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Cytotoxicity and anaphylaxis of nab-paclitaxel in female beagle dogs-A case report

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Abstract

A bio equivalent (open labeled, single dose, cross over) study of paclitaxel and Nab-Paclitaxel was conducted in beagle dogs. The dogs were divided into two groups of two each. The first group was administered with paclitaxel in suspension form with 50% ethanol and 50% polyethoxylated castor oil and the second group Nab-Paclitaxel which is a nano particle preparation meant to increase solubility, both were administered by intravenous infusion through the cephalic vein. Nab-paclitaxel administered dogs manifested anaphylactic signs and also cytotoxicity of the gut. Cross reactivity among the taxanes was evident as the dogs injected with paclitaxel were subsequently injected with Nab-paclitaxel, during cross over and such dogs showed severe signs of anaphylaxis. It is reported that hypersensitivity and anaphylaxis are seen even with Nab-paclitaxel although it is more water soluble than paclitaxel.

Keywords: Paclitaxel, nab-paclitaxel, beagle dogs, anaphylaxis

Introduction

Paclitaxel, a drug from plant, pacific yew (*Taxus brevifolia*), belonging to taxane group of anti-cancerous drugs which is extensively used to treat a variety of malignancies as second line of treatment in ovarian and breast cancer and also in non-small cell lung cancer, head and neck, pancreatic, colon and non-Hodgkin's lymphoma in human medicine¹. In veterinary medicine, paclitaxel is used in treating lymphoma and mammary tumors. The primary toxicity or adverse effect associated with the drug is hypersensitivity reaction during infusion which could be seen at first infusion or repeated infusions. The literature accompanying the drug suggests pre-treatment with anti-anaphylactic agents such as corticosteroids, anti-histamines and H₂ antagonists. But in some cases the occurrence of anaphylactic reaction has been reported in spite of pretreatment. Added to the hypersensitivity, taxanes are cytotoxic. In a bio equivalent study (open labeled, single dose, cross over) paclitaxel or Nab-Paclitaxel were infused and the adverse or toxic reaction that developed and their management are presented.

Material and methods

Four adult female beagle dogs aged 5-6 ½ years were employed in the present study. They were maintained under standard housing conditions and fed with commercial diet supplied by pedigree®. Clean and fresh water was provided *Ad libitum*. The dogs used in this study were approved by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) (approval no. 32/13). The dogs were divided into two groups of two each. To the first group paclitaxel was administered @ 20 mg/30 minute and to the second group Nab-Paclitaxel @ 20 mg/30 minute and both drugs were administered in the suspension form with 50% ethanol and 50% polyethoxylated castor oil given by intravenous infusion through the cephalic vein.

Results and Discussion

Case 1: Two female beagle dogs (ID No. 2 & 4) aged 5-6 ½ years were presented with signs of malaena, straining, dullness and depression. The animals were off feed passed bloody stools 3-6 times/day and were severely dehydrated.

Management: The cases were treated with Ringer's lactate, Dextrose normal saline alternatively every 8th hour. Injection of Natchrome @ 2 mg/kg IV was administered every day. Pekto-cab syrup -10 ml TID orally. On the 3rd day of treatment animal infused with Nab-Paclitaxel succumbed whereas the other survived.

Case 2: Three female beagle dogs (ID No. 1, 3 & 4) of the same age as mentioned above were infused with Nab-Paclitaxel and Paclitaxel. While infusion, the dogs developed signs of anaphylaxis. The clinical signs noted were salivation, shivering, chills, vomitions, facial oedema, labored breathing, dyspnoea and the skin over the face was folded posteriorly exposing teeth. Two out of three passed blood in stools.

Management: The infusion was discontinued immediately and the dogs were treated with Dexamethasone injection @ 0.5-1.0 mg/kg by I/M, Chlorophenamine maleate injection @ 1-2 mg/kg by I/M, Adrenaline injection (1:1000) @ 0.05-0.5 mg/kg by S/C and Ringer lactate and Normal saline S/C to counter hypovolemic shock. Dog no. 4 was also injected with Ondansetron @ 0.1 to 0.25 mg/kg to control emesis.

Taxanes (Paclitaxel, Docetaxel and Nab-Paclitaxel) are unique in their action as they promote formation of microtubules and inhibit mitosis unlike other plant based drugs like vinca alkaloids, estramustine and epothilones (Ixabepilone) which are microtubule damaging compounds. Taxanes, are known for their cytotoxicity, mucositis, neutropenia and hypersensitivity type I or anaphylaxis. Pre-medication to counter anaphylaxis is recommended as per the accompanying literature but being a bio-equivalent study the use of anti-anaphylactic drugs was not preferred.

Paclitaxel is poorly water soluble and is administered in the form of suspension with a vehicle containing 50% ethanol and 50% polyethoxylated castor oil. The vehicle is said to be responsible for a high rate of hypersensitivity reactions². Docetaxel is more water soluble and Nab-Paclitaxel is a albumin bound nanoparticle for infusion. Water solubility decreases hypersensitivity (Nab-Paclitaxel), whereas modification in the side chain at C₁₃ position (responsible for anti tumour activity) decreases toxicity and enhances efficacy (Docetaxel). Hence, paclitaxel was expected to show hypersensitivity, and Nab-paclitaxel to exhibit cytotoxicity. In contrast, Nab-paclitaxel administered dogs manifested anaphylactic signs and also cytotoxicity of the gut. Females are more susceptible in humans. Coincidentally the same was found in the experiment. To our surprise Nab-paclitaxel which is supposed to be safe has caused signs of anaphylaxis and cytotoxicity.

Anaphylaxis is type I hypersensitivity reaction. In dogs liver is the shock organ and hepatic signs predominantly with hepatic congestion, portal hypertension lead to vomiting and diarrhea. Dermal signs include facial angio-oedema which was observed during the study. Epinephrine is the drug of choice³ and counters circulatory shock mainly by its β_1 action on heart. Added, stimulation of β adrenergic receptors increases Camp through hydrolysis of ATP by adenylyl cyclase. Camp inhibits the Ag-induced release of histamine, triptase and other anaphylactic mediators⁴. Based on its β_2 agonist action it brings about bronchodilation. Antihistamines, glucocorticoids and administration of isotonic crystalloid forms adjunct therapy. H₁ antagonists relieve Nitric oxide (NO) mediated vasodilatation, pruritis and rash. H₂ antagonists reduce gastric acid secretion. H₃ receptors are present on presynaptic nerve endings and inhibit release of nor epinephrine which further aggravates circulatory failure. This can be attenuated by administering H₃ blocker, example, thioperamide. Cross reactivity among the taxanes was evident as the dogs injected with paclitaxel were subsequently injected with Nab-paclitaxel and such dogs showed severe signs of anaphylaxis.

Summary

Based on the present study it is concluded that the hypersensitivity and anaphylaxis are seen even with Nab-paclitaxel although it is more water soluble than paclitaxel. Hence, caution is advised while administering these groups of drugs.

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