Loperamide – investigating a human medication toxic to pets

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Loperamide, a synthetic diphenylpiperidine derivative, is a common, low-cost, "over-the-counter" medication. It is used in human medicine for the symptomatic treatment of acute and chronic diarrhoea in adults, under a variety of brand names.

Loperamide is available as capsule (2mg), tablet (2mg) or syrup (1mg/5ml), is becoming an increasingly popular drug for recreational abuse and represents a "growing public health danger"[1,2].

Pets can accidentally ingest the capsules intended for their human owners or be overdosed by owners. The American Society for the Prevention of Cruelty to Animals Animal Poison Control Centers reported 903 exposures to loperamide during 2000-6, involving 862 dogs and 33 cats[3]. Vets should be aware of potential lethal toxicity of loperamide for pets[3].

Loperamide properties

Pharmacokinetics

Loperamide is a weak basis (acid dissociation constant 8.6), high lipid soluble (partition coefficient

5.5)4. It has a low oral bioavailability and, at therapeutic doses, is excluded from the CNS by P-glycoprotein (P-gp)[4,5].

Absorption

In dogs, 20% of an oral dose, is absorbed from the gastrointestinal tract[6]. In humans, the loperamide from the syrup formulation is absorbed more rapidly than from the capsule formulation, with the peak serum levels respectively observed at a mean time of 2.4 ± 0.7 hours for the syrup and 5.2 ± 0.3 hours for the capsule[7].

Distribution

Less than 0.5% of an oral dose reaches the systemic circulation4. In the blood, loperamide is 97% bound to albumin[5,7].

Biotransformation

Loperamide undergoes extensive hepatic first-past metabolism by oxidative N-demethylation and glucuronide conjugates[8].

Elimination

In humans, loperamide is excreted mainly in faeces (30%) as unchanged drug and in urine (less than 2%)[5,7]. In dogs, the plasma half-life of the parent compound ranges from 6 to 14 hours[6].

Pharmacological properties

Loperamide is a peripheral opioid agonist at the mu-opiate receptors in the myenteric plexus of the large intestine, decreasing the motility of the circular and longitudinal smooth muscles of the intestinal wall (antimotility antidiarrhoeal) and by affecting water and electrolyte movement through the bowel[9].

Loperamide may also reduce intestinal secretion induced by prostaglandin E23.

Risk assessment

The oral median lethal doses (LD_{50}) of loperamide in dogs is 40mg/kg[6]. Young animals may be more sensitive to CNS effects than adults10. Susceptible breeds include collies, collie-type breeds such as Australian shepherd dogs, Old English sheepdogs, longhaired whippets, Shetland sheepdogs, Skye terriers and silken windhounds[10,11].

In dogs, doses of 1.25mg/kg/day to 5mg/kg/day produced vomiting, depression, severe salivation and weight loss[3]. In the experience of Veterinary Poisons Information Services, doses greater than 0.1mg/kg in collie breeds might produce toxic effects[12]. Cats may be more sensitive because of their low capacity of glucuronide formation. Loperamide can cause severe side effects (excitatory behaviour) and is not recommended in this species[3].

Loperamide sensitivity (such as ivermectin sensitivity) is derived from a frameshift deletion mutation of the multidrug resistance (MDR-1) gene, resulting in a severely truncated, non-functional protein product. The product of the MDR-1 gene, P-gp, is a large adenosine triphosphate-dependent transmembrane protein transporter found in the blood-brain barrier among other tissues[13,14].

Loperamide is an avid substrate for P-gp. P-gp pumps substrates (more than 20 vital drugs are known substrates) in the brain back into the blood. Mutation deletion of MDR-1 causes non-functional P-gp[13-16]. Loperamide can be very dangerous for dogs with the MDR-1 gene mutation for P-gp, in which it crosses the blood-brain barrier and causes CNS toxicity[13-16].

Loperamide exhibits many drug interactions. For example, concomitant administration of antifungal (ketoconazole and itraconazole) increase significantly loperamide plasma concentrations by inhibiting P-gp[3].

Toxic mechanism

In susceptible breeds or ingestion of a massive dose in non-collie breeds, loperamide crosses the blood-brain barrier and activates opioid receptors in the brain: mu (mainly), delta and kappa, and causes toxic effects. Loperamide also leads to cardiac toxicity and induces torsade de pointes or other ventricular arrhythmias[1,2]. As a piperidine derivative, loperamide is a calcium channel blocker[17]. Loperamide also inhibits potassium channels, which would explain the QT prolongation on ECG[18]. Any QRS widening seen is caused by sodium channel blockade[19].

Clinical features

Clinical signs of toxicosis occur within 30 minutes and usually within 6 hours following large ingestion[12]. These signs are digestive, neurological and cardiac[3,10,12,15,16].

The common reported clinical signs include:

- anorexia
- drowsiness
- vomiting
- abdominal pain
- hypothermia

- hypersalivation
- ataxia
- hindlimb paresis
- hyperexcitability
- vocalisation
- mydriasis

ECG shows cardiac conduction disturbances[1,18,19]:

- widening of the QRS complex (normal values QRS duration – large dogs ? 0.06s; small dogs ? 0.05s, cats ? 0.04s)
- prolonged QT interval (normal values – dogs 0.15s to 0.25s; cats 0.12s to 0.18s, depending on heart rate)

Laboratory values indicate hyperamylasaemia and hyperlipasaemia[3]. Death is caused by cardiac arrest.

Diagnosis

The diagnosis of loperamide intoxication is based on the history of exposure, rapid onset of significant clinical signs (such as vomiting, hypersalivation, ataxia, rear limb weakness and hyperexcitability) and ECG disturbances.

Toxicological diagnosis is based on analysis of vomit, blood and urine. Liver and kidneys can also be used to detect the presence of loperamide in tissue collected postmortem.

The presence of loperamide can be confirmed by liquid chromatography-mass spectrometry and liquid chromatography-tandem mass spectrometry[8,20].

Management

Naloxone, a pure competitive opioid antagonist with a high affinity for all three types of opioid receptors, is the antidote to treat severe cases of intoxication by loperamide[6,12,21]. It crosses the blood-brain barrier readily and has a very rapid onset of action (one to two minutes IV) to reverse opioid effects[21,22].

The recommended dosage is 0.04mg/kg IV infusion, IM or SC in dogs and 0.02mg/kg to 0.04mg/kg IV infusion in cats[3]. Duration of action of naloxone (45 to 90 minutes) is limited due to its short plasma half-life[3,21,22]. Since the duration of action of loperamide is longer than that of naloxone, repeated treatment with naloxone for at least 24 hours may be required. Naloxone should be used cautiously in animals that have ingested a massive dose of loperamide[3]. The management of loperamide poisoning is listed in **Table 1**.

Naloxone is considered a safe drug with LD_{50} in dogs for IV administration of 80mg/kg[24]. The most prevalent adverse effect is pulmonary oedema[3,5]. IV lipid emulsion may also be a potential antidote involving highly lipid soluble drugs such as loperamide[25].

Naloxone hydrochloride is provided as a sterile injectable solution (0.02mg/ml, 0.4mg/ml or 1mg/ml) when given as an IV infusion – either 5% dextrose in water or normal saline should be used[3,5]. The pH ranges of commercial injectable solutions are from 3 to 4.5. Naloxone hydrochloride for injection should be stored at room temperature (15°C to 30°C) and protected from light. The shelf-life is three years[3].

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