ASPARAGINASE INJECTABLE DRUG HAS BEEN REPORTED EFFECTIVE FOR TREATING CANINE LYMPHOMA

KEY POINTS:

- Asparaginase has been reported to be effective for inducing remission in canine lymphoma.[1,2,3]
- The unique toxicities of asparaginase were not observed when asparaginase was administered intramuscularly (IM).[1,2,3]
- Adverse effects reported from IM asparaginase administration were generally mild and self-limiting.[1,3]

BACKGROUND:

Asparaginase is an antineoplastic chemotherapy drug used in the treatment of canine lymphomas, leukemias, and mast cell tumors. It is considered most useful in inducing remission of diseases, but it is also used in maintenance and rescue protocols.[4] Asparaginase is available as a generic injectable drug from Amatheon.

Asparaginase is classified as an enzyme and works by hydrolyzing asparagine into aspartic acid and ammonia **[Figure 1]**. Some malignant cells cannot synthesize asparagine and are dependent on exogenous asparagine for DNA and protein synthesis. Normal cells can synthesize asparagine intracellularly and thus will not be adversely affected by asparaginase—with the exception of some normal cells with high rates of protein synthesis that require some exogenous asparagine.[4]

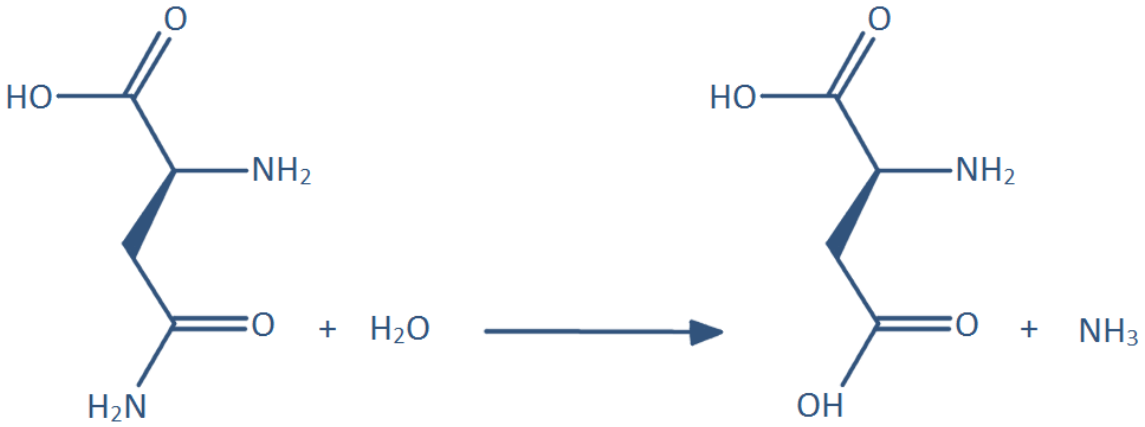

Figure 1. Asparaginase catalyzes the hydrolysis of asparagine into aspartic acid and ammonia.

ASPARAGINASE HAS BEEN REPORTED TO BE EFFECTIVE IN INDUCING REMISSION IN CANINE LYMPHOMA AND HAS BEEN SHOWN USEFUL IN MAINTENANCE OF REMISSION.[1]

Study 1. In this prospective study, 69 dogs with canine lymphoma were randomized into a polyethylene glycol conjugated (PEG) L-asparaginase group and a native L-asparaginase group. L-asparaginase was administered weekly as a single agent at a dose of 400 µ/kg IM for two weeks. After the two weeks, both groups received two cycles of combination chemotherapy. Then L-asparaginase was used every two weeks as a single agent for maintenance of remission.[1]

- No statistically significant differences were found in response rates, time to relapse, or survival between the two groups.
  - Median survival was 319 days for the L-asparaginase group and 356 days for PEG L-asparaginase.
  - 32 of the 34 dogs (94.1%) in the native L-asparaginase group achieved a complete response (CR) with a median time to relapse of 214 days.
  - 30 of the 35 dogs (85.7%) in the PEG L-asparaginase group achieved CR with a median time to relapse of 217 days.
- As a single agent, the overall response rate (CR + partial response [PR]) after the first two weeks of treatment was 77% for L-asparaginase and 81% for PEG L-asparaginase.
  - With the addition of other chemotherapy drugs, response rates (CR + PR) were 99% for native L-asparaginase and 94% for PEG L-asparaginase. **[Figure 2]**

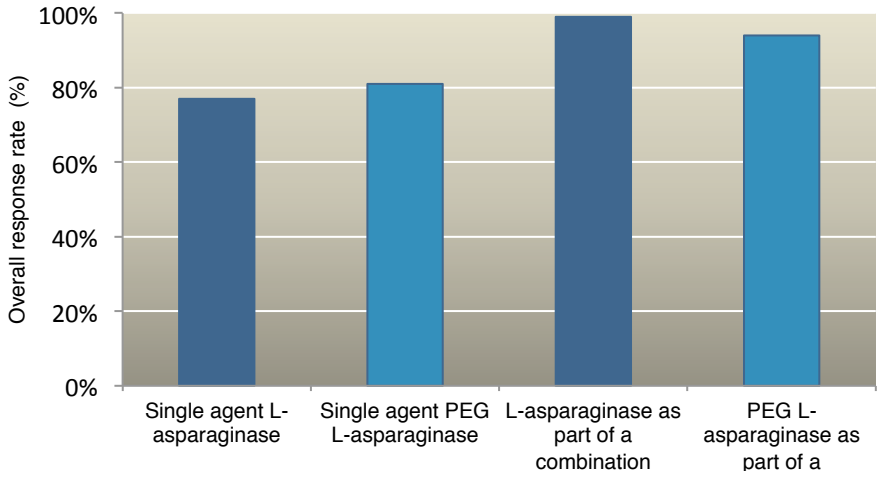

Figure 2. Response rate (CR + PR) after two treatment cycles

- 3 of the 69 dogs (4%) exhibited adverse effects.
  - 1 dog in PEG exhibited a mild, generalized urticarial reaction.
  - 2 dogs in L-asparaginase exhibited severe allergic reactions.

IM ADMINISTRATION HAS BEEN REPORTED TO BE THE MOST EFFECTIVE ADMINISTRATION METHOD FOR ASPARAGINASE USE IN DOGS.[2]

Study 2. In this prospective study, 49 dogs with multicentric lymphoma were randomly assigned to receive three weekly treatments of asparaginase at 10,000 U/m^2 per body surface area subcutaneous (SC) or IM. The dogs also received doxorubicin every three weeks for five treatments, with the first doxorubicin dose administered 24 hours prior to the first asparaginase dose.[2]

- Median days to achieve CR was 9 days for the IM group.
- Median days to achieve CR and 15 days for the SC group.
  - Number of days to achieve CR was significantly shorter in dogs in clinical stage IV (using the World Health Organization's staging system) in the IM group (8 days)
- There was no significant difference in duration of first remission and survival time for the IM group and SC group.
  - Duration of first remission for the IM group was 191 days and survival time was 286 days.
  - Duration of first remission for the SC group was 109 days and survival time was 198 days.
- Duration of first remission and survival were significantly longer in dogs in clinical state III that received asparaginase IM (191 and 289 days, respectively), compared with SC (103 and 209 days, respectively).
- No clinical signs or serum biochemical values related to adverse effects of asparaginase treatment were observed in dogs, regardless of route of administration.

WHEN ADMINISTERED IM, DOGS TREATED WITH ASPARAGINASE DEMONSTRATE NO CLINICAL SIGNS OF THE TOXICITIES RELATED TO ASPARAGINASE ADMINISTRATION.[3]

Study 3. In this prospective study, 81 dogs with malignant tumors were treated with L-asparaginase IM (10,000 IU/m^2). L-asparaginase was administered weekly for up to four treatments and every three weeks thereafter until remission was obtain or the clinician documented that the dog did not respond to therapy. The mean number of treatments was 2.9 (range, 1–10).

- Overall response rate (CR + PR) was 79.5% for the 39 dogs treated with L-asparaginase as a single agent.
- Overall response rate (CR + PR) was 78.9% for the 19 dogs that had not had any other chemotherapy prior to the L-asparaginase treatment.
- None of the dogs developed clinical signs related to the unique toxicities of L-asparaginase administration.
- 20 of the 39 dogs (52%) exhibited mild and self-limiting adverse effects.

TREATMENT RECOMMENDATIONS

The results support the use of asparaginase in inducing remission in canine lymphoma—both as a single agent and as part of combination chemotherapy treatment. The studies reported high response rates, and asparaginase treatment was infrequently associated with adverse effects. Authors observed few clinical signs related to the unique toxicities of asparaginase administration, and other adverse effects were generally mild and self-limiting. Asparaginase was also reported to be effective for maintenance of remission.

In particular, these studies support the use of IM administration of asparaginase. Authors observed that IM administration significantly increased the duration of first remission and survival for dogs in clinical stage III and decreased the days to achieving CR for dogs in clinical stage IV, when compared to dogs treated via SC administration.[2] Previous studies have shown that intravenous (IV) administration may increase risk for anaphylaxis.[4]

In addition, compounded asparaginase is considered to be safe to use.

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[1] MacEwen, E. G., et al. (1992). Evaluation of L-asparaginase: Polyethylene glycol conjugate versus native L-asparaginase combined with chemotherapy. *Journal of Veterinary Internal Medicine, 6*(4), 230–233.

[2] Valerius, K. D., et al. (1999). Comparison of the effects of asparaginase administered subcutaneously versus intramuscularly for treatment of multicentric lymphoma in dogs receiving doxorubicin. *Journal of the American Veterinary Medical Association, 214*(3), 353–356.

[3] Ogilvie, G. K., et al. (1994). Prevalence of anaphylaxis associated with the intramuscular administration of L-asparaginase to 81 dogs with cancer: 1989–1991. *Journal of the American Animals Hospital Association, 30*, 62–64.

[4] Plumb, D. C., (2015). Asparaginase. In *Plumb's Veterinary Drug Handbook* (8th ed.). Vin Foundation.