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Reactions to tick antitoxin serum and the role of atropine in treatment of dogs and cats with tick paralysis caused by *Ixodes holocyclus*: a pilot survey

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Objective To determine the incidence and nature of adverse reactions of dogs and cats to tick antitoxin serum and to re-evaluate the role of atropine in the treatment of tick paralysis.

Design A retrospective questionnaire of veterinarians.

Procedure Questionnaires were posted to 320 veterinarians in tick-endemic regions of Australia. Questions referred to dogs and cats treated for tick paralysis over a period of three years: the number treated, treatment protocols and adverse systemic reactions to tick antitoxin serum. Ninety completed questionnaires were returned and responses analysed.

Results Veterinarians reported that approximately 3% of dogs exhibited adverse reactions immediately following treatment with tick antitoxin serum. Eighteen percent of these reactions were described as anaphylaxis, with the remaining 82% attributed to the Bezold-Jarisch reflex. Six percent of cats treated with tick antitoxin serum reacted adversely and the majority of reactions (63%) were ascribed to the Bezold-Jarisch reflex. Atropine was used routinely by 10% of responding veterinarians in the treatment of dogs and cats with tick paralysis. A similar number of veterinarians used atropine only in selected cases. Most veterinarians (76%) reported that they never used atropine in the treatment of tick paralysis in either dogs or cats. Within the survey population, premedication with atropine reduced the number of Bezold-Jarisch reactions following tick antitoxin administration approximately five-fold in dogs and four-fold in cats.

Conclusions Data from this pilot survey indicate that more cats than dogs have adverse systemic reactions to tick antitoxin serum and that the majority of these reactions in both dogs and cats could be related to the Bezold-Jarisch reflex. The number of reactions to tick antitoxin serum in dogs and cats could be significantly reduced by the routine use of atropine prior to administration of tick antitoxin serum.

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Key words: Tick paralysis, B-J reflex, anaphylaxis, atropine, tick antitoxin serum, cat, dog.

B-J reflex	Bezold-Jarisch reflex
IV	Intravenouslly
SC	Subcutaneous/ly
TAS	Tick antitoxin serum

Tick paralysis, the condition induced by the Australian paralysis tick, *Ixodes holocyclus*, affects some 10,000 dogs and cats along the eastern coast of Australia every year.[1] Treatment involves the use of TAS to neutralise the clinical effects of the tick's toxin, which acts on the neuromuscular junction to inhibit neurotransmission.[2] However, TAS administration carries with it the risk of possible adverse systemic reaction that has often been termed anaphylaxis. However, anecdotal evidence complied by the National Tick Paralysis Forum in 1998 (unpublished) indicates that there is some confusion concerning TAS reactions and that the term anaphylaxis may be used inaccurately. If true anaphylaxis occurs rarely, then precautions and drugs administered to prevent possible TAS adverse reactions may be ill-directed. The aim of this pilot survey was to determine the incidence and nature of clinical reactions to TAS in dogs and cats in order to re-evaluate prophylactic protocols.

Materials and methods

In December 1999, a retrospective questionnaire was mailed (with invoices sent by Veterinary Pathology Services, Brisbane) to 320 veterinarians practising in tick-endemic regions of Queensland and New South Wales. The survey comprised short-answer and alternate-answer questions and covered the 3-year period ending January 2000. The number of dogs and cats treated annually for tick paralysis by each veterinarian and the total numbers of reactions to TAS were recorded. Respondents were asked to provide actual numbers from practice records if available.

For those animals reacting adversely to TAS, respondents were asked to specify reactions that could best be described by bradycardia, mucous membrane pallor, clinical signs of hypotension, weakness, depression and reduced heart sounds, as opposed to reactions that involved tachycardia, injected mucous membranes, anxiety or restlessness, piloerection on the back of the neck. swelling of the lips, cutaneous wheals, erythema, diarrhoea, vomiting, dyspnoea and coughing. The first of these clinical presentations describes the B-J reflex[3-6] while the latter typifies anaphylaxis[7-13] (Table 1). No reference was made on the survey form to the name of each reaction type in order to minimise inaccurate responses arising from preformed conclusions.

Only responses of veterinarians who routinely used atropine prior to TAS and those who never used atropine were assessed statistically. Data from respondents (n=11) who administered atropine at the same time or after administration of TAS, in all or selected animals, were excluded. This was necessary to assess more accurately the possible prophylactic effect of atropine premedication against the B-J reflex. Chi-squared tests were used to test for association in 2x2 contingency tables. Yates correction was made for one degree of freedom. Significance was assigned a P-value of < 0.001.

Results

Ninety veterinarians returned completed survey forms. Of these, 12% were able to provide exact figures from practice records for the total number of tick paralysis cases treated and 60 to 70% of respondents gave the actual numbers of dogs and cats that reacted to TAS during the survey period. All other figures were estimations.

Dogs

Veterinarians reported treating 14,550 dogs for tick paralysis during the 3-year period and reported an adverse clinical reaction following TAS administration in 3.3% of these dogs. Eighty-two percent of adverse reactions to TAS were described as being clinically characterised by bradycardia, mucous membrane pallor, hypotension, weakness, depression and reduced heart sounds. The remaining 18% of adverse reactions to TAS were clinically characterised by tachycardia, injected mucous membranes, anxiety or restlessness, piloerection on the back of the neck, swelling of the lips, cutaneous wheals, erythema, diarrhoea, vomiting, dyspnoea and coughing. This equated to 2.7% of all dogs treated with TAS exhibiting clinical signs consistent with the B-J reflex and 0.6% of all dogs similarly treated developing anaphylaxis (Table 2).

In the treatment of dogs with tick paralysis, 10% (n=9) of veterinarians reported that they routinely used atropine, 14% (n=13) used it occasionally and 76% (n=68) never used atropine. Dogs that were given atropine before administration of TAS (n=2,640) had fewer B-J reactions: 0.5% developed a B-J reaction compared with 2.7% of dogs treated with TAS alone ($P < 0.001$).

Cats

Surveyed veterinarians recalled treating 6,054 cats for tick paralysis during the 3 years prior to January 2000. Adverse systemic reactions to TAS were observed in 6.2% of these cats. The reactions characterised by clinical signs of bradycardia, mucous membrane pallor, clinical signs of hypotension, weakness, depression and reduced heart sounds were described in 63% of cases, reflecting a 3.9% B-J reaction rate of all cats treated with TAS. Accordingly, 37% of adverse reactions to TAS (2.3% of all cats treated) were described by clinical signs of tachycardia, injected mucous membranes, anxiety or restlessness, piloerection on the back of the neck, swelling of the lips, cutaneous wheals, erythema, diarrhoea, vomiting, dyspnoea and coughing and were considered characteristic of anaphylaxis (Table 2).

The rate of atropine usage in cats was similar to that in dogs. The majority of veterinarians (76%; n=68) reported never using the drug in treatment of tick paralysis, 13% (n=12) used it

Table 1. Summary of differences between the Bezold-Jarisch reflex and anaphylaxis in dogs and cats.

	B-J Reflex[3-6]	Anaphylaxis[7-13]
Pathophysiologic effects	Chemical stimulation of cardiac receptors in the posterior wall of the left ventricle initiates a vagally mediated cholinergic response.	Foreign antigens act on mast cells and basophils to cause cellular degranulation and release of endogenous chemicals that affect multiple organ systems.
Physiologic responses	Bradycardia; systemic vasodilation; reduced total peripheral resistance, and slight, though insignificant, reduction in myocardial contractility.	Peripheral vasodilation; increased vascular permeability; constriction of smooth muscle of bronchi, gastrointestinal tract, and coronary artery; pulmonary vasoconstriction, and increased production of airway mucus.
Clinical signs	Bradycardia; pale mucous membranes; hypotension; weakness; depression, and reduced heart sounds.	Tachycardia; injected mucous membranes; anxiety or restlessness; piloerection on the back of the neck; swelling of the lips; cutaneous wheals; erythema; diarrhoea; vomiting; coughing, and dyspnoea.
Treatment	Atropine 0.1-0.2 mg/kg IV	Adrenaline 0.01mL/ kg of 1: 1000 IV or IM up to a maximum of 0.2-0.5 rnL. Repeat every 15 to 20 minutes if needed.

IM = intramuscularly, IV = intravenously

Table 2. Reported incidence of reactions following TAS administration.

	Dogs	Cats
Animals treated with TAS (n)	14,550	6,054
Reactions to TAS (n)	480	375
Reactions to TAS (%)	3.3	6.2
TAS reactions attributed to the B-J reflex (%)	82	63
Incidence of B-J reactions (%)	2.7	3.9
Incidence of B-J reactions when premedicated with atropine (%)	0.5	0.9
TAS reactions attributed to anaphylaxis (%)	18	37
Incidence of anaphylaxis (%)	0.6	2.3

occasionally and 11% (n=10) routinely administered atropine. Cats that were given atropine prior to administration of TAS (n=1,035) had a significantly reduced number of B-J reactions: 0.9% compared with a reaction rate of 3.9% when atropine was not administered ($P < 0.001$).

Dogs and cats

Significantly fewer dogs than cats showed clinical signs consistent with an anaphylactic reaction following TAS administration ($P < 0.001$).

Discussion

Most adverse reactions that were reported to follow TAS administration in both the dog and cat were characteristic of clinical manifestations of the B-J reflex[3-6] (Table 1), which is a vagally mediated reflex initiated by chemical stimulation of cardiac receptors in the posterior wall of the left ventricle.[3] Bradycardia, hypotension, reduction in total peripheral resistance and a slight, though insignificant, reduction in myocardial contractility occurs with activation of these receptors. The vagal reflex induces bradycardia while hypotension results from a combination of sympathetic withdrawal and cholinergic vaso-dilation. The minor negative inotropic component is solely dependent on the negative chronotropic response.[3] If untreated, persistent bradycardia and hypotension, together with poor ventricular function, will lead to a further decline in cardiac output and systemic arterial pressure, with subsequent induction of circulatory stock.[5]

Due to the cholinergic nature of the B-J reflex, atropine will attenuate or abolish its clinical manifestations.[3,5] This was reflected in the survey results in which only 0.5% of dogs premedicated with atropine developed a B-J reaction following administration of TAS, which is a five-fold reduction compared with dogs not receiving atropine and of which 2.7% exhibited a B-J reaction. Similarly, cats treated with atropine prior to TAS administration had a B-J reaction rate of 0.9% compared with 3.9% for cats not receiving atropine, which is a four-fold reduction in association with atropine administration. In experimental studies, the B-J reflex in dogs was blocked using 0.1 to 0.2 mg/kg IV of atropine.[3,5] Although the present study did not investigate dose rates, the recommended dose rate of atropine is 0.04 mg/kg.[14] If high dose rates block the reflex more completely, this may explain why a small percentage of the survey dogs developed a B-J reaction despite premedication with atropine.

Traditionally, atropine has been used in supportive treatment of tick paralysis to ease dyspnoea by effecting bronchodilation and to reduce salivation and pharyngeal pooling, thereby decreasing the risk of aspiration and airway obstruction. However, since Ilkiw's work[15,16] the use of atropine as part of the treatment for tick paralysis has become unpopular. This trend was seen in the current survey with so few veterinarians routinely administering atropine. Ilkiw proposed that sympathetic overdrive and autonomic imbalance were responsible for the cardiovascular changes documented in dogs with tick paralysis. It followed that atropine, which would attenuate the vagal reflex essential for the body to compensate for excessive sympathetic stimulation, would be contraindicated. However, plasma catecho-lamines were not measured to substantiate the theory and the work was based on only a small group of dogs (n=10, six of which provided results) that had experimentally induced tick paralysis and were heavily instrumented. Recent work on naturally occurring tick paralysis in dogs has not been able to validate Ilkiw's hypothesis and suggests no contraindication for the use of atropine (unpublished).

Anaphylaxis occurs when a foreign antigen acts on host cells to cause release of vasoactive factors. When the rate of release of vasoactive molecules is greater than the body's ability to compensate for the rapid changes in its cardiovascular system, as occurs with rapid IV injection of antigen, anaphylaxis ensues. Multiple organ systems are affected resulting in clinical signs characteristic of anaphylaxis (Table 1).[7-13] Amongst the animals in this survey, the risk of anaphylaxis following TAS administration was minimal. Only 0.6% of all dogs and 2.3% of all cats treated with TAS developed clinical signs consistent with anaphylaxis. The fact that cats were significantly more at risk of anaphylaxis than dogs is not surprising considering that TAS is collected from hyperimmune dogs, and is, therefore, a protein that is foreign to the cat The most important drug in the prevention and treatment of anaphylaxis is adrenaline. It acts via beta-receptors to provide positive chronotropic and inotropic effects and bronchodilation. It also impairs synthesis and release of some mediators of anaphylaxis. Its alpha-agonist properties increase systemic vascular resistance and increase diastolic blood pressure, thereby improving venous return and cardiac perfusion to increase cardiac output further.[7,10]

Premawardhena et al[17] demonstrated that in humans receiving treatment for snakebite the use of SC adrenaline immediately before administration of the antivenom serum significantly reduced the incidence of anaphylactic reactions to serum. Similarly, Malik[18] routinely uses 3 mL of 1:10,000 adrenaline SC 3 to 4 minutes before IV administration of TAS to help prevent anaphylaxis in cats.

Anaphylactic reactions to TAS administration should be treated using 0.01 mL/kg of 1:1000 adrenaline up to a maximum dose of 0.2-0.5 mL. The dose can be repeated 15 to 20 minutes later if needed.[7] Other drugs, such as cortico-steroids, antihistamines, aminophylline and, in selected cases, atropine, may ameliorate the consequences of anaphylaxis. However, the use of these drugs does not eliminate the need for immediate administration of adrenaline.[7,10]

There are some obvious limitations to interpretation of the results of this survey. The sample population of veterinarians was restricted to one client base, and the data may not be representative of the general veterinary or animal population. Veterinarians were asked to provide information about tick paralysis cases and adverse reactions to TAS administration over

a 3-year period. The majority of respondents submitted exact numbers of adverse reactions to administration of TAS but fewer were able to give precise figures for the total number of cases treated. This resulted in many estimations. Additionally, only two choices of reaction category were offered and some mild clinical events following TAS administration may have been unnecessarily included. Similarly, some overlap between reaction categories may exist. For example, the injected mucous membranes accompanying peripheral vasodilation of early anaphylaxis[8,9] may become less injected as shock develops and as neuroendocrine reflexes stimulate peripheral vasoconstriction to redirect blood from skin to vital organs.[8,12,13] A larger prospective survey would overcome these problems, but, while overall figures may vary with a subsequent survey, the significant trends illustrated are unlikely to change. Moreover, this survey has highlighted areas for potential improvement in the treatment of tick paralysis that have not been previously addressed.

Although only a small percentage of animals that receive TAS may have adverse reactions, recognition of the clinical nature of the reaction is vital in order to effectively treat any such reactions. Adrenaline is the most important drug in the prevention and treatment of anaphylaxis. However, because sympathetic withdrawal mediates only a small fraction of the B-J reflex, adrenaline will be of little, if any benefit in the treatment of a B-J reaction. Similarly, administration of atropine prior to administration of TAS will block the B-J reflex, but will not prevent or attenuate anaphylaxis. With such a large proportion of adverse reactions to TAS administration ascribable to the B-J reflex, the routine use of atropine as a premedication in tick paralysis cases may substantially reduce the number of adverse clinical reactions to TAS.

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