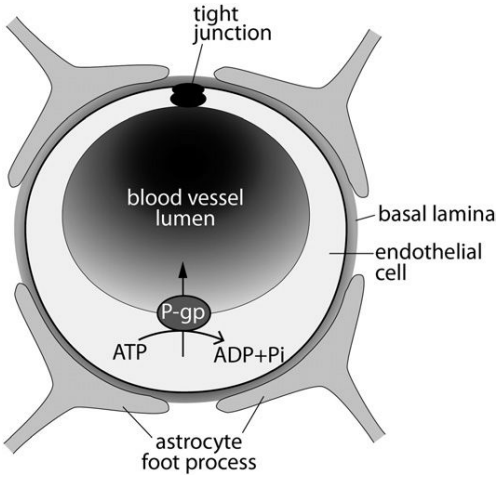
Macrocyclic lactones

- Avermectins
    - Abamectin
    - Ivermectin
    - Eprinomectin
    - Doramectin
    - Selamectin
- Milbemycin
    - Moxidectin
    - Milbemycin
    - Nemadectin
- Bind ligand-gated chloride channels
    - Glutamate-gated channels specific to invertebrates
    - $GABA_A$-gated channels in mammals
        - Only present in CNS
            - Kept out by BBB
            - Overdoses can allow passage through BBB
        - Other ligand and voltage gated channel binding occurs in mammals in overdose condition
        - Hyperpolarization of excitatory neurons leading to decreased firing
            - Avermectins can cause increased firing at lower doses causing paradoxic excitatory signs: tremors
- Permeability glycoprotein (P-gp)
    - Transmembrane efflux protein
    - Important in keeping many drugs out of CNS
    - ABCB-1 is one of these genes
        - Formerly called MDR-1
        - Dogs can have mutation in the gene (homozygous or heterozygous)
            - These dogs (homozygous moreso) are at risk of increased of toxicosis, even without overdose
- Ivermectin (for all the other drugs, see chart at end)
    - Toxicity (none of the below animals were tested for ABCB-1, so take with grain of salt)
        - 0.08 to 0.34 mg/kg in breeds sensitive to ivermectins
            - This is still >10x the dose in HW preventatives
            - Dose for demodex or microfilaricide can cause toxicosis
        - 0.2 mg/kg for ‘normal’ animals
            - Mild signs
        - 1 to 2.5mg/kg for ‘normal’ animals
            - More severe signs
- Toxicokinetics of Macrocyclic lactones
    - Highly fat soluble
    - Quickly absorbed enterally

        - Usually around 4 hours max plasma levels
    - SC absorption much slower
        - Usually >24 hours
    - LONG half-lives
        - Ivermectin is 3.3 DAYS
- ABCB-1 Mutants
    - Herding breeds
        - Collies
            - 35% homozygous, 42% heterozygous
        - shetland sheepdogs
        - australian shepherds
            - 10% homozygous, 37% heterozygous
    - ABCB-1 mutation is NOT only mutation that can cause ivermectin sensitivity
    - Non-herding
        - Longhaired whippets
        - Old english sheepdogs
        - Silken windhounds
        - White swiss shepherds
        - German shepherds
    - Genetic testing available
- Ketoconazole inhibits efflux pump P-gp
    - Increases plasma levels and longer ½ life
    - Increases amount within brain



- Obese animals need to be treated for longer duration
- Clinical Signs
    - Mydriasis
    - Depression, Stupor, Coma
    - Tremors (at lower doses)
    - Ataxia
    - Vomiting
    - Hypersalivation

        - Seizures (less common)
        - Bradycardia
        - Blindness
            - Retinal edema
- Decontamination
    - Induce emesis as long as patient is not neurological or was not a oily delivery system
    - Effect of activated charcoal not established, but recommended Q8h for up to 2 days
- Treatment
    - Monitoring for respiratory depression
        - Mechanical ventilation if needed
    - Thermal support
    - Atropine for bradycardia
    - Seizures
        - Avoid benzodiazepines (this is controversial)
            - Can lead to worsening of CNS signs after seizure resolves
    - Lipid therapy
        - This paper is conservative with their recommendations, however:
        - All Macrocyclic lactones are lipid soluble
        - Give lipids!
- Diagnostics
    - Mostly history and clinical signs
    - Plasma or stomach contents can be submitted for macrocyclic lactone testing
- Prognosis
    - Depends on degree of intoxication
    - All symptoms can resolve, but may take days or even weeks due to long ½ life
    - Blindness is also reversible

Table 1
Therapeutic, nontoxic, and toxic dosages of macrocyclic lactones in both normal and sensitive dogs and in cats

Agent	Formulations	Therapeutic Dosages (Labeled and Off-Label) (mg/kg)	Acute, Subacute or Chronic Dosages Published as Safe (mg/kg)	Toxic Dosages ML Sensitive Dogs (mg/kg)	Acute Toxic Dosage Normal Dog/Cat (mg/kg)	References
Ivermectin	Tablets, oral liquid, oral paste, feed premix, injectable, topical, otic	0.006–0.6 PO D 0.024 PO C 0.2–0.4 SC D, C	0.5 PO daily × 12 weeks[a] D 0.06 PO Collies 0.2–1.33[a] PO or SC C 0.72 PO C	0.1–0.4[b] PO 0.2–0.25[b] SC	0.2–2.5 PO D 0.3 SC C	16,22,25 26,27,32 69,85,87
Selamectin	Topical	6 topical D, C	6 PO D, C[c] 40 topical Collies 72–114 topical D 236–367 topical C	5 PO[d]	None found	16,88,93
Moxidectin	Tablets, oral drench, injectable, topical	0.003 PO D 0.17 sustained release SC D 2.5 topical D 1 topical C	1.15 PO daily × 1 year D 0.09 PO Collies 0.85 SC D, Collies	1 PO[e]	1.9–2.8 PO D 1 PO C[f]	2,16,28 89,90,94 95,96
Doramectin	Injectable, pour-on	0.6 SC D, C	0.5–1 PO daily × 91 days D 0.2 SC C	0.2[g]–0.7 SC	None found	16,37,38 86,91
Milbemycin	Tablets	0.5–2 PO D 2 PO C	10 PO Collies 10 PO C	5–10[g] PO 0.8 PO × 2 days 1.5 PO × 13 days	None found	16,33,34 92

Abbreviations: C, cat; collies, ivermectin-sensitive collies; D, dog; PO, orally; SC, subcutaneously.
[a] It should be noted that some animals are also reported to have problems at this dosage.
[b] Many of the collies in these reports were not tested for the *ABCB1-1Δ* gene defect.
[c] Cats exhibited drooling and intermittent vomiting with oral dosing.
[d] One collie was ataxic after this dosage in the safety studies, but others tolerated up to 15 mg/kg PO.
[e] Administered as a product containing 2.5% moxidectin and 10% imidacloprid.
[f] Generally only mild signs seen.
[g] Collies at these dosages were not tested for the *ABCB1-1Δ* gene defect.

Questions

1. What is the current name of the gene that, when mutated, can increase the risk of macrocyclic lactone overdose
2. What is the mechanism of action ivermectin in mammals?
    a. Prevent opening of $GABA_A$ ligand gated chloride channels resulting in depolarization of neurons
    b. Prevent opening of $GABA_A$ ligand gated chloride channels resulting in hyperpolarization of neurons
    c. Prevent opening of Glutamate ligand gated chloride channels resulting in depolarization of neurons
    d. Prevent opening of Glutamate ligand gated chloride channels resulting in hyperpolarization of neurons
3. What is the approximate time to peak plasma levels after oral ingestion and approximate half-life of ivermectin in the dog
    a. 12 hours; 48 hours
    b. 1 hour; 12 hours
    c. 2 hours; 6 hours
    d. 4 hours; 72 hours

Answers:

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   ABCB-1

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