PAPERS

Safety of Cartrophen Vet in the dog: review of adverse reaction reports in the UK

Suspected adverse reactions (SARs) reported for Cartrophen Vet (100 mg sodium pentosan polysulphate/ml) to the Veterinary Medicines Directorate in the UK for the period January 1991 to October 1999 were reviewed. Of the 161 reports, 28 were probably product related, 54 were possibly product related, 71 were unlikely to be related and eight were unclassified. An estimated real incidence of adverse reactions probably and possibly associated with Cartrophen Vet of 0·074 per cent on an individual dose basis was calculated (assuming only 10 per cent were documented due to underreporting). Sixty-two SARs (38·5 per cent) documented emesis, 22 (35·5 per cent) of which were product related (onset five to 15 minutes after administration). Sixty-eight SARs (42·2 per cent) documented general changes to demeanour, 10 (14·7 per cent) were product related (lethargy and/or mild depression and/or mild inappetence lasting up to two days after administration). Six SARs were considered likely to be associated with concurrently administered carprofen. Cartrophen Vet had a low incidence of side effects that were mild and transitory.

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INTRODUCTION

Osteoarthritis (OA) is the most common joint disease affecting dogs (Bennett and May 1995) and is not a single disease but a syndrome affecting all moveable (diarthrodial) joints (Johnston 1997, Vaughan-Scott and Taylor 1997, Hulse 1998). OA is a progressive degenerative disease and is characterised pathologically by focal fibrillation and erosion of articular cartilage, subchondral bone changes including sclerosis, osteolysis, osteophytosis and synovial inflammation resulting in pain and disability (Gardner 1983, Mankin and others 1986, Ghosh 1991, Hamerman 1993, Vaughan-Scott and Taylor 1997, McLaughlin 2000).

The need to develop new agents which would specifically target the metabolic imbalances which exist in tissues of osteoarthritic joints is now generally recognised as a rational approach to treatment (Burkhardt and Ghosh 1987, Jones and Doherty 1992, Lequesne 1994, Lequesne and others 1994, Theiler and others 1994, Dougados and others 1996, McNamara and others 1997, Ghosh 1999). While investigations into the pathogenesis of OA are still the subject of worldwide research, recent advances in the understanding of joint tissue (cartilage, bone and synovium) metabolism has identified pathways which may be amenable to therapeutic intervention.

The pentosan polysulphates (PPS) represent a new class of agents that have been shown to correct many of the metabolic imbalances that exist in osteoarthritic joints (Ghosh 1999). The sodium derivative of PPS, sodium pentosan polysulphate (NaPPS), formulated as a sterile veterinary injectable formulation under the brand name of Cartrophen Vet (100 mg NaPPS/mlitre) has gained marketing approval for the treatment of canine OA in Australia, New Zealand and Canada and, within the EU, Finland, Denmark, Ireland, Germany, Sweden and the UK. Cartrophen Vet is administered as a course of four individual subcutaneous doses at 3 mg/kg at seven day intervals.

Ghosh (1999) reviewed the many pharmacological properties of PPS that support the contention that this class of agents is classified as a disease-modifying anti-osteoarthritis drug (DMAOD). The primary pharmacological activities of NaPPS target the pathology of arthritic cartilage, periarticular tissues and blood vessels. However, NaPPS also has effects on blood coagulation, fibrinolytic and lipid/cholesterol systems and so, in principle, the use of Cartrophen Vet as a treatment for canine OA could be associated with haematological abnormalities.

In this review, the data for Cartrophen Vet comprising unsolicited SARs reported to the pharmacovigilance system of the Veterinary Medicines Directorate (VMD) of the then Ministry of Agriculture, Fisheries and Food in the UK, between January 1991 and October 1999, was examined.

Table 1. Number of Cartrophen Vet SAR accessions in the UK, January 1991 to October 1999, with estimated real incidences based on number of courses (% Course) and number of individual doses (% Dose)

Year	Number of SARs	% Course	% Dose
1991	19	1·8095	0·4524
1992	11	0·3896	0·0974
1993	11	0·2721	0·0680
1994	18	0·8170	0·2042
1995	26	0·8000	0·2000
1996	15	0·4045	0·1011
1997	17	0·4502	0·1125
1998	29	0·7583	0·1896
To October 1999	15	0·5018	0·1254
Total	**161**	**0·5819**	**0·1455**

Table 2. Dog breeds reported in SARs to Cartrophen Vet in the UK, January 1991 to October 1999 (n=159)

Breed	% SARs	Placing in top 20 breeds 1999*
Labrador retriever	16·4	1
German shepherd dog	13·2	2
Unspecified	11·9	N/A
Crossbreed	9·4	N/L
Golden retriever	6·9	4
Rottweiler	6·3	11
Spaniel	3·1	6
Border collie	2·5	N/L
Boxer	2·5	9
Burnese mountain dog	1·9	N/L
Collie	1·9	N/L
Great dane	1·9	N/L
Yorkshire terrier	1·9	10
Cocker spaniel	1·3	5
Old English sheepdog	1·3	N/L
Dachshund	1·3	N/L
Dobermann	1·3	15
English setter	1·3	N/L
West Highland white terrier	1·3	3
Bulldog	0·6	N/L
Bull mastiff	0·6	N/L
Cavalier King Charles spaniel	0·6	7
Corgi	0·6	N/L
German pointer	0·6	N/L
Gordon setter	0·6	N/L
Greyhound	0·6	N/L
Irish wolfhound	0·6	N/L
Jack Russell terrier	0·6	N/L
Lauchlen	0·6	N/L
Miniature dachshund	0·6	N/L
Poodle	0·6	N/L
Red and white setter	0·6	N/L
Rhodesian ridgeback	0·6	N/L
Samoyed	0·6	N/L
Staffordshire bull terrier	0·6	8
Terrier	0·6	N/L
Weimaraner	0·6	19

*Data supplied by The Kennel Club, London
N/A Not applicable, N/L Not listed

The objective was to determine whether the reported SARs could be related to the known pharmacodynamic activities of NaPPS, in particular its effects on blood coagulation and fibrinolysis.

MATERIALS AND METHODS

Pharmacovigilance data reported by veterinarians in the UK, where Cartrophen Vet has been sold for more than 12 years, and covering the period January 1991 to October 1999, was reviewed. The reports received by the company were classified on the case documentation provided, including the type of change and its severity, into four categories of association with the product (as described by the Veterinary Medicines Directorate [1996]); namely, A = probable, B = possible, O = unclassified and N = unlikely to be drug related.

SARs are known to be underreported. Reports submitted to the passive pharmacovigilance system that operates in the USA account for 1 per cent or less of the actual adverse experiences that occur, as a result of underreporting by veterinarians and owners and report filtering by the industry (Bataller and Keller 1999). While the pharmacovigilance system run by the VMD to monitor veterinary drugs in the UK is also passive, whereby reporting of SARs by veterinarians and owners is voluntary but encouraged, the 'yellow form system' used in the UK has to some degree reduced the underreporting of SARs that can arise in such passive systems (A. Gray, VMD, personal communication). Furthermore, the company distributing Cartrophen Vet has a policy of actively investigating all SAR reports, and would submit a SAR report if the veterinarian did not, thus avoiding industry filtering. While it is only possible to estimate real incidence rates for SARs, not actual incidences, in this review, the assumption is made that the UK yellow form pharmacovigilance system has lessened underreporting and industry filtering, resulting in 10 per cent of actual adverse experiences being reported.

RESULTS

Between January 1991 and October 1999, 161 SARs to Cartrophen Vet (the numerator) relating to 159 dogs and two cats, were reported in the UK; this represented an observed incidence based on individual doses of 0·0145 per cent (the denominator for this calculation is derived from sales in this region during this period) and an observed incidence based on number of courses of 0·0582 per cent (the denominator for this calculation assumes four individual doses per course as per the label recommendations). Assuming that the UK yellow form pharmacovigilance system has ameliorated the issues of underreporting and filtering to some degree, resulting in up to 10 per cent of actual adverse experiences being reported, then the estimated real incidence of SARs to Cartrophen Vet is calculated as 0·145 per cent on an individual dose basis. It is noteworthy that a higher number of reports compared to Cartrophen Vet sold was observed while the product was gaining use. Table 1 summarises the number of SAR accessions per year following the launch of Cartrophen Vet, in 1991 through to 1999, and the observed incidences of SARs based on the number of courses and the number of individual doses.

A wide range of conditions were described in the 159 SARs involving dogs, affecting many different breeds, ages and both sexes. Of the two SARs involving cats, one was a three-year-old male neutered Persian, while the age, sex and breed of the other was unspecified. Table 2 summarises the 37 dog breeds identified, with the most commonly reported being Labrador retrievers (16·4 per cent), German shepherd dogs (13·2 per cent) and crossbreeds (9·4 per cent). Also in Table 2 is data showing the ranking of breeds in

Table 3. Adverse effects reported in SARs to Cartrophen Vet in the UK, January 1991 to October 1999 (n=161)

Adverse effect reported	Number of SARs	% of SARs showing effect
General change in demeanour	68	42·2
Vomiting	62	38·5
Death	29	18·0
Diarrhoea	29	18·0
Haemorrhage	27	16·8
Collapse	23	14·3
Respiratory	20	12·4
Cardiovascular	14	8·7
Oedema	13	8·1
Central nervous system	12	7·5
Pyrexia	12	7·5
Haematological	8	5·0
Cutaneous	8	5·0
Genitourinary	7	4·3
Injection site reaction	6	3·7
Hepatic	3	1·9
Skeletal	3	1·9
Ocular	2	1·2
Lameness	2	1·2

terms of their registrations from 1 to 20 in 1999 (data supplied by The Kennel Club). Breeds were unspecified in 11·9 per cent of SARs involving dogs. It can be seen that the representation of breeds in the SARs is probably similar to their respective proportions in the UK population over the January 1991 to October 1999 period, rather than reflecting any clear breed association.

The age of the dog was unspecified in 32 SARs. In the remaining 127 SARs, the age distribution was as follows: 46 dogs (35·9 per cent) were 9·1 to 12·0 years; 33 (25·8 per cent) were 6·1 to 9·0 years; 21 (16·4 per cent) were 3·1 to 6·0 years; 19 (15·6 per cent) were 0 to 3·0 years; and eight (6·3 per cent) were 12·1 to 15·0 years. In total, 108 of the 127 SARs where age was reported (84·4 per cent) involved dogs aged 3·1 years or older. This predominance of mature dogs in the pharmacovigilance data is not surprising given that OA has been estimated to affect as much as 20 per cent of the dog population over one year of age (Pfizer Animal Health, unpublished proprietary market research data). The sex of the dog was unspecified in 42 SARs. In the remaining 117 SARs, 59 (50·4 per cent) were males and 58 (49·6 per cent) were females. Assuming there was no bias with respect to the sex among those dogs where it was not specified, no sex association was apparent.

The nature of the wide range of conditions described in the 161 SARs reported for Cartrophen Vet is detailed in Table 3. A general change in demeanour (including 'off colour', listlessness, lethargy, anorexia, and reduced or increased activity) was the most common adverse effect reported and was noted in 42·2 per cent of SARs. Emesis was the other major effect noted, accounting for 38·5 per cent of the SARs including both reports involving cats.

Of the 161 SARs reported, the relationship to administration of Cartrophen Vet was considered as follows: 28 probable, including one cat being treated for chronic cystitis; 54 possible; eight unclassified; and 71 unlikely to be related, including the other cat being treated for feline urological syndrome and urethral blockage which died of renal failure. SARs considered to be probably related included those animals that presented with vomiting very shortly (ie, within five to 15 minutes) following administration of Cartrophen Vet (35·5 per cent of all reports recording vomiting) and with a general change in demeanour for up to one to two days, typified by lethargy and/or mild depression and/or mild inappetence (14·7 per cent of all reports recording a change in demeanour). Such cases recovered quickly, usually with no supportive treatment.

The signs observed in the SARs considered probably related included vomiting (22 reports) and general change in demeanour (10 reports), while other generalised signs were described in another 16 reports. The signs observed in the SARs considered possibly related included vomiting (23 reports), general change in demeanour (29 reports), death (12 reports), diarrhoea (12 reports) and haemorrhage (12 reports), while other generalised signs were described in another 39 reports. The type of general demeanour changes reported in SARs considered probably and possibly related were as follows: anorexia/inappetence (10 reports), depression (11 reports) and lethargy (19 reports), while other generalised signs were described in 17 reports. Of the 161 SARs reported, 71 were considered unlikely to be related to the administration of Cartrophen Vet, as the presenting signs did not relate to the known pharmacology or toxicity of the drug, and were typical of normally occurring clinical conditions. Eight of the 161 cases were unclassified, as the clinical signs reported in the SARs were inconclusive as to their relationship with Cartrophen Vet.

Twenty-nine deaths were recorded, including seven cases of euthanasia. No deaths were considered probably related to Cartrophen Vet, while 41·4 per cent were considered possibly related, 41·4 per cent were considered unlikely to be related and 17·2 per cent were unclassified. Fifteen of the 29 deaths were investigated by postmortem examination and significant underlying pathologies unrelated to Cartrophen Vet were confirmed in each case and considered to be the cause of fatality. Twelve cases where death was recorded, including five cases of euthanasia, were classified as possibly related. However, not all of the 12 cases could be investigated by postmortem examination. Confirmed postmortem diagnoses in possibly related cases included bleeding haemangiosarcoma (one), bleeding hepatic peliosis/telangiectasis (one), renal amyloidosis and hepatic peliosis (one), osteosarcoma (one), undefined liver tumour (one), nodular hyperplasia and fatty change of the liver (one), mammary and adrenal neoplasia (one), bleeding liver and splenic neoplasia

Table 4. General signs noted in SARs involving death where the cause of death could not be established, the number of cases involved and the relationship to Cartrophen Vet

Sign	A	B	C	N
Abdominal pain				1
Abnormal oral mucosa			2	2
Anaemia		1	1	1
Anorexia		1		
Cold ears and lips			1	
Collapse		1	4	1
Diarrhoea		1	2	3
Died in sleep				1
Dyspnoea			1	1
Haemorrhage		2	1	2
Heart failure				1
Jaundice		1		
Lethargy			1	
Liver dysfunction				1
Lymphadenomegaly			1	
Melaena			1	1
Oedema				1
Pain				1
Pyrexia		1		1
Quietness		1	2	2
Respiratory difficulty			1	2
Seizures				1
Shock			1	
Stiffness		1		
Swollen legs				1
Tachycardia			1	1
Tachypnoea		1	1	
Vomiting			1	2
Weakness		1		

A = Probable, B = Possible, C = Unclassified, N = Unlikely to be related (Veterinary Medicines Directorate 1996)

Table 5. The site of bleeding in SARs where haemorrhage was reported, the number of cases involved and the relationship to Cartrophen Vet

Site of bleeding	A	B	C	N
Gastrointestinal	1	4	1	9
Thoracic cavity		2		
Abdominal cavity		5		
Pericardium		1		
Musculoskeletal		1		1
Episclera				1
Retina				1
Subcutis		1		
Oral labia		1		
Nasal cavity		1		1
Genitourinary	1	1		1

A = Probable, B = Possible, C = Unclassified, N = Unlikely to be related (Veterinary Medicines Directorate 1996)

(one), and adenocarcinoma of mammary gland and secondary mammary carcinoma (one). Confirmed postmortem diagnoses in cases classified as unlikely to be related included gastric dilatation/torsion (one), acute hepatic cirrhosis/ necrosis (one), renal tubular necrosis (one), brain tumour (one), multifocal liquefactive necrotising steatitis and hepatocellular carcinoma (one), and haemorrhagic diarrhoea and septicaemia (one). Table 4 details the general signs noted in cases where the cause of death could not be established.

Haemorrhage was recorded in 27 of the SARs and the site of bleeding and the association with Cartrophen Vet is summarised in Table 5. The 15 cases of bleeding into the gastrointestinal tract and their relationship to Cartrophen Vet (in parentheses) were as follows: haemorrhagic diarrhoea (one probable, three possible, one unclassified and five unlikely to be related); melaena (four unlikely to be related); and haematemesis (one possible and one unlikely to be related). In four of the 27 SARs where haemorrhage was recorded, there was concurrent use of NSAID therapy (meloxicam, flunixin meglumine, tolfenamic acid, cinchophen/ prednisolone) and in one case there was concurrent use of steroids (methylprednisolone acetate). In eight of the 27 SARs, bleeding was associated with malignancies, which included haemangiosarcoma (one), unspecified splenic tumour (one), unspecified multiple hepatic tumours and single splenic tumour (one), mammary and adrenal neoplasia (one), mammary adenocarcinoma (one), suspected prostatic malignancy (one), unspecified multiple hepatic tumours (one) and hepatic peliosis and telangiectasis (one). The administration of Cartrophen Vet was possibly contributory to a bleeding episode in seven of the eight SARs where malignancy was reported. However, in two cases the animal involved had recently received treatment with NSAIDs, which have been recognised to negatively affect haemostasis (Isaacs 1996, Mathews 2000). One report where bleeding was described, involved a dog suffering from gastric dilatation and volvulus syndrome. Another report of haemorrhagic diarrhoea occurred in an animal where no other medical anti-inflammatory treatments were noted in the immediate or recent history; however, the animal had received Cartrophen Vet on previous occasions with no ill effect.

Use of the NSAID carprofen (Rimadyl, Pfizer; Zenecarp, C-Vet) was reported in 18 SARs and its use was concurrent with Cartrophen Vet administration in six SARs. In particular, the following signs were noted: anorexia, dullness, lethargy, collapse, vomiting, haemorrhagic and non-haemorrhagic diarrhoea, haemorrhage, anaemia, pyrexia, skin disorders including rash, pain, oedema, swelling and death. The six SARs in which there was concurrent use of carprofen were classified as probably related to carprofen, while the involvement of carprofen could not be excluded in a further six of the 18 SARs where it was reported.

There was no evidence of spontaneous haemorrhage (local or systemic) attributable to Cartrophen Vet such as that observed with heparin in the pharmacovigilance data reviewed.

DISCUSSION

A wide range of adverse effects was reported in the 161 unsolicited SARs that comprised the pharmacovigilance data for Cartrophen Vet in the UK covering the sales period January 1991 to October 1999. Assuming that the UK pharmacovigilance system receives reports of 10 per cent of actual adverse reactions, then

the estimated real incidence of SARs to Cartrophen Vet is 0·145 per cent on an individual dose basis. Of the 161 reports, 28 were probably related, 54 were possibly related, 71 were unlikely to be related and eight were unclassified. An estimated real incidence of SARs probably and possibly associated with Carttrophen Vet is 0·074 per cent on an individual dose basis.

No breed, age or sex association was apparent in the reports. Only vomiting occurring soon after treatment or general demeanour changes such as quietness, lethargy and inappetence for one or two days after an injection were considered to be related to administration of the product. Lethargy was the major change reported in the probably and possibly related SARs, followed by depression and anorexia or inappetence. The bleeding episodes reported were often associated with significant underlying pathologies and/or recent use of anti-inflammatory medications. Indeed, the concurrent use of NSAIDs or corticosteroids in 14·3 per cent of the SARs may have contributed to some of the adverse side effects reported.

The NSAID carprofen was reported in 18 SARs and its use was concurrent with Cartrophen Vet administration in six SARs. The following signs were conspicuous: anorexia, dullness, lethargy, collapse, vomiting, haemorrhagic and non-haemorrhagic diarrhoea, haemorrhage, anaemia, pyrexia, skin disorders including rash, pain, oedema, swelling and death. It is noteworthy that SARs reported for carprofen during clinical use in the USA comprise: gastrointestinal disturbances (including vomiting, diarrhoea, anorexia, inappetence, gastrointestinal bleeding); hepatopathy and hepatic dysfunction (including inappetence, vomiting, acute hepatic toxicity, hypoalbuminaemia – one-quarter of hepatic carprofen SARs were in Labrador retrievers); haematological disturbances (epistaxis, blood loss anaemia, immune-mediated haemolytic anaemia, immune-mediated thrombocytopenia); urinary system abnormalities (including polyuria, polydipsia, urinary incontinence); immunological conditions or hypersensitivity (facial swelling, hives, erythema); neurological disturbances (including vestibular signs, paresis, ataxia, seizures, disorientation); behavioural disturbances (including hyperactivity, aggression, depression, lethargy); dermatological signs (including pruritus, increased shedding, ventral ecchymosis); and death (Anon 2003). Given the adverse effects to carprofen reported during clinical use in the USA, the involvement of carprofen could not be excluded in 12 of the 18 Carttrophen Vet SARs where carprofen was recorded.

It is acknowledged that the under-reporting of SARs is a complication of passive pharmacovigilance reporting systems such as that which operates in the UK and that the data accumulated from such a system is biased. However, if such limitation is duly recognised, it is apparent that the overall number of reported SARs to Cartrophen Vet is relatively small given the wide usage of the product over a broad demographic range of the population. In comparison with the known adverse effects on the gastrointestinal tract, kidney and liver produced by conventional NSAID treatments (Palmoski and Brandt 1980, Innes 1995, Isaacs 1996, Vaughan-Scott and Taylor 1997, Hulse 1998, McLaughlin 2000, Mathews 2000), the reports for NaPPS are comparatively few and mild. Moreover, since clinical efficacy in the treatment of OA with Cartrophen Vet is between 70 and 80 per cent (Hay 1992, Turner 1992, Hallikainen 1994, Bouck and others 1995, Read and others 1996, Smith and others 2001), the risk/benefit ratio is very high.

Significantly, however, only one of the SARs classified as probably related and 14 of the SARs classified as possibly related could be linked to known haematological or lipolytic activities of this drug (Ghosh 1999) – minor unspecified haematological changes (one), anaemia, thrombocytopenia and haemorrhage (one), anaemia and haemorrhage (one) and haemorrhage (11). It is noteworthy that malignancies were present in seven of the 14 possibly related cases where bleeding and/or haematological dysfunction was recorded.

Among the wide range of animals of differing ages, breeds and sex reported, there was no evidence of either local or systemic spontaneous haemorrhage that was attributable to Cartrophen Vet. While NaPPS is a member of the heparinoid family of drugs, it lacks the haematological potential of heparin (Ghosh 1999). Therefore, should evidence of bleeding occur during a course of Cartrophen Vet treatment, the course should be stopped and an investigation initiated immediately to determine the cause of the bleeding, as the bleeding episodes reviewed in the pharmacovigilance data were often associated with significant underlying pathologies (Tables 3, 4 and 5).

The fact that no spontaneous local or systemic haemorrhage attributable to Cartrophen Vet was observed is supported by laboratory findings on the effect of the drug on seven clotting parameters assessed in the dog under controlled conditions at doses of 3, 15 and 30 mg NaPPS/kg (data on file, Biopharm Australia Pty). A dose-related increase in thrombin time (TT) and activated partial thromboplastin time (APTT) was observed at the recommended dose of 3 mg/kg, was most pronounced two hours after administration and disappeared with time. A slightly increased APTT and TT were noted in the high-dose groups 24 hours after administration. It is noteworthy that the remaining clotting parameters were not influenced by the test substance and were within normal ranges. Substance-related local intolerance reactions such as haematoma and evidence of systemic bleeding (eg, ecchymosis or gastrointestinal bleeding) were not observed at any dose.

The vomiting and mild depression observed in some dogs following Cartrophen Vet administration could be the canine equivalent of the hypersensitivity to NaPPS occasionally described as migraine

or headache in human patients (Arthropharm, unpublished data). This reaction to NaPPS may be explained by recent research findings that have shown that certain polysulphated polysaccharides can act like negatively charged surfaces, thereby contributing to the initiation of the contact system.

Plasma kallikrein is a product of the contact activation pathway when prekallikrein and factor XII (Hageman factor) become activated in the presence of kininogen by tissue injury or contact by a negatively charged substrate. Kinins, produced by activation of kininogen, are known to increase capillary permeability, produce oedema and pain and contract or relax various smooth muscles (Douglas 1980). In experiments described by Brunnee and others (1997), it was shown that soluble fractions of mast cell derived heparins of molecular weights within the range of 17,000 to 69,000 Da were potent initiators of contact activation. Moreover, synthetic polysulphated polysaccharides, such as dextran sulphate, were also found to reproduce this physiological response and several earlier studies had shown that the potency of activation by these polyanions was dependent on the number and position of sulphate ester groups on the individual polysaccharide rings (Hojima and others 1984, Silverberg and Diehl 1987a,b).

Although the average molecular weight of NaPPS of 5700 Da (Ghosh 1999) is below the threshhold suggested by Brunnee and colleagues (1997) to trigger the contact reaction, the drug is nevertheless a polydispersed polymer and higher molecular NaPPS species are present, albeit in small amounts, in the Cartrophen Vet preparation manufactured by Biopharm Australia. Significantly, the proportion of these higher molecular weight polysulphated species in commercial NaPPS preparations from other sources is even greater than in Cartrophen Vet (Degenhardt and others 2001). These higher molecular weight NaPPS fractions would, by structural analogy with the mast cell heparins (Brunnee and others 1997) and dextran sulphates (Hojima and others 1984, Silverberg and Diehl 1987a,b), be expected to participate in the contact activation reaction and mediate the release of kinins into plasma.

Alternatively, or in addition to the suggested direct interaction of NaPPS in the contact reaction is the possibility that, because of the high charge density of this anionic polymer, it displaces some of the heparin proteoglycans from their endogenous binding sites on plasma proteins and/or mast cell granules. On the basis of this hypothesis, it could be predicted that, in hypersensitive dogs, modest tissue injury as might be produced by the process of subcutaneous injection, in combination with the perfusion of the damaged site by the small proportion of high molecular weight fractions in the polydispersed NaPPS or endogenous heparins, could initiate the contact activation pathway and the release of kallikrein. While this explanation remains speculative at this stage, it is significant that in four of the SAR reports it was noted that subcutaneous oedema in the facial area following administration of Cartrophen Vet could be ameliorated by treatment with antihistamines, suggesting that mast cell degranulation and histamine release may have occurred.

The 29 deaths reported were not considered to be related to Cartrophen Vet administration or its ability to mediate contact activation. Fifteen of the 29 deaths were investigated by postmortem examination and significant underlying pathologies were confirmed in each case that were unrelated to the therapy and explained the fatality. There is no evidence of clustering, either in the confirmed diagnoses or in the general signs, in cases where the cause of death could not be established (Table 4). It is considered that the deaths represent chance findings. Furthermore, there was no evidence of any disease condition (eg, kidney, heart or liver failure), being exacerbated by Cartrophen Vet treatment.

Conclusions

It is acknowledged that an underreporting of SARs has occurred and that the pharmacovigilance data accumulated for Cartrophen Vet is biased. However, it can be concluded from this review of available data that the low frequency of reported SARs to NaPPS demonstrates that Cartrophen Vet treatment is associated with a low incidence of mild, quickly reversible side effects.

References

Anon (2003) Medicinal products for human and veterinary use, Vol 9 - Pharmacovigilance. Veterinary Medicines Directorate, London. pp 163-164

Bataller, N. & Keller, W. C. (1999) Monitoring of adverse reactions to veterinary drugs. *Veterinary Clinics of North America: Food Animal Practice* **15**, 13-30

Bennett, D. & May, C. (1995) Joint diseases of dogs and cats. In: Textbook of Veterinary Internal Medicine. Ed S. J. Ettinger. W. B. Saunders, Philadelphia. pp 2053-2059

Bouck, G. R., Miller, C. W. & Taves, C. L. (1995) A comparison of surgical and medical treatments of fragmented coronoid process and osteochondritis dissecans of the canine elbow. *Veterinary and Comparative Orthopaedics and Traumatology* **8**, 177-183

Brunnee, T., Reddigari, S. R., Shibayama, Y., Kaplan, A. P. & Silverberg, M. (1997) Mast cell derived heparin activates the contact system: a link to kinin generation in allergic reactions. *Clinical and Experimental Allergy* **27**, 653-663

Burkhardt, D. & Ghosh, P. (1987) Laboratory evaluation of anti-arthritic drugs as potential chondroprotective agents. *Seminars in Arthritis and Rheumatism* **17** Supplement 1, 3-34

Degenhardt, M., Ghosh, P. & Watzig, H. (2001) Studies on the structural variations of pentosan polysulfate sodium (NaPPS) from different sources by capillary electrophoresis. *Archive der Pharmazie – Pharmaceutical and Medicinal Chemistry* **334**, 27-29

Dougados, M., Devogelaer, J. P., Annefeldt, M., Avouac, B., Bouvenot, G., Cooper, C., Dieppe, P., Ethgen, D., Garattini, S. & Jones, E. A. (1996) Recommendations for the registration of drugs used in the treatment of osteoarthritis. *Annals of the Rheumatic Diseases* **55**, 852-857

Douglas, W. W. (1980) Polypeptides – angiotensin, plasma kinins and others. In: Goodman and Gilman's The Pharmalogical Basis of Therapeutics, 6th edn. Eds A. G. Gilman, L. S. Goodman and A. Gilman. Macmillan Publishing, New York. pp 647-681

Gardner, D. L. (1983) The nature and causes of osteoarthrosis. *British Medical Journal* **286**, 418-424

Ghosh, P. (1991) Osteoarthritis: aetiopathogenesis and management. *Modern Medicine Australia* **68**, 68-80

Ghosh, P. (1999) The pathobiology of osteoarthritis and the rationale for the use of pentosan polysulfate for its treatment. *Seminars in Arthritis and Rheumatism* **28**, 211-267

Hallikainen, A. (1994) The use of pentosan polysulphate sodium in the treatment of musculoskeletal disease in the dog – an open clinical study. Graduate thesis. University of Helsinki, Finland

Hamerman, D. (1993) Aging and osteoarthritis: Basic mechanisms. *Journal of the American Geriatrics*

Society **41**, 760-770

HAY, L. E. (1992) The use of pentosan polysulphate following the repair of cranial cruciate ligament rupture in dogs. MSc Thesis. Murdoch University, Perth, Western Australia

HOJIMA, Y., COCHRANE, C. G., WIGGINS, K. F. & STEVENS, R. L. (1984) In vitro activation of the contact (Hageman Factor) system of plasma by heparin and chondroitin sulfate E. *Blood* **63**, 1453-1459

HULSE, D. (1998) Treatment methods for pain in the osteoarthritic patient. *Veterinary Clinics of North America: Small Animal Practice* **28**, 361-375

INNES, J. (1995) Diagnosis and treatment of osteoarthritis in dogs. *In Practice* **17**, 102-109

ISAACS, J. P. (1996) Adverse effects of non-steroidal anti-inflammatory drugs in the dog and cat. *Australian Veterinary Practitioner* **26**, 180-186

JOHNSTON, S. A. (1997) Osteoarthritis: joint anatomy, physiology and pathobiology. *Veterinary Clinics of North America: Small Animal Practice* **27**, 699-723

JONES, A. C. & DOHERTY, M. (1992) The treatment of osteoarthritis. *British Journal of Clinical Pharmacology* **33**, 357-363

LEQUESNE, M. (1994) Symptomatic slow-acting drugs in osteoarthritis: A novel therapeutic concept? *Revue du Rhumatisme* (English edition) **61**, 75-79

LEQUESNE, M., BRANDT, K., BELLAMY, N., MOSKOWITZ, R., MENKES, C. J., PELLETIER, J-P. & ALTMAN, R. (1994) Guidelines for testing slow acting drugs in osteoarthritis. *Journal of Rheumatology* **21** (Supplement 41), 65-73

MCLAUGHLIN, R. (2000) Management of chronic osteoarthritic pain. *Veterinary Clinics of North America: Small Animal Practice* **30**, 933-949

MCNAMARA, P. S., SPENCER, D. V. M., JOHNSTON, S. A. & TOCHUNTER, R. J. (1997) Slow acting, disease modifying osteoarthritis agents. *Veterinary Clinics of North America: Small Animal Practice* **27**, 863-881

MANKIN, H. J., BRANDT, K. D. & SHULMAN, L. E. (1986) Workshop on etiopathogenesis of osteoarthritis, proceedings and recommendations. *Journal of Rheumatology* **13**, 1126-1160

MATHEWS, K. (2000) Non-steroidal anti-inflammatory analgesics: indications and contraindications for pain management in dogs and cats. *Veterinary Clinics of North America: Small Animal Practice* **30**, 783-804

PALMOSHI, M. J. & BRANDT, K. D. (1980) Effects of some nonsteroidal antiinflammatory drugs on proteoglycan metabolism and organization in canine articular cartilage. *Arthritis and Rheumatism* **23**, 1010-1020

READ, R. A., CULLIS-HILL, D. & JONES, M. P. (1996) Systemic use of pentosan polysulphate in the treatment of osteoarthritis. *Journal of Small Animal Practice* **37**, 108-114

SILVERBERG, M. & DIEHL, S. V. (1987a) The autoactivation of Factor XII (Hageman factor) induced by low Mr heparin and dextran sulphate. *Biochemical Journal* **248**, 715-720

SILVERBERG, M. & DIEHL, S. V. (1987b) The activation of the contact system of human plasma by polysaccharide sulfates. *Annals of the New York Academy of Sciences* **516**, 268-279

SMITH, J. G., HANNON, R. L., BRUNNBERG, L., GEBSKI, V. & CULLIS-HILL, D. (2001) A randomised, double-blind, comparator controlled study of the efficacy of sodium pentosan polysulfate injections and carprofen capsules in arthritic dogs. *Osteoarthritis and Cartilage* **9**, Supplement B, 21

THEILER, R., GHOSH, P. & BROOKS, P. (1994) Clinical, biochemical and imaging methods of assessing osteoarthritis and clinical trials with agents claiming 'chondromodulating' activity. *Osteoarthritis and Cartilage* **2**, 1-23

TURNER, T. (1992) An assessment of Cartrophen Vet in practice. *Veterinary Practice* **24**, 6-9

VAUGHAN-SCOTT, T. & TAYLOR, J. H. (1997) The pathobiology and medical management of canine osteoarthritis. *Journal of the South African Veterinary Association* **68**, 21-25

VETERINARY MEDICINES DIRECTORATE (1996) VMD Guidance Note AMELIA 12 – Marketing Authorisations for Veterinary Medicinal Products: Interim Guidance on Pharmacovigilance. pp 1-12