

Ivermectin fact sheet

Ivermectin was the first of the avermectins to be used in veterinary medicine and has been widely used as an endectocide in a variety of species, including humans, for 30 years [1, 2]. A macrolide antibiotic in the avermectin group, it is an agonist for the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and can be administered orally, topically or by injection [3]. The drug acts by binding GABA-gated chloride and invertebrate-specific glutamate-gated anion channels in peripheral neuromuscular synapses, suppressing nerve impulse conduction [4]. Its usefulness as an anthelmintic results from differences in the distribution of GABA receptors between mammals and arthropods or nematodes: GABA receptors in mammals are mostly in the central nervous system (CNS) protected by the blood brain barrier, whereas in arthropods and nematodes they are found in the peripheral nervous system at the neuromuscular junction. Stimulation of GABA receptors in endo- and ecto-parasites causes flaccid paralysis and inhibits feeding of the parasite [2, 5].

Potential adverse effects of ivermectin

Although ivermectin has a wide margin of safety in most mammalian species, some animals are particularly sensitive to toxicity. Ivermectin toxicity can appear in the form of severe central nervous system side effects such as depression, coma, and death [2]. Animals exhibiting these symptoms are believed to have an absence or functional deficiency of P-glycoprotein in nervous system capillary endothelium [2]. P-glycoprotein plays a role in the blood brain barrier, acting as an efflux pump to prevent the entry of specific drugs into the nervous system [6]. Ivermectin is highly lipophilic and thus usually has very poor penetration of the blood brain barrier, due to the action of the drug efflux transporters. Deficiency or disruption of this gene leads to enhanced absorption and exposure of the brain to a number of drugs, including ivermectin. Treatment has also been reported to cause subtle effects on behavior [7] and on immune function [8, 9].

Severe central nervous system side effects of ivermectin been reported particularly in collie dogs and CF-1 mice. Sensitive collies show reactions at 1/200th of the dose required to show toxicity in other dogs [2]. These collies have a genetic deletion that generates a frame shift, resulting in premature termination of the synthesis of p-glycoprotein [2]. Mice with abnormal P-glycoprotein, and thus ivermectin sensitivity, include a subpopulation of about 25% of CF-1 mice [1, 10] and other mice homozygous for disruption of the *Abcb1a* (previously known as *mdr1a*) P-glycoprotein gene [1, 11]. These mice are phenotypically the same, and show enhanced central absorption of ivermectin, while blood and hepatic levels are the same as wild-type mice, showing that differences in ivermectin disposition arise through a deficiency in p-glycoprotein rather than through an alteration in drug metabolism [2]. Ivermectin-sensitive CF-1 mice and P-glycoprotein-deficient mice evidence the severe neurologic side effects of coma and rapid death. In addition to side effects related to genotype, reports have described ivermectin toxicity in neonatal rodents [12], perhaps because P-glycoprotein protein expression in brain capillary cells is incomplete until postnatal day 21 [13]. Surprisingly, ivermectin did not alter seizure responses in either seizure-prone or seizure-resistant mice [14].

Reports of toxicity exist in other species include humans. Horses, cattle, pigs and rabbits show signs of neurotoxicity including depression, ataxia, rigidity, and impaired vision when given doses in excess of 4-8 times the recommended dose [1].

Aside from toxicity, treatment with ivermectin has been reported to cause subtle effects on behavioral testing and immune function in mice. In one study, treated mice were normal with regard to body weight, motor behaviors and the performance of a spatial memory task. However, ivermectin produced real changes in other behaviors. Mice were significantly more active in the open field exploration test during ivermectin treatment than before treatment, had a greater acoustic startle amplitude than control mice, and had variably lower prepulse inhibition, depending on mouse strain [7]. These results showed that ivermectin affected the behavioral responses to certain stimuli and not others, potentially stemming from a hyperreactivity to environmental stimuli in certain circumstances. In terms of immune function, ivermectin was shown to have anti-inflammatory properties, significantly diminishing the recruitment of immune cells and cytokines in a mouse model of asthma [15]. Other studies have showed an immunomodulatory effect on T-helper cells [9] and T-cell related genetic deletion in transgenic mice administered ivermectin [16].

References

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