Ivermectin, neurotoxicity and p-glycoprotein

Ivermectin induces tonic paralysis in invertebrate organisms by potentiating glutamate-gated chloride channels, and/or gamma amino butyric acid (GABA)-gated chloride channels of the peripheral nervous system. In most mammals, the blood brain barrier prevents access of ivermectin to the central nervous system, and since GABA receptors in mammals are restricted to sites within the central nervous system, mammals are generally protected from the neurological effects of ivermectin. Ivermectin exhibits poor penetration of the blood-brain barrier of vertebrate animals due to the presence of a drug transporting p-glycoprotein. The protein product of MDR1a/ABCB1, called P-glycoprotein (P-gp), is a 170-kD transmembrane protein pump that is present at high concentrations in the apical membrane of brain capillary endothelial cells; substrates of P-gp include a variety of large, structurally unrelated hydrophobic compounds, including naturally occurring compounds such as ivermectin, cyclosporin and digoxin. After substrates are bound by P-gp, they are actively extruded from the endothelial cell into the capillary lumen. P-gp plays a pivotal role in protecting the brain from the toxic effects of ivermectin.

Abrogation of P-gp results in failure of the blood brain barrier. High concentrations of ivermectin accumulate in brain tissue from mdr1a(-/-) mice and neurotoxicity ensues.[1] Furthermore, it is well established in the veterinary world that certain breeds of dogs, such as collies, are sensitive to the neurotoxic effects of ivermectin as a loss of function in the mdr1a gene in these breeds allows for an accumulation of ivermectin within the brain.[2;3] A deletion mutation of the mdr1 gene is associated with ivermectin sensitivity. A 4-base pair deletion results in a frame shift, generating several stop codons that prematurely terminate P-gp synthesis. Premature termination of P-gp synthesis as a result of the frame shift yields a severely truncated protein, that is less than one-tenth its normal length. Dogs that are homozygous for this deletion mutation display the ivermectin-sensitive phenotype, while those that are homozygous normal or heterozygous do not display increased sensitivity to ivermectin. In these dogs' symptoms of neurotoxicity include lethargy, drooling, tremors/seizures, inability to stand, disorientation, and coma.

A single case of encephalopathy and coma following the ingestion of ivermectin has been recorded in the world literature. [4] MDR1a genetic sequencing in this 13-year-old boy identified the child as a compound heterozygote for two nonsense mutations. Each *MDR1a* mutation generated a premature stop codon that predicted two incomplete copies of the transporter. This patient was reported to have made a rapid and complete recovery. While extremely rare, it is likely that additional patients have this compound mutation and ivermectin should be immediately stopped in patients who develop severe neurological problems after taking ivermectin. Although polymorphisms in P-gp expression and function have been documented in people, none has been associated with ivermectin sensitivity. [7-9] Ivermectin has been administered to over seven million ethnically diverse human patients at doses (mg/kg) greater than those required to induce neurotoxicity in affected collies and CF-1 mice, without evidence of adverse effects. [7;9] However, a large number of drugs including cyclosporines,

calcium channel antagonists, various antimicrobial agents, HIV protease inhibitors and others, are able to effectively inhibit P-gp function. [10] Concurrent administration of P-gp-inhibiting drugs with ivermectin could precipitate neurotoxicity in any patient, as a result of increased brain concentrations of ivermectin.

It should also be noted that patients with severe Loa Loa parasitemia are at an increased risk of neurological side effects when being treated with ivermectin.[5;6] This is likely related to the high parasite load within the central nervous system. Curiously, almost all of these cases were reported from the African country of Cameroon. .[5;6] Patients with severe Loa Loa should be treated with slowly escalating doses of ivermectin, and they should be closely monitored.

Reference List

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