Megaoesophagus due to acrylamide neuropathy

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SUMMARY Greyhound dogs exposed to oral acrylamide for a period of eight weeks developed a sensorimotor peripheral neuropathy that had many features in common with acrylamide neuropathy seen in other species. Most of the animals also developed the clinical and radiological features of megaoesophagus. The association of neuropathy and megaoesophagus suggests that an axonopathy of the vagus may be an aetiological factor in this disorder.

Megaoesophagus occurs spontaneously in the dog and is of uncertain aetiology.¹ It has also been produced surgically,^{2,3} by exposure to the organophosphorus compound di-isopropyl fluorophosphate,^{4,5} and has been described in a single case of giant axonal neuropathy.⁶ It is of interest because some characteristics of the canine disorder resemble those seen in human oesophageal motility disturbances.

It was observed during a study of acrylamide neuropathy in the dog that some affected animals developed megaoesophagus. The mechanism of this disturbance has been the subject of the present study. A brief preliminary account has been given.⁷ Although acrylamide has been given to many species,⁸ the effect of the neurotoxin in the dog has been incompletely described.⁹ In the present study, the clinical effect of acrylamide on the dog is described and contrasted with the illness produced in other species.

Methods

Fourteen greyhounds with an approximate age range of 1 to 5 years were vaccinated against distemper (Combined Distemper Vaccine) and were given a broad spectrum worming agent (oxontel pamoate, 380 mg; pyrantel pamoate, 100 mg). Acrylamide monomer (99% pure) was dissolved in water at a concentration of 200 mg ml⁻¹ and injected into the daily feed. The animals were weighed, examined clinically and given acrylamide orally at a dose of 7 mg kg⁻¹ day⁻¹; a pilot study had previously indicated that this dose produced a neuropathy after six to eight weeks. The animals were examined daily and a record was kept of their weight, clinical signs and the accumulated dose of acrylamide.

The oesophagus was examined radiologically in the right lateral position in trained animals that had eaten a

mixture of contrast agent (Baritop) and dog food. No restraint was applied to the animals and no premedication was used. Radiology was carried out using a Toshiba 12 pulsed diagnostic X-ray apparatus, (Model KX0-1000). If no contrast material was apparent in the oesophagus and the animals showed no signs of aspiration, 20-25 ml of contrast solution (X-Opaque Powder) were injected into the animal's mouth while in the right lateral position.

Means are expressed with standard deviations, which were all corrected for small numbers. A normal distribution was assumed for all measurements when comparing the normal and acrylamide affected groups. Means were compared using Student's two-tailed *t* test; probability values less than 0.05 were considered to indicate significance.

The study received ethical approval from the Animal Ethical Review Committee of the Faculty of Medicine, University of Sydney.

Results

Clinical features

Toe scuffing, which is a sign of early peripheral neuropathy is the sound made as the toenails of the paws hit the ground; it is not present in normal animals. When toe scuffing was heard on two consecutive days the first day was recorded as the time at which the sign became positive. Toe scuffing occurred from 20 to 38 days after the start of acrylamide administration (mean, 31; SD, 5). The accumulated dose of acrylamide at the onset of toe scuffing ranged from 150 to 270 mg kg⁻¹ (mean, 210; SD, 40).

The first sign of ataxia was limb crossing when animals ascended or descended steps or gutters. Later the animals stood with a widened hindlimb base and walked with a rolling motion of the hindquarters. Only when these last two signs were seen was ataxia recorded. Ataxia was seen from 28 to 53 days after the start of acrylamide administration (mean, 40; SD, 7). The accumulated dose of acry-

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Received 9 June 1981, accepted 6 August 1981

lamide at the onset of ataxia ranged from 210 to 390 mg kg⁻¹ (mean, 290; SD, 50). The duration of the period from the start of acrylamide exposure to the onset of ataxia was significantly longer than the duration to the onset of toe scuffing.

Muscle weakness did not become apparent until after the onset of ataxia. A test for muscle strength employed in the present study consisted of holding the animal stationary for one minute, with the hindlimbs and forelimbs equally spread and the front of the hindpaws vertically below the posterior margin of the buttock. Muscle weakness was regarded as being present if the knees sank to the

same vertical height as the insertion of the Achilles tendon on the calcaneus during this period (fig 1A). The onset of muscle weakness occurred from 44 to 67 days after the start of acrylamide administration (mean, 54; SD, 6). The accumulated dose of acrylamide at the onset of muscle weakness ranged from 340 to 460 mg kg⁻¹ (mean, 390; SD, 30). Muscle weakness occurred after a significantly longer duration of acrylamide exposure than ataxia. (table 1).

Toe folding was a late sign of sensory impairment seen in most animals. Toe folding was regarded as present if the animals remained stationary on

Fig 1 Clinical signs of neuropathy in the dog (A10) A Muscle weakness is shown by the sagging hindquarters. The knees are below the insertion of the Achilles tendon on the calcaneus. B Toe folding suggests sensory impairment in the hindpaw.

Table 1 Clinical features of acrylamide neuropathy in the dog

Animal	Toe folding		Ataxia		Muscle weakness		Toe folding		Regurgitation
	Day	Dose/kg	Day	Dose/kg	Day	Dose/kg	Day	Dose/kg	
A2	31	190	36	230	67	460	—	—	68
A3	38	270	40	290	47	340	55	400	65
A4	31	200	38	270	58	420	60	430	61
A5	28	190	37	270	47	350	—	—	—
A6	20	150	34	250	53	390	61	470	—
A7	37	260	46	340	57	420	58	420	58
A8	32	240	34	250	44	370	48	420	—
A9	27	140	36	250	52	380	54	390	54
A10	29	200	44	330	51	370	55	400	—
A11	28	210	53	390	55	400	—	—	58
A12	33	220	44	320	51	360	54	370	—
A13	38	240	40	320	55	390	58	420	58
A14	34	210	45	290	64	430	66	430	64
A15	28	210	28	210	59	350	59	350	66
Mean	31	210	40	290	54	390	57	410	61
SD	5	40	7	50	6	30	5	30	5

plantarflexed hindpaws for at least three seconds; both hindpaws had to be involved before the sign was regarded as positive (fig 1B). During this manoeuvre the animals showed no signs of distress and pain sensation was normal (see below). Toe folding occurred naturally late in the illness and caused the animals to stumble while walking. The onset of toe folding occurred from 48 to 66 days after the start of acrylamide administration (mean, 57; SD, 5). The accumulated dose of acrylamide at the onset of toe folding ranged from 350 to 470 mg kg⁻¹ (mean, 410; SD, 30). Toe folding did not occur after a significantly longer duration of acrylamide exposure than muscle weakness.

Regurgitation was observed late in the illness. The first manifestation of the feeding disturbance was the presence of small pools of frothy white fluid on the animal-room floor; sometimes this was bile stained. Later the animals were seen to regurgitate material in a characteristic manner. The animals gave little warning of regurgitation and upon extending and lowering the head produced material quickly and with little effort. Regurgitation occurred more frequently at feeding time but was also observed while walking and if the animal became excited. Regurgitated feed was often eaten, partially regurgitated and eaten again. The regurgitated material initially appeared undigested and covered with mucus; it was often sausage shaped. Later in the illness the undigested quality was lost and the oesophageal cast appeared homogeneous. The onset of regurgitation was difficult to identify precisely: it ranged from 54 to 68 days after the start of acrylamide administration (mean, 61; SD, 5).

Nine of the fourteen animals developed regurgitation. Four animals (A6, A8, A10, A12) that did not regurgitate were not given the neurotoxin after the appearance of toe folding; it was likely that virtually all animals would have developed regurgitation if acrylamide had been administered longer. The duration of acrylamide exposure to the onset of toe folding and to the onset of regurgitation was not significantly different.

Weight loss was a consistent feature of all animals exposed to acrylamide. Normal dogs not exposed to acrylamide gained weight in the animal house. The average weight of the fourteen dogs at the end of the exposure to acrylamide was 92% of their weight on arrival at the animal house and 88% of their maximum recorded weight during the dosage period.

There were no signs of autonomic disturbance. In particular, bitches continued to have normal cycles and one male dog was known to have had intercourse when neuropathy was present. There was no urinary or faecal incontinence. Urination in male dogs often resulted in the animal falling sideways. When the neuropathy was clinically obvious, both sexes would fall backwards into their faeces unless assisted. The clinical signs principally involved the hindlimbs late in the illness; the forepaws were occasionally seen to "knuckle" and there was a widened forelimb stance. Greyhounds are relatively mute animals and no change in the bark was noticed. There was no sign that the animals had trouble chewing the daily feed. A complete neurological examination was carried out every four weeks on all animals in the present study. At the time when the acrylamide was stopped, there were a number of clinical features that

Table 2 *Clinical findings at end of acrylamide administration*

Sign	Animal grade*	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12	A13	A14	A15
Anorexia	+ / 0	+	+	+	0	0	0	+	0	+	0	0	0	0	+
Diarrhoea	+ / 0	+	0	+	0	0	0	+	0	+	0	0	0	0	0
Incontinence	+ / 0	0	+	0	0	0	0	0	0	0	0	0	0	0	0
Dehydration	++ / + / 0	+	0	+	0	0	0	++	0	+	0	0	0	0	0
Vomiting	+ / 0	+	+	+	0	0	+	0	+	0	+	0	+	+	+
Cranial nerve abnormality	+ / 0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Corneal reflex	+ / 0	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pain sensation	+ / 0	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Anal reflex	+ / 0	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ataxia	++ / + / 0	++	++	++	++	+	+	++	+	++	++	++	++	++	++
Forelimb toe scuffing	+ / 0	0	+	0	0	+	+	0	+	+	0	+	+	0	+
Forelimb weakness	+ / 0	+	+	0	0	+	+	0	+	+	0	+	+	0	+
Hindlimb tone	++ / + / 0	++	+	++	++	+	++	+	++	++	++	++	++	++	++
Hindlimb weakness	+++ / ++ / +	++	+++	++	++	++	++	+++	++	++	++	++	++	++	++
Patellar reflex	++ / + / 0	++	0	+	+	++	++	++	+	+	++	+	+	+	0
*GRADE															
+++ / ++ / +	+++	Unable to move hindlimbs at all			++	Able to walk but distance limited					+	Only sign present			
++ / + / 0	++	Ataxia, dehydration: marked disturbance			+	Ataxia, dehydration: mild deficit only					0	No features present			
	++	Tone, patellar reflex: normal response			+	Tone patellar reflex: obvious reduction					0	Flaccid animal or no reflex present			
+ / 0	+	Present									0	Absent			

were common to all animals (table 2). There was normal pain sensation and a normal cranial nerve examination. When tested the anal reflex was present. Ataxia was variable in degree. The tone of the forelimb muscles appeared normal in all animals and ataxia localised to the forequarters was not seen. Hindlimb tone was occasionally reduced and all animals showed moderate to severe hindlimb weakness with preservation of proximal power. The patellar reflex was normal in four animals and totally absent in one animal with most being variably reduced.

RADIOLOGICAL FEATURES

Three of the fourteen animals exposed to acrylamide were examined radiologically. The lower thoracic oesophagus in a control greyhound retained very little contrast food mixture. A bolus of contrast agent had a normal tear-drop shape and left a faint coating on the mucosal folds. An acrylamide affected animal (A11) developed regurgitation after 58 days;

the oesophagus appeared atonic and distended with the contrast food mixture. Some contrast material was seen in the stomach (fig 2).

Another animal (A14) was studied before and after the onset of regurgitation. After 54 days of exposure to acrylamide, there were signs of toe scuffing and ataxia; the eating behaviour was normal and the radiographic examination was normal. Seven days later regurgitation was observed and three days later radiographic examination revealed a dilated oesophagus. Dilatation involved the whole of the intrathoracic portion of the oesophagus, and contrast material was seen in the stomach. At this time muscle weakness and toe folding were present. The radiographic appearance was constant over a period of fifteen minutes and no secondary waves or tertiary contractions were seen on the image intensifier (fig 3).

The last animal (A15) was studied frequently during the evolution of peripheral neuropathy. Abnormal feeding behaviour was suspected after 63

Fig 2 Barium swallow examination of the lower thoracic oesophagus in a control (upper panel) and acrylamide affected (lower panel) greyhound (A11). The uniform dilatation of the thoracic oesophagus in the affected animal contrasts with the tear-drop shaped bolus of the control animal. (Picture in the lower panel taken by Dr A Wood.)

Fig 3 Barium swallow examination of the lower thoracic oesophagus in an acrylamide affected animal (A14) before (upper panel) and after (lower panel) the onset of regurgitant vomiting. Faint traces of contrast material remain in the oesophagus before dilatation; later there is a gross accumulation of contrast agent and food. There is contrast material in the stomach as well.

days of acrylamide administration; radiographic examination 3 days later revealed the typical appearance of megaesophagus (fig 4). At this stage all the signs of neuropathy were present.

Discussion

ACRYLAMIDE AND THE DOG

The effects of chronic acrylamide administration were similar in the dog to those in other species. The predominant clinical feature was a mild progressive sensorimotor peripheral neuropathy. Previous studies suggested that muscle weakness, ataxia and disturbed postural reflexes were the clinical signs in dogs exposed to acrylamide.⁹ In the present study these signs were observed as well as marked sensory impairment, weight loss and feeding disturbance. Atrophy has been reported in affected dogs but was not seen in the present study. Ataxia was a consistent

early sign in dogs and has been a prominent feature of acrylamide intoxication in man, primates and the cat.⁸ In man the ataxia is truncal; in the cat the ataxia has been attributed to proprioceptive impairment by some and non vestibular cerebellar dysfunction by others.⁸ The ataxia in the dog was not accompanied by the other features of cerebellar disease in domestic animals, namely tremor, head titubation, hyperreflexia, hypertonia or nystagmus.¹⁰ Although the ataxia was consistent with proprioceptive impairment alone, cerebellar or spinocerebellar tract involvement could not be completely excluded on clinical grounds. All species have developed muscle weakness after chronic exposure to acrylamide.⁸ Weakness was not an early feature of the neuropathy in the dog. In the primate and man, weakness involving the upper limbs has been seen;^{11 12} while forelimb weakness has been reported in the cat^{8 13} it was not a feature of the canine illness.

Fig 4 Barium swallow examination of the lower thoracic oesophagus in an acrylamide affected animal (A15). The upper panel shows the appearance of the oesophagus before any acrylamide had been given. The lower panel shows the appearance of the oesophagus 15 days after acrylamide was ceased when there was regurgitant vomiting and all the signs of neuropathy.

Sensory impairment was a prominent clinical feature in the dog; it has been reported in man¹⁴ but has been difficult to detect in the cat and the primate.⁸ Toe folding was a reproducible sign in the dog which was consistent with proprioceptive impairment; the ability of the affected animals to stand on the dorsal surface of their hindpaws suggested that there was a marked sensory disturbance in the hindlimb extremities. This predominant sensory impairment in the dog also involved the forelimbs. Pain sensation has remained normal in all species including the dog.⁸

Clinical autonomic disturbance is relatively common in man¹² although rare in animals exposed to acrylamide. The presence of normal sexual function suggested that the dog did not have clinical autonomic dysfunction. Although voice change was not noticed in the dog it has been reported in the cat and baboon.⁸ Weight loss was a consistent feature of all dogs exposed to acrylamide and has also been described in man and primates. In baboons, weight

loss occurs despite gastric tube feeding.¹¹ Dogs lost weight despite a good appetite and unlimited food.

The susceptibility of dogs and cats to acrylamide is similar and both species develop similar neurological deficits. The primate seems less sensitive to the neurotoxic action of acrylamide but this may reflect the different eating habits of primates compared with dogs. Acrylamide administration produced a peripheral neuropathy in the dog that is very similar clinically to the neuropathy reported in all other species exposed to the neurotoxin.

MEGAESOPHAGUS AND NEUROPATHY

While the peripheral neuropathy in the dog exposed to acrylamide was similar to that described in other species, the feeding disturbance reported in the present study has not been seen in other animals or man exposed to this neurotoxin. Monkeys have difficulty in chewing food when there is severe neuropathy¹⁵ but this is quite distinct from the feeding disorder seen in the dog. The association of

neuropathy and megaesophagus was observed clinically in nine out of fourteen animals. Four of the five animals that retained normal eating behaviour were not given acrylamide after the appearance of marked sensory impairment of the hindpaws; it was likely that continued neurotoxin administration would have resulted in regurgitation due to megaesophagus. In the present study the association of megaesophagus and neuropathy seemed a strong one; virtually all the previous reports of megaesophagus in adult dogs fail to mention any neurological abnormality.^{1 16 17} As it is unlikely that the degree of neuropathy described in the present study could be missed in so many clinical descriptions it would seem probable that canine megaesophagus can result from a number of pathological processes.

Organophosphorus compounds and acrylamide produce peripheral neuropathies with very similar clinical features although there are ultrastructural differences in the degenerative changes seen in axons.^{17 19} When dogs have been exposed to diisopropyl fluorophosphate they develop oesophageal dilatation.^{4 5} Although the presence of neuropathy was not discussed or proven in these animals⁵ hindquarter weakness was described. It is probable that acrylamide and organophosphorus compounds, which both cause an axonopathy affecting the largest diameter nerve fibres produce a similar clinical picture of sensorimotor neuropathy and megaesophagus in the dog.

The clinical association of neuropathy and megaesophagus has been described in an Alsatian dog with naturally occurring giant axonal neuropathy.⁶ Ultrastructural studies revealed enlarged axons swollen with neurofilaments. Similarly an ultrastructural characteristic of acrylamide damage in other species has been the accumulation of neurofilaments in axons.^{19 8}

The clinical features of naturally occurring and artificially induced megaesophagus were identical.^{1 16 17} Since all the dogs that were exposed to acrylamide were adult and were not recently weaned, the clinical features of megaesophagus in the present study more closely resembled the naturally occurring disease in the older animal. The presence of megaesophagus was confirmed radiologically. This has been the standard method for establishing the presence of oesophageal dilatation.^{17 20} The radiological features of oesophageal dilatation in the present study mimicked those described in naturally occurring megaesophagus,^{11 16 17 20} although the degree of dilatation did not match the gross sac-like enlargements occasionally reported in the spontaneous disorder.²¹

A pathological process that has been suggested as a cause of naturally occurring canine megaesophagus

is dysfunction of the neuromuscular control of the oesophagus.²²⁻²⁴ Although vagal abnormalities could not be demonstrated in animals with naturally occurring megaesophagus,²⁴ the association of megaesophagus and acrylamide administration in the present study emphasises the importance of degenerative changes in the neural innervation of the oesophagus in this disorder; acrylamide has no direct effect on skeletal or smooth muscle.⁸ The consistent feature of acrylamide neuropathy has been the greater degree of functional changes in sensory nerves that occur before changes in motor nerves.²⁵ Thus it can be suggested that in those cases of canine megaesophagus which can be attributed to dysfunction of the neural innervation, the site of functional disturbance is more likely to be in the sensory innervation of the oesophagus.

Acrylamide megaesophagus is easy to produce and is quite reproducible. It offers a unique opportunity to study an oesophageal motility disorder as it evolves. While oesophageal abnormalities have not been described in other species exposed to acrylamide there are structural and functional differences of the canine oesophagus which could account for the vulnerability of this organ when dogs suffer a sensorimotor peripheral neuropathy. The stimulus for oesophageal peristalsis produced by an intraluminal bolus differs according to its site and the animal species.²⁶ In species with a predominantly striated muscle oesophagus it is only the dog that has an absolute requirement for the presence of a bolus in the cervical oesophagus.²⁷ These observations provide indirect evidence that megaesophagus in the dog exposed to acrylamide is due to damage to vagal afferent nerve fibres.

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