ToxTalks

A Bulletin for Healthcare Professionals Who Manage Poisoned Patients

Blue Ridge Poison Center | University of Virginia Health | October 2021

IVERMECTIN

Background

Ivermectin is a member of the class of compounds known as avermectins, which are macrocylic lactones produced by the soil dwelling bacterium *Streptomyces avermitilis* (a species of Actinomyces). It was first approved for use in animals in 1981 and for use in humans in 1987. Ivermectin is approved by the FDA for treatment of various helminthic and arthropod parasitic infections. It is available in both topical and oral forms. Topical ivermectin is used to control head lice while the oral form is used to treat non-disseminated strongyloidiasis of the intestines caused by the worm *Strongyloides stercoralis* and onchocerciasis (river blindness) caused by the parasitic worm *Onchocerca volvulus*. It is used to treat a variety of other conditions as well, which include rosacea, ascariasis, lymphatic filariasis, *Loa loa* infection, enterobiasis, *Wuchereria bancrofti* infection, and malaria (adjunctive therapy). It is used in veterinary medicine for the prevention and treatment of parasitic infections in dogs, cats, livestock and horses.

How does ivermectin work?

Ivermectin exerts its anti-parasitic activity by selectively binding to high affinity glutamate-gated chloride channels present in invertebrates (not present in vertebrates). Binding of these receptors, located on muscle and nerve cells of worms, causes increased permeability of chloride ions resulting in hyperpolarization of the cells and subsequent paralysis and death of the parasite. There is also emerging evidence that ivermectin acts on novel site on the γ-aminobutyric (GABA) receptors and causes a greater

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News and Notes:

Welcome to Ryan Cole, M.D., the newest member of our clinical team! Dr. Cole is beginning his two year fellowship in medical toxicology at the University of Virginia. Dr. Cole attended medical school at Quinnipiac University and completed his emergency medicine residency at the University of Connecticut. His professional interests outside of toxicology and emergency medicine include critical care and medical education. He is the author on this month's article on ivermectin.

potentiation of GABA action on this receptor.

Ivermectin does not readily cross the blood-brain barrier (BBB) due to the presence of P-glycoprotein drug pumps. These pumps lie on the blood side of the cells lining the BBB. Any ivermectin that crosses into the cell gets immediately pumped back out, excluding the drug from the central nervous system (CNS). Because it is not able to readily cross into the CNS, it usually does not cause adverse neurological effects.

Neurotoxic effects can be seen in a few instances. One involves a mutation in the P-glycoprotein drug pump, making it ineffective at pumping ivermectin out of the CNS. This mutation is seen in some breeds of dogs, namely collies, in which ivermectin can cause severe and sometimes fatal neurotoxic effects. There are a few case reports of humans suffering serious adverse neurological effects due to mutations in the gene coding for this pump, however this appears to be extremely rare. A vast majority of mutations in this gene are silent and do not affect the activity of the pump. Ivermectin can also enter the human CNS following a massive overdose, which overwhelms the pump and allows the drug access to the brain.

Ivermectin and COVID-19

At the onset of the COVID-19 pandemic, many treatments, including ivermectin, were investigated to determine if they provide any therapeutic benefit in the treatment of SARS-CoV-2. Ivermectin has been shown in laboratory studies to inhibit enzymes responsible for the transport of viral proteins in coronaviruses. While ivermectin is generally well tolerated at doses used for anti-parasite activity, the dosage required to provide anti-viral activity is considerably higher than that which can be safely achieved in humans. The dose used for anti-parasite activity has not been showed to be effective against COVID-19. Clinical trials are still ongoing, however the Infectious Disease Society of America (IDSA) recommends against the use of ivermectin for the treatment of patients with COVID-19 infection both in the inpatient and outpatient setting outside of the context of a clinical trial. This finding was also echoed in a Cochrane Review of the subject, which indicated very low to low certainty evidence regarding the efficacy and safety of ivermectin in the treatment or prevention of COVID-19.

Metabolism

Ivermectin is metabolized by the cytochrome P450 system in the liver. It is primarily a substrate of CYP3A4, which breaks it down into metabolites that are then excreted in primarily in feces. Other medications that induce or inhibit CYP3A4 may have an impact on the concentration of ivermectin circulating in the body. Inhibitors such as erythromycin, ketoconazole, cyclosporine, verapamil, diltiazem, and grapefruit may lead to increased levels by slowing down ivermectin metabolism. Ivermectin has also been shown to enhance GABA's effects. Drugs that increase GABA activity such as alcohol, benzodiazepines, and barbiturates have the theoretical potential to increase ivermectin toxicity.

Adverse Effects

When taken at therapeutic doses, ivermectin is relatively free of neurotoxic effects due to the presence of the P-glycoprotein pump. Some common adverse effects when taking ivermectin at therapeutic doses for parasitic infections include itchiness, hives, and dizziness. When treating helminthic infections, there is the possibility of a Mazzotti-type reaction which includes fever, arthralgias, enlarged and tender lymph nodes, pruritus, hives, and edema. This reaction

is thought to be from the treatment of the worm infection rather than from ivermectin itself. Serious neurological effects have been reported in patients being treated for river blindness with concomitant high burden *Loa loa* infections. These effects included inability to walk, tremors, decreased level of consciousness, seizures, encephalopathy, and coma.

Overdose

The most frequent signs of overdose in humans includes nausea, vomiting, drooling, tachycardia, and hypotension. When taken above the therapeutic dose, increased concentrations of ivermectin may overwhelm the ability of the P-glycoprotein pumps to keep it out of the CNS by saturating the pump. This can lead to neurotoxic effects such as ataxia, tremors, myoclonus, seizures, encephalopathy, and coma.

Care for ivermectin overdose is largely supportive. Consider activated charcoal if ingested within 1 hour and patient is maintaining their airway. Treat hypotension with IV fluids and pressors if needed. Seizures should be initially treated with a benzodiazepine. Ivermectin is a highly lipid soluble drug and there is evidence in the veterinary literature citing successful use of intralipid emulsion (ILE) for the treatment of ivermectin neurotoxicity with successful reversal of neurological symptoms. If significant neurotoxic effects are present, treatment with ILE would be reasonable to consider. Because of its high lipid solubility, hemodialysis is not effective at removal.

If overdose or toxicity is encountered, please contact the University of Virginia Health's Blue Ridge Poison Center at 1-800-222-1222, or use our healthcare provider hotline: 1-800-451-1428. Our center is collecting data associated with ivermectin human exposures and can help with management questions.

References available upon request.

The Blue Ridge Poison Center receives funding from University of Virginia Health, the Virginia Department of Health, and the U.S. Health Resources Services Administration (HRSA). We are accredited by the American Association of Poison Control Centers. We've been proudly serving the Commonwealth since 1978.