-induced apoptosis in canine renal tubular cells and primary rat hepatocytes.

Webster CRL, Boria P, Usechak P, Anwer MS.⁵

This study demonstrated that cultures of rat hepatocytes were protected against apoptosis by preconditioning with Denosyl. It was also found that there was significant protection of MDCK-Ntcp cells, though not to the same degree as the hepatocytes, against apoptosis. These cells are a canine renal tubular cell line that expresses a bile acid transporter. These results demonstrate that Denosyl protects hepatocytes against bile acid-induced apoptosis and has the potential to protect epithelial cells of other organs.

S-adenosylmethionine (SAME) in a feline acetaminophen model of oxidative injury.

Webb CB, Twedt DC, Fettman MJ, Mason G.¹⁵

Cats were randomly assigned to one of three groups: Denosyl, acetaminophen, or Denosyl + acetaminophen. Denosyl administration given one hour after acetaminophen ingestion protected erythrocytes from oxidative damage by limiting the formation of Heinz bodies and erythrocyte destruction over time.

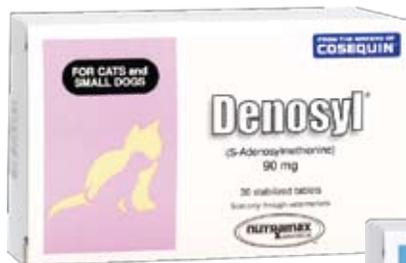
Case Study

S-adenosyl-l-methionine (SAME) for the treatment of acetaminophen toxicity in a dog.

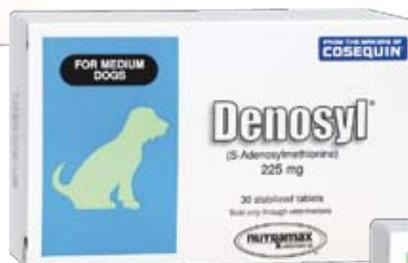
Wallace KP, Center SA, Hickford FH, et al.¹⁶

After ingesting 20 grams of acetaminophen, a Shetland Sheepdog was administered Denosyl at a loading level and then a maintenance amount for 7 days combined with intravenous fluid administration and a blood transfusion, but without concurrent cimetidine or n-acetylcysteine. Measurement of RBC glutathione values at time of presentation and after Denosyl administration demonstrated rapid resolution of marked glutathione depletion and recovery from Heinz body hemolytic anemia.

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