EMORY UNIVERSITY | Division of Animal Resources
Emory Integrated Core Facilities

Ivermectin Fact Sheet

Executive Summary:

- Ivermectin belongs to the avermectin class of antiparasitic drugs. Ivermectin is frequently used in animal research facilities to treat pinworm and fur mite infestations. Ivermectin has a wide margin of safety in most mammalian species. However, toxicity can appear in animals with an absent or functional deficiency of P-glycoprotein in the endothelium of the central nervous system. Clinical signs that can present mainly affect the central nervous system and include whole body tremors, ataxia, lethargy, depression, coma, and death.
    - Specific rodent strains demonstrate varying sensitivities to ivermectin, based on the functionality of P-glycoprotein. Examples of common strains with this sensitivity include CF-1 mice and Mdr1a KO rats. Gene synonyms for these knockouts include *Mdr1a*, *Mdr3*, *Pgp*, *Pgy3*, and *Abcb1a*.
    - Ivermectin did not alter seizure responses in either seizure-prone or seizure- resistant mice in one report.[1]
- Aside from toxicity, treatment with ivermectin has been reported to cause subtle and short-term effects on performance on sensitive behavioral tests and antibody production in mice.[2-4] However, parasite infestation itself significantly affects immune function and inflammation in mice.[4-12]
- There are two reports that suggest treatment with ivermectin may yield the unintended effect of altering transgene activity in mice.[13, 14]

About Ivermectin

Ivermectin was the first of the avermectins to be used in the field of veterinary medicine and has been widely used as an endectocide in a variety of species, including humans, for 30 years.[15, 16] As an anthelmintic in the macrocylic lactone class, ivermectin is an agonist for the inhibitory glutamate-gated chloride and gamma-aminobutyric (GABA) channels of the muscle and nerve cells of parasites.[18] Ivermectin offers flexibility with agent administration, as it can be administered orally, topically, or by injection.[17] Ivermectin's usefulness as an anthelminthic 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 the ability of the parasite to feed.[15, 19]

Potential Adverse Effects of Ivermectin

Although ivermectin has a wide margin of safety in most mammalian species, some animals have an increased sensitivity to the drug. Though rare, ivermectin toxicity can

appear in the form of severe central nervous system side effects such as depression, coma, and death.[15] Animals exhibiting these symptoms are believed to have an absent or functional deficiency of P- glycoprotein in nervous system capillary endothelium.[15] 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.[20] 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 several drugs, including ivermectin. Treatment has also been reported to cause subtle effects on behavior and on immune function.[2-4]

Mice with abnormal P-glycoprotein, and thus ivermectin sensitivity, include a subpopulation of about 25% of CF-1 mice and other mice homozygous for disruption of the *Abcb1a* (previously known as *mdr1a*) P-glycoprotein gene.[16, 21, 22] These mice are phenotypically normal but show enhanced central absorption of ivermectin, attributed to a deficiency in P-glycoprotein rather than an alteration in drug metabolism.[15] Ivermectin-sensitive CF-1 mice and other P- glycoprotein-deficient mice present with the severe neurologic side effects of coma and rapid death. In addition to side effects related to genotypes, reports have described ivermectin toxicity in neonatal rodents, perhaps because P-glycoprotein expression in brain capillary cells is incomplete until postnatal day 21.[23, 24] Surprisingly, ivermectin did not alter seizure responses in either seizure-prone or seizure-resistant mice.[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, ivermectin- treated mice were normal concerning their body weight, motor behaviors, and the performance of a spatial memory task. However, ivermectin produced 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 pre-pulse inhibition, depending on mouse strain.[3] These results demonstrate the effect that ivermectin can have on behavioral responses to certain stimuli and not to others, potentially stemming from a hyperreactivity to environmental stimuli in only some 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.[25] Other studies have shown an immunomodulatory effect on T-helper cells and T-cell related genetic deletion in transgenic mice administered ivermectin.[2, 13] Similarly, a recent publication reports that the offspring of transgenic mice exposed to ivermectin during pregnancy and nursing exhibit altered recombinase activity, thus demonstrating that ivermectin may have unintended consequences on gene activation studies in mice.[14]

Use of Ivermectin

Ivermectin-impregnated rodent chow has an advantage over other commonly utilized

schemes for treating endo- and ectoparasites. Ivermectin provided in the diet of rodents has demonstrated efficacy in eliminating external fur mites, as well as internal pinworms. Another scheme commonly utilized for targeting fur mites and pinworms requires a series of topical applications of selamectin and provision of a fenbendazole-impregnated rodent chow. Fenbendazole is a member of the benzimidazole class of antiparasitics. Generally, like ivermectin, fenbendazole exhibits a wide margin of safety for many mammalian species. However, some data suggests that fenbendazole is capable of inducing an effect on immune function and behavior.[26,28,30] A study describing the use of topical selamectin to target fur mites showed a positive effect for 1-month duration, yet mite egg casings were detected at time periods of 2- and 6-months post-treatment.[29] A recent study demonstrated that ivermectin was effective at eliminating mites in as little as 2 weeks of diet provision. However, colony health surveillance methods may lag relative to this therapeutic effect, as the study also demonstrated that PCR detection of fur mites was highly dependent upon the presence of fur mite-associated particles (including defecate, chitin shells, egg casings, and adult mites). Since sufficient biologic waste is required for reliable PCR screening, 4 weeks of ivermectin dietary treatment is recommended. A four-week duration of ivermectin treatment further allows for time to demonstrate action against all life stages of the fur mites, which varies by species of fur mite and could be approximately 8 to 23 days.[27]

References

1. Diggs, H., et al. (1990). "Effect of chronic ivermectin treatment on GABA receptor function in ethanol withdrawal-seizure prone and resistant mice." Laboratory animal science 40(1): 68-71.
2. Blakley, B. and C. Rousseaux (1991). "Effect of ivermectin on the immune response in mice." American journal of veterinary research 52(4): 593-595.
3. Davis, J. A., et al. (1999). "Behavioral effects of ivermectin in mice." Comparative Medicine 49(3): 288-296.
4. Johnston, N. A., et al. (2009). "Assessment of immune activation in mice before and after eradication of mite infestation." Journal of the American Association for Laboratory Animal Science 48(4): 371-377.
5. Morita, E., et al. (1999). "Fur mites induce dermatitis associated with IgE hyperproduction in an inbred strain of mice, NC/Kuj." Journal of dermatological science 19(1): 37-43.
6. Pochanke, V., et al. (2006). "Induction of IgE and allergic-type responses in fur mite-infested mice." European journal of immunology 36(9): 2434-2445.
7. Moats, C. R., et al. (2016). "Ectoparasite burden, clinical disease, and immune responses throughout fur mite (Myocoptes musculinus) infestation in C57BL/6 and Rag1–/–mice." Comparative Medicine 66(3): 197-207.
8. Agersborg, S. S., et al. (2001). "Intestinal parasitism terminates self tolerance and enhances neonatal induction of autoimmune disease and memory." European journal of immunology 31(3): 851-859.
9. Baker, D. G. (2003). Natural pathogens of laboratory animals: their effects on research, American Society for Microbiology (ASM).
10. Bugarski, D., et al. (2006). "Hematopoietic changes and altered reactivity to IL-17 in Syphacia obvelata-infected mice." Parasitology international 55(2): 91-97.
11. Grencis, R. (1997). "Th2–mediated host protective immunity to intestinal nematode infections." Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 352(1359): 1377-1384.
12. Michels, C., et al. (2006). "Infection with Syphacia obvelata (pinworm) induces protective Th2 immune

responses and influences ovalbumin-induced allergic reactions." Infection and immunity 74(10): 5926-5932.
13. Corbo-Rodgers, E., et al. (2012). "Oral ivermectin as an unexpected initiator of CreT2-mediated deletion in T cells." Nature immunology 13(3): 197-198.
14. Kropp, P. A., et al. (2020). "Unexpected effects of ivermectin and selamectin on inducible CreER activity in mice." Laboratory Animal Research 36(1): 1-5.
15. Edwards, G. (2003). "Ivermectin: does P-glycoprotein play a role in neurotoxicity?" Filaria journal 2(1): 1-6.
16. Woodward, K. (2012). "Toxicity in animals: target species." Current Pharmaceutical Biotechnology 13(6): 952-968.
17. Klement, P., et al. (1996). "An oral ivermectin regimen that eradicates pinworms (Syphacia spp.) in laboratory rats and mice." Laboratory animal science 46(3): 286-290.
18. Ricart Arbona, R. J., et al. (2010). "Treatment and eradication of murine fur mites: I. Toxicologic evaluation of ivermectin-compounded feed." Journal of the American Association for Laboratory Animal Science 49(5): 564-570.
19. Roder, J. and E. Stair (1998). "An overview of ivermectin toxicosis." Veterinary and human toxicology 40(6): 369-370.
20. Kiki-Mvouaka, S., et al. (2010). "Role of P-glycoprotein in the disposition of macrocyclic lactones: a comparison between ivermectin, eprinomectin, and moxidectin in mice." Drug metabolism and disposition 38(4): 573-580.
21. Umbenhauer, D. R., et al. (1997). "Identification of a P-glycoprotein-deficient subpopulation in the CF-1 mouse strain using a restriction fragment length polymorphism." Toxicology and applied pharmacology 146(1): 88-94.
22. Didier, A. D. and F. Loor (1995). "Decreased biotolerability for ivermectin and cyclosporin A in mice exposed to potent P-glycoprotein inhibitors." International journal of cancer 63(2): 263- 267.
23. Skopets, B. (1996). "Ivermectin toxicity in young mice." Lab. Anim. Sci. 46: 111-112.
24. Tsai, C. E., et al. (2002). "P-glycoprotein expression in mouse brain increases with maturation." Neonatology 81(1): 58-64.
25. Yan, S., et al. (2011). "Anti-inflammatory effects of ivermectin in mouse model of allergic asthma." Inflammation Research 60: 589-596
26. Duan, Q., et al. (2012). “Use of fenbendazole-containing therapeutic diets for mice in experimental cancer therapy studies.” Journal of the American Association for Laboratory Animal Science 51(2), 224–230.
27. Hanson, W. H., et al. (2024). “Evaluating a Reduction in Treatment Duration of Ivermectin Diet for Fur Mite (Radfordia affinis) Eradication in Mice.” Journal of the American Association for Laboratory Animal Science, 10.30802/AALAS-JAALAS-24-000007.
28. Hicks, K. L., et al. (2021). “Effects of Maternal Fenbendazole on Litter Size, Survival Rate, and Weaning Weight in C57BL/6J Mice.” Journal of the American Association for Laboratory Animal Science 60(6), 630–636.
29. Mook, D. M., et al. (2008). “Use of selamectin and moxidectin in the treatment of mouse fur mites.” Journal of the American Association for Laboratory Animal Science, 47(3), 20–24.
30. Villar, D., et al. (2007). “Biologic effects of fenbendazole in rats and mice: a review.” Journal of the American Association for Laboratory Animal Science 46(6), 8–15