Evaluation of toxicosis of liposome-encapsulated *cis*-bis-neodecanoato-*trans*-R,R-1,2-diaminocyclohexane platinum (II) in clinically normal cats

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Objective—To determine adverse effects of single and multiple doses of liposome-encapsulated *cis*-bis-neodecanoato-*trans*-R,R-1,2-diaminocyclohexane platinum (II) (L-NDDP) administered IV to healthy adult cats.

Animals—10 healthy adult cats.

Procedure—8 cats were given a single dose of L-NDDP (at rates of 75, 100, 150, or 200 mg/m^2), and 2 cats were given liposomal lipid (1,500 mg/m^2). Six of the 10 cats were given doses of L-NDDP at the maximum tolerated dosage (100 mg/m^2) or a lower dosage (75 mg of L- NDDP/m^2) at 21-day intervals, for a total of 4 treatments. Hematologic and serum biochemical analyses, urinalyses, and physical examinations were used to monitor effects of L-NDDP.

Results—All cats had transient pyrexia, lethargy, vomiting (1 to 3 times/24 h), inappetence, and an acute species-specific infusion reaction that was prevented by administration of atropine-diphenhydramine. Dose-limiting toxicosis was evident as a 10-day course of lethargy, intermittent vomiting, and diarrhea. In cats given multiple doses, dose-related thrombocytopenia, cumulative myelosuppression, transient increased hepatic transaminase activity, and mild to moderate hepatic hydropic degeneration and proximal renal tubular lipidosis in excess of lipidosis expected for this species were detected. Bone marrow hypoplasia was detected in some cats that received higher doses (cumulative dosages of 300 or 400 mg of L-NDDP/m^2).

Conclusion—Cats can safely be given L-NDDP at potentially therapeutic dosages without inducing renal or pulmonary toxicoses.

Clinical Relevance—Because L-NDDP has better tumoricidal activity than cisplatin (in vivo and in vitro) and is not cross resistant, it may be similarly or more efficacious than cisplatin in humans and dogs. (*Am J Vet Res* 1999;60:257–263)

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Cisplatin (**cis dichlorodiamine platinum[II]**; CDDP) is among the most widely used antineoplastic agents in human cancer patients. It is effective in the treatment of ovarian, nonseminomatous testicular, and transitional cell carcinomas, carcinomas involving the head and neck, osteosarcomas, and pulmonary neoplasms in humans.[1-3] In dogs, CDDP is effective in the treatment of osteosarcomas, transitional cell carcinomas, squamous cell carcinomas, and germinal cell tumors, and can be use in combination with other agents for the treatment of soft-tissue carcinomas and sarcomas.[4-12] In humans and dogs, adverse effects of CDDP administration include nausea, vomiting, myelosuppression, alopecia, and dose-limiting nephrotoxicity.[13-15]

In cats, CDDP administration in accordance with the accepted therapeutic regimen for dogs (60 to 70 mg/m^2 administered as an IV bolus during a 20-minute period, after administration of saline [0.9% NaCl] solution) causes acute pulmonary vasculitis resulting in fulminant, fatal pulmonary edema.[16] Even when given at a lower dosage (40 mg/m^2), it results in unacceptably prolonged anorexia.[17] Additionally, repetitive dosing, using a low dosage (10 mg/m^2, 3 times a week for 10 treatments), will result in reversible pulmonary edema and renal insufficiency.[17] When infused at a rate of 30 mg/m^2 during a 3-hour period every 5 weeks, only 1 of 7 cats with oral squamous cell carcinoma developed fatal pulmonary edema. However, low-grade pyrexia, lethargy, inappetence (duration of 1 to 10 days), and tumor progression were observed in all cats.[a]

Liposome-encapsulation of antineoplastic agents alters pharmacokinetics and organ distribution, resulting in increased therapeutic index and decreased toxicity.[18,19] Liposomes are phospholipid vesicles that form when an aqueous solution is added to a lipid powder or film. A conventional 10- to 20-µm multilamellar liposome is composed of lipid bilayers with interspersed aqueous layers arranged much like the layers of an onion. When conventional liposomes are administered intravenously, they concentrate in monocytes, macrophages, and the reticuloendothelial system of the liver, lungs, spleen, and bone marrow. Preferential accumulation of liposomes has been documented in some solid tumors.[18] Attempts to decrease CDDP toxicity and to improve antitumor activity by liposomal encapsulation have been unrewarding because of poor encapsulation