CASE REPORT

Ivermectin toxicosis in a neonatal foal

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Introduction

Ivermectin is a widely used anthelmintic in horses due to its broad spectrum of activity and high efficacy (DiPietro and Todd 1987). It has a wide safety margin in most species (Campbell *et al* 1983), but increased sensitivity to ivermectin has been reported in Collie dogs (Paul *et al* 1987), an Old English Sheepdog (Houston *et al* 1987), Murray Grey cattle (Seaman *et al* 1987) and in young animals (Button *et al* 1988).

This report describes the clinical signs, case progression and serum concentrations of ivermectin in a neonatal foal after the accidental administration by the owners of 2111 µg/kg (10.6 times the recommended adult dose) of ivermectin paste.

Case Report

A 54 kg Thoroughbred filly foal had a normal birth and sucked within 12 hours of birth. At 16 hours of age, she developed diarrhoea and was treated by the owner with kaolin and pectin, and 6.08 g ivermectin paste (10.6 times the recommended adult dose, or 2111 µg/kg) orally. Over the next few hours the filly became incoordinated and began head-pressing and walking into objects. At 27 hours of age, she was referred to the Veterinary Teaching Hospital of Michigan State University.

On presentation the filly could stand with assistance, but was very ataxic in all four limbs. She was very dull and depressed with a rectal temperature of 37.2°C, heart rate of 100 beats/min and respiratory rate of 40 breaths/min. Mucous membranes were dark pink with a capillary refill time of 1.5 sec. Increased borborygmi were audible on auscultation, with evidence of diarrhoea. The packed cell volume was 0.42 L/L, total plasma protein was 38 g/L and blood glucose was 4.7 mmol/L. The total white cell count was 8.810×10^9/L with 6.870×10^9 neutrophils/L and 0.260×10^9 band cells/L with many, mildly toxic neutrophils. The serum IgG concentration was 2.29 g/L. A serum chemistry profile was normal for her age with the exception of hypoproteinaemia, which was attributed to failure of passive transfer of immunoglobulins. A neurological examination was performed. Cranial nerve function was normal, but there was central nervous system depression and generalised paresis in all four limbs. Differential diagnoses included ivermectin toxicosis, septicaemia with meningitis or encephalitis secondary to failure of passive transfer, neonatal maladjustment syndrome and trauma. To pursue the possibility of ivermectin toxicosis, serum was collected at admission and every 8 to 12 hours over the following 3 days. Serum was separated and frozen at -20°C until analysis.

After examination at the hospital, intravenous fluid therapy with lactated Ringer's solution and 5% dextrose was initiated. Because of the possibility of septicaemia, ticarcillin (44 mg/kg IV every six hours) and flunixin meglumine (100 mg IV) were then given. Cimetidine (6.6 mg/kg IV every six hours) was used to minimise the likelihood of gastric ulceration. To treat failure of passive transfer of immunoglobulins, 4 L of plasma were administered intravenously commencing about one hour after admission. Twenty-four hours after plasma administration, serum IgG concentration was 12.2 g/L. Additional supportive care included a foam crash helmet to protect the head and enteral feeding by an indwelling nasogastric tube every hour.

The filly gradually improved and stood unassisted at 24 hours after presentation. She was still very ataxic, walking into objects and head pressing. At this time, the haemogram was normal. At 48 hours after presentation, her coordination had improved and she recommenced sucking from the mare. Fluid therapy and enteral feeding were discontinued at this time. On day 3, she was behaving normally and the diarrhoea had resolved. All treatment was discontinued and she was discharged the following day. On conversation with the owners 5 days and one year later, the filly was reported to be normal.

Serum samples were analysed by radioimmunoassay (Marschke 1989) (Table 1). The assay employs tritiated ivermectin as tracer with rabbit anti-ivermectin antibodies, and is sensitive to about 1 µg/L. The vials containing the serum samples, which were collected 11 hours (on admission) and 63 hours after ivermectin administration, broke during transit to the laboratory. Serum ivermectin concentration at 23 hours after administration was 94.1 µg/L and serum concentrations reduced only slightly over the 3-day measurement period. The data points for ivermectin concentrations were fitted to a monoexponential curve, using standard computer software for pharmacokinetic analysis[¶] and the elimination half-life was calculated to be 17 days.

The pharmacokinetics of ivermectin in this foal are similar to that reported in sheep (Prichard *et al* 1985).

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TABLE 1
Serum ivermectin concentrations after administration of 6.08 g ivermectin paste

Time after administration (hours)	Ivermectin concentration (µg/L)
23	94.1
31	92.9
39	87.9
47	96.5
55	86.9
71	83.1
79	87.7

Discussion

Ivermectin is an antiparasitic drug the action of which is attributed to the inhibition of nerve impulse transmission. The binding site of avermectin B_{1a}, a major component of ivermectin is thought to be closely coupled to the binding site of gamma-aminobutyric acid (GABA) and also the chloride ion channel (Pong and Wang 1982). Avermectin B_{1a} has been shown to increase the number of post-synaptic GABA receptors, which may lead to an opening of chloride ion channels and membrane hyperpolarisation (Pong and Wang 1982). Avermectin B_{1a} has also been shown to increase the synaptosomal release of GABA (Pong et al 1980). In mammals, GABA is an inhibitory neurotransmitter only in the central nervous system (CNS), whereas in nematodes and arthropods it regulates peripheral muscles (Campbell et al 1983). In mammals in which ivermectin does not readily cross the blood-brain barrier, the drug has a wide margin of safety (Campbell et al 1983) and at least 10 times the therapeutic dose is required to produce toxic effects in most normal mammals (Bennett 1986).

Leaning (1983) reported the effects of high doses of ivermectin in adult horses. No adverse reactions were seen after an oral dose of 1200 μg/kg (6 times the recommended dose), but 5 of 11 horses developed mild ataxia, depression, and visual impairment within 21 hours of a dose of 2000 μg/kg (10 times the recommended dose). Four horses given IM injections of ivermectin at 12 000 μg/kg (60 times the recommended dose) showed depression, mydriasis, ataxia, depressed respiratory rate and a drooping lower lip. Two of 4 horses receiving 6000 μg/kg (30 times the recommended dose) and 2 of 8 horses receiving 3000 μg/kg (15 times the recommended dose) showed mydriasis and lack of pupillary light and menace response.

Ivermectin is not recommended for administration to foals less than 4 months of age, as safety has not been demonstrated in adequate numbers of foals of this age. However, doses as high as 1000 μg/kg have been tolerated by foals less than 30 days of age without signs of toxicity (DiPietro and Todd 1987). The foal in this report received twice this dose (2111 μg/kg), and was a neonate at only 16 hours of age when the drug was given. The neurological signs shown by this foal were more severe than after administration of ivermectin at a similar dose in adult horses (Leaning 1983).

Several reports describe apparent increased sensitivity to the toxic effects of ivermectin in certain circumstances. Collie dogs have developed toxicosis after the recommended 200 μg/kg dose (Paul et al 1987) and an Old English Sheepdog showed similar signs after a 150 μg/kg dose (Houston et al 1987). In the Collies, CNS concentrations of ivermectin were found to be much higher than the concentrations in liver or serum, which suggests greater penetration of ivermectin through the blood-brain barrier (Pulliam et al 1985). A similar situation has also been reported in Murray Grey cattle, where brain avermectin B_1 concentrations were ten-fold higher in affected cattle than in unaffected cattle after receiving similar doses. Seaman et al (1987) proposed that the affected Murray Grey cattle had some characteristics that allowed avermectin B_1 to penetrate the CNS more readily than would normally be expected.

Enhanced sensitivity to ivermectin has also been reported in young animals. Avermectin at 1.5 to 3 times the recommended dose produced toxicity in calves aged 3 weeks to 6 months. The proposed explanation was greater permeability of the blood-brain barrier in young animals (Button et al 1988). Newborn rats have also been shown to be more susceptible to the neurotoxic action of ivermectin, compared

with adult rats (Poul 1988). Many investigators have noted that the blood-brain barrier of immature animals is more permeable than that of adults (Betz and Goldstein 1981). Increased permeability of the blood-brain barrier in the neonatal foal could explain why the clinical signs of ivermectin toxicity in this foal were greater than reported for the same dose in adult horses (Leaning 1983). Concurrent sepsis, secondary to failure of passive transfer might also have been present and the associated inflammation might have contributed to the increased permeability of the blood-brain barrier. Alternatively, ivermectin pharmacokinetics may differ between foals and adults. Ivermectin is a lipophilic drug and neonates are known to have a lower percentage of body fat compared with adults (Kami et al 1984). For this reason blood concentrations reached after dosing may be higher and persist for longer in a neonate compared with an adult. Finally, the greater severity of neurological signs may be related to the receptor sites, since a reduction in receptor sites or decreased affinity of the receptors for the drug with age could account for an apparent decreased susceptibility with increasing age. However, to the best of our knowledge nothing is known about the changes in receptor sites with age in any species.

Interestingly, clinical signs of neurological disease improved in this foal, before serum ivermectin concentrations decreased significantly. The resolution of neurological signs may have been associated with decreasing permeability of the blood-brain barrier, either as a result of ageing or after resolution of inflammation. Another plausible explanation for the improvement in neurological signs despite persistent high serum ivermectin concentrations, is a decrease in the affinity or number of drug receptor sites over the first few days of age in the foal.

The foal in this report showed more severe neurological signs compared with that reported in adult horses after a similar dose (Leaning 1983). These signs also resolved despite persistently high serum concentrations. Due to the possible enhanced sensitivity of neonatal foals to ivermectin, the drug may have a narrower safety margin in this age group. For this reason, apart from a lack of justification for its use, the administration of ivermectin to neonatal foals should be avoided.

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