GABAPENTIN

Kyra Berg, DVM

Gabapentin is an anticonvulsant drug that is considered a first-line medication against neuropathic pain in humans,[1] and there is increasing evidence of a similar effectiveness in veterinary medicine. In humans, gabapentin is indicated for post-herpectic neuralgia, painful diabetic neuropathy, painful polyneuropathy, partial seizures, and lower back pain.[1,2]

Neuropathic pain encompasses lesions or diseases of the somatosensory system, which has been classified as peripheral or central.[1] When a patient suffers from neuropathic pain it is often severe and difficult to manage, often becoming a chronic condition. Gabapentin's use for chronic and neuropathic pain, in addition to refractory or complex partial seizures in animals, is a rapidly developing field of research interest.[3]

MECHANISM OF ACTION

Gabapentin binds to the alpha-2/delta-1 subunit of voltage-gated calcium channels that are located within the central nervous system (CNS) and spinal cord.[1] These subunits are only expressed in the CNS and spinal cord, and the channels are located on presynaptic terminals to control neurotransmitter release.[1] Voltage-gated calcium channels open in response to action potentials, which allows the influx of calcium ions and subsequent synaptic vesicle fusion and neurotransmitter release into the synaptic cleft.[1] The alpha-2/delta-1 subunit of the voltage-gated calcium channel is considered an accessory subunit, and its roles include trafficking, localization, and stabilization of the channel in the plasma membrane.[1] These channels increase in conditions of neuropathic pain, which may prolong unwanted neurotransmission in the spinal cord.[1] Although gabapentin does not directly influence the current of electrolytes, there is speculation that binding to the alpha-2/delta-1 subunit results in destabilization between the calcium channel and the membrane, and subsequent internalization; this may therefore alter the quantity and availability of calcium channels in the plasma membrane.[1] As these channels are responsible for the release of excitatory neurotransmitters, gabapentin may play a role in preventing allodynia or hyperalgesia.[3]

The alpha-2/delta-1 subunit expression is particularly high in brainstem structures, which is the origin for descending modulatory fibers.[1] The antinociceptive properties of gabapentin may also be associated with descending noradrenergic and serotonergic activity, which also modulates pain transmission in the spinal cord.[1] Although gabapentin is structurally similar to GABA, it does not appear to influence GABA in any mechanism.[3]

PHARMACOKINETICS AND PHARMACODYNAMICS

In humans, gabapentin is absorbed intestinally by the system-L protein family amino acid transporters (LAT) and, in particular, the LAT1 transporter.[1] There may be dose-limited absorption in gabapentin secondary to transporter saturation. Gabapentin is excreted unmodified by the kidneys and is not involved in the cytochromic P450 system, indicating general safety when used in combination with other analgesic drugs.[1] Gabapentin is absorbed slowly, and exhibits a non-linear (zero-order) process in the form of saturable absorption.[2] Therefore, bioavailability of the drug is variable, and it has been reported that gabapentin bioavailability decreases by 50% when the dosage quadruples.[2] In humans, plasma concentrations of >2 μg/ml are considered effective in treating epilepsy and providing a clinical analgesic response.[4]

Although caution is merited in veterinary patients with renal insufficiency, dogs partially metabolize gabapentin.[3] Oral bioavailability in dogs is approximately 80% at a dose of 50 mg/kg.[3] In cats, oral bioavailability is approximately 90%, however, there appears to be a wide interpatient

From the Louisiana State University, School of Veterinary Medicine, Department Veterinary Clinical Sciences, Baton Rouge, LA 70803, USA
Address correspondence to: Kyra Berg, DVM, Louisiana State University, School of Veterinary Medicine, Department Veterinary Clinical Sciences, Skip Bertman
Dr., Baton Rouge, LA 70803. Tel.: 225-635-3502; fax: 225-578-9798. E-mail: kjberg@ucdavis.edu

variation when gabapentin is dosed in this manner.[3]

Gabapentin is absorbed independently of sodium influence on the transportation process in rats and rabbits.[5] In rabbits, When compounded gabapentin suspensions were administered to Hispaniolan Amazon parrots (HAP) at 30 mg/kg intravenously, 10 mg/kg orally, and 30 mg/kg orally, mild sedation was only noted after intravenous administration.[6] Oral bioavailability in the HAP was 80 to 89% and volume of distribution was high, indicating wide distribution to body tissues. Therefore, oral administration of gabapentin appears to be an appropriate method to give this drug to HAP.[6] Effective plasma concentrations for anti-neuropathic pain properties of gabapentin have not been established in zoological species.

Great horned owls were administered a single dose of gabapentin suspension, 11 mg/kg orally, and plasma concentrations were determined to reach the human therapeutic level for approximately 8 hours.[4] Higher peak plasma concentrations were observed in great horned owls faster than children and beef calves.[4] Bioavailability of gabapentin could not be determined because a commercially available injectable solution was not available.

SIDE EFFECTS

In humans, dizziness and somnolence occur in more than 20% of patients that have been treated with gabapentin; other less common side effects include confusion and peripheral edema.[1] These adverse side effects appear to be dose-dependent.[1]

In animal subjects, ataxia and sedation are the most likely adverse side effects associated with gabapentin use.[3] Moreover, gabapentin has been linked with an increased rate of pancreatic adenocarcinoma in male rats when this drug was administered in very high dosages.[7,8]

An incidental overdose of 110 mg/kg was given orally to a prairie falcon, which was recognized 1 hour after administration and treated with activated charcoal and balanced crystalloids.[9] Approximately 2 hours after administration, the bird exhibited diarrhea, ataxia, and obtundation.[9] The day following the accidental overdose, the bird was eating and eliminating normally, but was determined to be agitated, hyperesthetic, and displayed occasional body tremors.[9]

Caution is required regarding the use of the commercially available human oral solution in veterinary patients, as it contains xylitol.[3] Gabapentin is commercially available as an oral solution, tablet, and capsule.[3]

ZOOLOGICAL SPECIES-SPECIFIC USES

Birds

An African grey parrot diagnosed with a presumed acute ischemic stroke was managed for seizures secondary to the stroke with many antiepileptic agents.[10] Approximately 11 months after the initial diagnosis the bird was still having sporadic seizures, at which time gabapentin 20 mg/kg orally was prescribed every 12 hours and other antiepileptic medications were adjusted.[10] After the adjustment of antiepileptics and the addition of gabapentin, only 1 seizure was observed in a 9-month period.[10]

A prairie falcon managed for suspect neuropathic pain was prescribed gabapentin at 11 mg/kg to be given orally, twice daily.[9] The bird continued to self-mutilate in spite of multimodal analgesia, consequently the gabapentin dose was increased to 82 mg/kg to be given orally, twice daily.[9] The gabapentin dose and other analgesics were gradually reduced when self-mutilation behavior resolved.[9]

On the basis of effective plasma concentrations reported for human patients, computer simulation estimates recommended gabapentin 15 mg/kg orally every 8 hours in HAP.[6] In great horned owls, gabapentin 11 mg/kg orally every 8 hours provides maintenance of plasma concentrations at the human therapeutic threshold.[4]

Mammals

Rabbits receiving spinal cord ischemic injury using the aortic occlusion model were administered gabapentin at 200 mg/kg and 30 mg/kg intraperitoneally.[11] Gabapentin reduced the post-traumatic oxidation of proteins in these ischemia-reperfusion rabbits to normal levels.[11]

In a study assessing severity and presence of cecal adhesion formation in rabbits, administering gabapentin 30 mg/kg orally daily for 10 days resulted in more severe adhesions.[12] However, it was suggested that gabapentin had no significant effect on wound healing and that studies extending beyond the immediate 10-day post-operative period were warranted.[12] Assessment of the presence of the alpha-2/delta-1 subunit in the myenteric plexus is also warranted to determine its efficacy on afferent visceral pain in rabbits.

Ex vivo studies of guinea pig hippocampi in bath solutions exposed to epileptiform field potentials did not benefit from gabapentin alone; however, there was evidence that gabapentin potentiated the antiepileptic properties of vigabatrin, a GABA inhibitor.[13] More studies are indicated to determine the effects of gabapentin in guinea pigs,