

## **Mectins poisoning vs Avermectin poisoning**

Yang CC.

1. Department of Environmental and Occupational Medicine, School of Medicine, National Yang-Ming University, Taipei. 2. Division of Clinical Toxicology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan.

**Introduction:** Avermectins are a family of macrocyclic lactones which have a novel mode of action against a broad spectrum of nematodes and arthropods in doses as low as 10 µg/kg (1, 2). Avermectins were first found in the fermentation broth of a soil-dwelling microorganism, *Streptomyces avermitilis*, at the Kitasato Institute in Japan. After conducting numerous bioassays in Merck laboratories, 8 natural avermectin components, namely A1a, A1b, A2a, A2b, B1a, B1b, B2a, and B2b, were discovered. Compounds of the B series of avermectins were found to be extremely effective against helminthes and arthropods, and ivermectin (22, 23-dihydro-avermectin B1) was released for use in animals and humans in 1981 (2). Because of its high tolerability, prolonged post-treatment effect, and broad spectrum of anti-parasitic activity, ivermectin has become a popular drug in the treatment of many animal and human parasite infestations, such as onchocerciasis (3). Other avermectins, including abamectin, doramectin, and emamectin were subsequently commercialized and were used as agricultural insecticides and miticides in animal health and/or crop protection as well (2).

**Pharmacology/toxicology:** Various avermectin components differ in their potency and safety (2, 6). Nevertheless, all avermectins are believed to share common pharmacologic/toxicologic mechanisms (1). Avermectins exert their anti-parasitic activity via the activation of a glutamate-gated chloride channel present in the invertebrate nerve and muscle cells (3, 4), and/or through the effect on gamma-aminobutyric acid (GABA) receptors (1, 3, 5), leading to paralysis and death of target organisms. In vertebrates, avermectins can produce GABA-mimetic effects by acting as an agonist at GABA<sub>A</sub> receptor, stimulating the release of GABA, or through other mechanisms (1, 6, 7). Mammals, however, are less susceptible to the toxic effects of avermectins because GABA-mediated nerves occur only in the central nervous system (CNS) and avermectins do not readily cross the blood-brain barrier (BBB; 1). In addition to GABA-mimetic effects, avermectins may induce hypotension in vertebrates through an increase in serum nitric oxide levels (11). **Pharmacokinetics/toxicokinetics:** Avermectins can be absorbed orally, parenterally and dermally. Following their absorption, maximum serum concentrations of ivermectin appeared 2.7 to 5 hours after oral dosing, and elimination half-life was 28±10 hours among healthy volunteers and treated subjects (8-10). Avermectins are largely excreted into the bile and feces, and urinary excretion accounts for only 0.5% to 2.0% of the administered doses (1). Information on the distribution and elimination of avermectins in poisoned subjects is not yet available.

**Animal toxicity:** Although avermectins have a wide margin of safety, high doses of avermectins or mutations in p-glycoprotein can allow avermectins to pass through the BBB to cause neurotoxicity in animals (3), manifesting mydriasis, emesis, diarrhea, drooling, depression, ataxia, stupor, coma, tremors, and death in the absence of histologic changes (5, 10, 13, 14). For example, cattle injected subcutaneously with 20 to

40 times the recommended dose of ivermectin (i.e. 4 to 8 mg/kg) developed toxicity and death (1, 5). Dogs (beagles) given a single dose of 5 mg/kg (> 200 times the therapeutic dose) of ivermectin manifested mydriasis, and tremors, and more pronounced toxicity occurred at 10 mg/kg (1). Dose-related toxicity was also found in chickens (13). Young animals are generally more sensitive to the toxicity of avermectins. A kitten was reported to exhibit toxicosis after receiving subcutaneous administration of 0.3 mg/kg of ivermectin (5). Certain breeds of dogs (e.g. collies) allow more avermectins into the CNS and are thus more vulnerable to avermectin poisoning (5). Animals deficient in p-glycoprotein, a component of the BBB, are also more sensitive to avermectin toxicity than animals with normal p-glycoprotein levels (14, 15). Solvents and additives of commercial avermectins (e.g. hexanol, butylated hydroxytoluene) may enhance the toxicity as well (12). **Human toxicity:** Adverse effects of ivermectin therapy are not uncommon and most of them appear within 48 hours of initiating therapy (16), presenting with myalgia, pruritus, painful skin edema, hypotension, and dyspnea (Mazzotti-type reaction; 15, 16). On the contrary, there is little data concerning human avermectin poisoning. Two children manifested vomiting, somnolence, tachycardia, hypotension, and mydriasis after avermectin overdose (15). A 46-year-old man developed marked drowsiness, unconsciousness, weakness, ataxia, and visual changes after iatrogenic overdose by 200 mg of ivermectin (17). Yang et al reported 19 patients with abamectin poisoning (15). Among them, most patients had certain CNS and gastrointestinal effects, such as diarrhea, nausea, vomiting, drowsiness, dizziness, weakness, and drooling after mild poisoning; and manifested hypotension and coma following severe poisoning. A 72-year-old man died because of severe aspiration pneumonia. Sriapha et al further reported 49 cases with abamectin poisoning (18). Most of the patients were asymptomatic or developed only mild symptoms. However, 16 cases (34%) had serious symptoms, manifesting coma, hypotension, and metabolic acidosis, and 5 of them died. Emamectin poisoning in a 67-year-old man produced similar toxic manifestations (19). **Management:** The therapy for avermectin poisoning is mainly symptomatic and supportive (15). Because absorbed avermectins are largely excreted through feces, prompt gastrointestinal decontamination followed by the administration of activated charcoal may be helpful, given that airway is secured. Picrotoxin, a GABA antagonist, has been proposed as an antidote in treating ivermectin toxicosis in animals (5). However, its use is not recommended because of its seizure activity and narrow margin of safety. Physostigmine and neostigmine were shown to have some effects in the management of comatose animals (5, 10, 20), possibly due to increased concentrations of acetylcholine in affected neurons. Avermectins nevertheless do not regulate cholinergic nerve transmissions (1) and both medications are unlikely to be effective. **Conclusion:** Avermectins are newer pesticides that have a wide margin of safety. Although avermectin poisonings are uncommon, avermectins can produce toxicity primarily through their effects on GABAergic neurons. Severe poisoned patients may then develop coma, hypotension, metabolic acidosis, and even death due to the toxicity of avermectins and/or the additives in the pesticides. Despite the lack of specific therapy, the prognosis of patients with avermectin poisoning is likely to be favorable unless they are complicated by severe hypotension or aspiration. **References:** 1. Campell WC, Fisher MH, Stapley EO, et al. Ivermectin: a potent antiparasitic agent. *Science* 1983;221:823-828. 2. Shoop WL, Mrozik H, Fisher MH. Structure and activity of avermectins

and milbemycins in animal health. *Vet Parasitol* 1995;59:139-156. 3. Burkhart CN. Ivermectin: an assessment of its pharmacology, microbiology and safety. *Vet Hum Toxicol* 2000;42:30-35. 4. Cully DF, Vassilatis DK, Liu KK, et al. Cloning of an avermectin-sensitive glutamate-gated chloride channel from *Caenorhabditis elegans*. *Nature* 1994;371:707-711. 5. Roder JD, Stair EL. An overview of ivermectin toxicosis. *Vet Hum Toxicol* 1998;40:369-70. 6. Dawson GR, Wafford KA, Smith A, et al. Anticonvulsant and adverse effects of avermectin analogs in mice are mediated through the  $\gamma$ -aminobutyric acidA receptor. *J Pharmacol Exp Ther* 2000;295:1051-60. 7. Coccini T, Candura SM, Manzo L, et al. Interaction of the neurotoxic pesticides ivermectin and lindane with the enteric GABAA receptor-ionophore complex in the guinea pig. *Eur J Pharmacol* 1993;248:1-6. 8. Ette EI, Thomas WO, Achumba JI. Ivermectin: a long-acting microfilaricidal agent. *DICP* 1990;24:426-33. 9. Edwards G, Breckenridge AM. Clinical pharmacokinetics of anthelmintic drugs. *Clin Pharmacokinet* 1985;15:67-93. 10. Agarwal AK: Avermectin. In Wexler P (eds): *Encyclopedia of Toxicology*, 1st ed. San Diego: Academic Press, 1998:89-90. 11. Hsu DZ, Chiang PJ, Hsu CH, et al. The elucidation of epinephrine as an antihypotensive agent in abamectin intoxication. *Hum Exp Toxicol* 2003;22:433-7. 12. Hsu DZ, Hsu CH, Huang BM, et al. Abamectin effects on aspartate aminotransferase and nitric oxide in rats. *Toxicology* 2001;165:189-93. 13. Kim JS, Crichlow EC. Clinical signs of ivermectin toxicity and the efficacy of antigabaergic convulsants as antidote for ivermectin poisoning in epileptic chickens. *Vet Hum Toxicol* 1995;37:122-6. 14. Lankas GR, Cartwright ME, Umbenhauer D. P-Glycoprotein deficiency in a subpopulation of CF-1 mice enhances avermectin-induced neurotoxicity. *Toxicol Appl Pharmacol* 1997;143:357-65. 15. Chung K, Yang CC, Wu ML, et al. Agricultural avermectins: an uncommon but potentially fatal cause of pesticide poisoning. *Ann Emerg Med* 1999;34:51-7. 16. De Sole G, Remme J, Awadz K, et al. Adverse reactions after large-scale treatment of onchocerciasis with ivermectin: combined results from eight community trials. *Bull World Health Org* 1989;67:707-19. 17. Graeme K, Giamcola J, Curry S. Visual changes after acute iatrogenic ivermectin poisoning. *J Toxicol-Clin Toxicol* 2000;38:515 (abstract). 18. Sriapha C, Tongpoo A, Sadabthummarak U, et al. Abamectin poisoning: an emerging pesticide poisoning. 5th International Congress of Asia Pacific Association of Medical Toxicology, Colombo, Sri Lanka, August 6-8 2006. 19. Yen TH, Lin JL. Acute poisoning with emamectin benzoate. *J Toxicol-Clin Toxicol* 2004;42:657-61. 20. Muhammad G, Jabbar A, Khan MZ, Sqaib M. Use of neostigmine in massive ivermectin toxicity in cats. *Vet Human Toxicol* 2004;46:28-9.