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Review

Characteristics of selected second-generation antiepileptic drugs used in dogs

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Abstract

A significant number of cases of clinical canine epilepsy remain difficult to control in spite of the applied treatment. At the same time, the range of antiepileptic drugs is increasingly wide, which allows efficient treatment. In the present paper we describe the pharmacodynamics and pharmacokinetics of the newer antiepileptic drugs which were licensed after 1990 but are still not widely used in veterinary medicine. The pharmacokinetic profiles of six of these drugs were tested on dogs. The results of experimental studies suggest that second generation antiepileptic drugs may be applied in mono- as well as in poli- treatment of canine epilepsy because of the larger safety margin and more advantageous pharmacokinetic parameters. Knowledge of the drugs' pharmacokinetics allows its proper clinical appliance, which, in turn, gives the chance to improve the efficiency of pharmacotherapy of canine epilepsy.

Key words: epilepsy, dogs, antiepileptic drugs, pharmacokinetics

Introduction

Epilepsy is the most common chronic neurological disorder in both humans and dogs. Clinically, the epilepsies are characterized by spontaneous, recurrent epileptic seizures, either convulsive or non-convulsive, which are caused by partial (focal) or generalized paroxysmal discharges in the central nervous system (CNS). In veterinary medicine the majority of canine epilepsies have been considered idiopathic (primary generalized epilepsy of unknown cause but with possible familial predisposition), and the mainstay of treatment is first generation antiepileptic drugs (first generation AEDs), such as phenobarbital (PB), potassium bromide (KBr), carbamazepine (CBZ) and benzodiazepines (BZD) (Podell et al. 1995, Rogvi-Hansen and Gram 1995, Berendt and Gram 1999). Primary or idiopathic epilepsy is diagnosed in approximately 80% of dogs with seizures (Podell et al. 1995). In human medicine during the last several years some new antiepileptic drugs were introduced (second and third generation AEDs) whereas canine epilepsy pharmacotherapy (as is the case with feline epilepsy) is based mainly on the appliance of first generation drugs, (PB being the most commonly used). This is caused, not exclusively, by the higher price of second generation drugs (in comparison to first generation antiepileptic drugs) but also by the very mediocre knowledge of the clinical efficiency and safety of the appliance of these drugs on dogs. It is worth emphasizing that in Poland, as well as in many other countries, there is a lack of antiepileptic drugs registered for use for the treatment of dogs which forces veterinarians to use drugs meant for treating epilepsy in humans. In the

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Table 1. Reported effects of new antiepileptic drugs (AEDs) on plasma concentration of commonly available AEDs.

Added drug	Commonly used AEDs						Reference
	CBZ	CBZE	PB	PHT	PRM	VPA	
FBM	↓	↑	↑	↑	↑	↑	Walker and Patsalos 1995
GBP	–	–	–	↑	–	–	
LEV	–	–	–	↑	–	–	
OXC	–	–	–	–	–	–	
TPM	–	–	–	↑	–	–	
ZNS	↑	–	–	–	–	–	

FBM – felbamate, GBP – gabapentin, LEV – levitiracetam, OXC – oxcarbazepine, TPM – topiramate, ZNS – zonisamide, CBZ – carbamazepine, CBZE – carbamazepine-epoxide, PB – phenobarbitone, PHT – phenytoin, PRM – primidone, VPA – valproic acid, (–) – no change, (↑) – increase concentration of commonly available AEDs, (↓) – decrease concentration of commonly available AEDs

available literature there is a significant amount information on the efficiency of "the old" generation of drugs in canine epilepsy pharmacotherapy as well as on the considerable number of side-effects (Dewey 2006, Thomas 2010). However, it is worth noting that an appreciable percentage of cases of canine epilepsy does not respond to conventional treatment, that is to treatment with the appliance of first generation drugs (Schwartz-Porsche et al. 1985). Increasing the dosage of PB and KBr may improve seizure control, while it is often linked with the intensification of side-effects such as polyuria, polydipsia, polyphagia, ataxia, hepatotoxicity, teratogenicity and embryotoxicity (Rogvi-Hansen and Gram 1995).

It is important to emphasize that the side-effects (including organ toxicity) in the case of use of the second generation drugs to humans have proven to be milder and less intense than those of many first generation drugs. Also, not insignificant is the fact that drugs such as PB or BZD prove to have serious addictive properties (Isbell and Fraser 1950, Longo and Johnson 2000), and the discontinuation of the administration of this kind of substance may negatively influence the animal's psyche which is, in turn, linked to unfavorable change in its behavior. In favor of the second generation drugs is also the matter of their relation to CNS, in addition to the considerably lower probability of their interaction with other drugs (Table 1), which renders their use as elements of the politherapy of epilepsy safe in comparison to the first generation drugs. Taking into consideration the aforementioned aspects, one should suppose that it is only a matter of time before second generation drugs are introduced to canine epilepsy treatment, at least as alternative drugs i.e. used in case of the inefficiency or the intolerance of first generation drugs.

The present paper is an attempt at summarizing the contemporary state of knowledge of the pharmacodynamics and pharmacokinetics of selected second generation drugs applied in the treatment of dogs. On the basis of the available test results regarding the pharmacokinetics of felbamate, gabapentin, levetiracetam, oxcarbazepine, topiramate and zonisamid used in dogs, the absorption, distribution, biotransformation and excretion of these drugs is characterized.

Felbamate

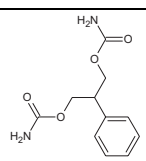
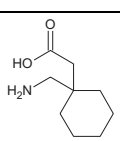
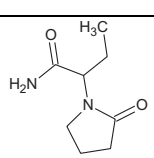
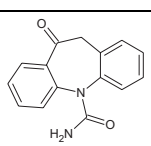
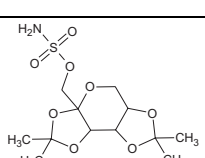
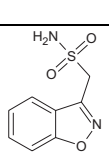
Felbamate (2-phenyl-1,3-propanediol dicarbamate; FBM) is a relatively simple molecule (Table 3) with a broad spectrum of antiepileptic activity, and its efficiacy has been evaluated in several animal models of epilepsy (Swinyard et al. 1986, Giorgi et al. 1996, Wlaz and Loscher 1997, Ebert et al. 2000). FBM has been shown to be efficacious in the treatment of multiple seizure types in humans, such as simple partial, complex partial and primary generalised tonic-clonic seizures (White et al. 1992, Bourgeois et al. 1993, Sofia et al. 1993, Mellick 1995). Additionally it is effective in Lennox-Gastuat syndrome resistant to other antiepileptic compounds (Ritter 1993). Moreover, several reports have indicated that this agent has a neuroprotective effect in a hippocampal slice and neonatal rat model (Wallis et al. 1992, Wasterlain et al. 1992, 1993, Chronopoulos et al. 1993). FBM has a multiple mechanism of action which is still not fully elucidated. It effects the N-Methyl-D-aspartic acid (NMDA) subtype of glutamate receptor (Taylor et al. 1995, Harty and Rogawski 2000), probably inhibits glutaminergic neurotransmission via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA)/kinate receptors (DeSarro et al. 1994) and potentates γ-aminobutyric acid type A receptor currents ($GABA_A$) through a barbiturate-like modulatory effect on this receptor complex (Rho et al. 1997). This agent also has an effect on ion channels such as the α-subunit of Na^+ currents and high-voltage-activated Ca^{2+} channels (L-type) (Stefani et al. 1996, Taglialatela et al. 1996).

Table 2. Pharmacokinetic parametrers of selected antiepileptic drugs in dogs.

Added drug	Parameter after single oral dose								Reference
	Dose (mg/kg)	F (%)	Vd (L/kg)	$t_{1/2kel}$ (h)	CL (ml/min/kg)	Protein binding (%)	Elimination (%)		
							urine	feces	
FBM	11	100	0.9-1.1	4.5-6.0	1.15-1.85	22-25	70	25	Adusumalli et al. 1991, 1992; Young et al. 1991, 1992
GBP	50	80	1.0	2.2-4.0	3.5-4.0	3	99	0.3-1.0	Vollmer et al. 1986; Radulovic et al. 1995; KuKanich et al. 2011
LEV	20, 54	100	0.45-0.6	2.3-4.0	1.5-2.3	0	89	Nd	Doheny et al. 1999; Isoherranen et al. 2001; Benedetti et al. 2004; Patterson et al. 2008
OXC	40	Nd	0.7-0.8	4.6	Nd	45	Nd	Nd	Schicht et al. 1996; Volosov et al. 1999
TPM	10, 40, 150	57	0.63	2.6-3.7	2.4-3.6	10	90	6	Streeter et al. 1995; Caldwell et al. 2005
ZNS	10	68	0.72	13-17	0.6	39.5	83	17	Matsumoto et al. 1983; Boothe and Perkins 2008; Orito et al. 2008

FBM – felbamate, GBP – gabapentin, LEV – levitiracetam, OXC – oxcarbazepine, TPM – topiramate, ZNS – zonisamide, F – absolute bioavailability, Vd – volume of distribution, $t_{1/2kel}$ – half-life in elimination phase, CL – total body clearance, Nd – no data

Table 3. Some antiepileptic drugs chemical and physical properties.

Compound	Structure	Molecular formula	Molecular weight [g/mol]
Felbamate		$C_{11}H_{14}N_2O_4$	238.23986
Gabapentin		$C_9H_{17}NO_2$	171.23678
Levetiracetam		$C_8H_{14}N_2O_2$	170.20896
Oxcarbazepine		$C_{15}H_{12}N_2O_2$	252.26798
Topiramate		$C_{12}H_{21}NO_8S$	339.36204
Zonisamide		$C_8H_8N_2O_3S$	212.22572

Following single oral administration of FBM at a dose of 11 mg/kg, approximately 100% (Table 2) was absorbed and absolute bioavailability (F) was unaffected by food (Adusumalli et al. 1991). Adusumalli et al. (1991, 1992) demonstrated that after multiple oral administration the maximal concentration (C_{max}) and area under the curve (AUC) were significantly smaller than in the single oral dose. These results indicate a change in the FBM disposition process after multiple dosing. In general, these changes are attributed to modifications in the absorption, distribution into tissue, and elimination of this agent. The time of maximum concentration (t_{max}) of FBM was reached in 4.0 to 5.5 h after the single and multiple oral dose, respectively and was not dependent on dose value. However, in pediatric dogs t_{max} was about 3.0 h (Adusumalli et al. 1992).

Adusumalli et al. (1991) proved that FBM is distributed readily into tissues and did not appear to accumulate in any particular tissue. It also easily crossed the blood-brain barier (BBB), as was demonstrated by the above mentioned authors. The volume of distribution (Vd) of this agent was 0.9 to 1.1 L/kg (Table 2), however, in pediatric dogs the value reached 1.2-1.9 L/kg (Adusumalli et al. 1992). FBM bound with plasma proteins from 22 to 25% (Table 2) and the albumin was responsible for most of the binding. Red blood cells were capable of binding 40% of this agent (Adusumalli et al. 1991).

Metabolism of FBM includes only a few enzymatic biotransformation reactions such as hydroxylation, hydrolysis, oxidation, conjugation of primary metabolites with glucuronic acid. Studies by Yang et al. (1991, 1992) indicated that 45-60% of the dose of this agent was metabolized into 2-(4-hydroxyphenyl)-1,3-propanediol dicarbamate (p-OHF), 2-hydroxy-2-phenyl-1,3-propanediol dicarbamate (2-OHF), 2-phenyl-1,3-propanediol monocarbamate (MCF), 3-carbamoyloxy-2-phenylpropionic acid (CPA) and 40-55% was not transformed. It should be noted that in pediatric dogs the sum of hydroxyl metabolites was significantly higher, but the contribution of each of the hydroxylation pathways did not change with age (Yang et al. 1991, 1992). This may be explained by the fact that the hydroxylation is more efficient in the case of younger dogs than it is for adult animals. Yang et al. (1991,1992) also indicated that none of the mentioned metabolites showed anticonvulsant activity comparable to FBM. Additionally Segelman et al. (1985) showed in rats that FBM was a mild hepatic cytochrome P450 inducer, which inticates that this drug has a moderate influence on the metabolism of other substances (Table 1).

Studies by Adusumalli et al. (1991) and Young et al. (1991, 1992) demonstrated that in the urine there was about 70%, and in the feces there was approximately 25%, of the excreted drug and its metabolites (Table 2). The value of half-life time in the elimination phase ($t_{1/2kel}$) for FBM was 4.5-6.0 h in adult (Table 2) and 2.5-3.5 h in pediatric dogs. The above-mentioned authors also indicate that body clearance (CL) was higher in young dogs (3.2-5.3 ml/min/kg) (Table 2) than in adult dogs (1.15-1.85 ml/min/kg), which is linked to faster metabolism of the drug.

Gabapentin

Gabapentin (1-(aminomethyl) cyclohexane acetic acid; GBP) is a cyclic GABA analogue (Table 3). Its mechanism of action, despite extensive research, remains unclear. Although gabapentin was originally synthesized as a GABA analogue, capable of penetrating the BBB, it does not possess a high affinity for either $GABA_A$ or $GABA_B$ receptors, does not influence neural uptake of GABA and does not inhibit the GABA-metabolizing enzyme such as GABA transaminase (Kelly 1998, Taylor et al. 1998, Sills 2006). Furthemore, gabapentin does not affect voltage-dependent sodium channels (the site of action of several antiepileptic drugs) and is inactive in assays for a wide range of other neurotransmitter receptors, enzymes and ion channels (Kelly 1998, Taylor et al. 1998, Sills 2006). Instead of this GBP binds intracellularly to the α2δ subunits of neuronal voltage-dependent Ca^{2+} channels (L-type), which leads to reduced neurotransmitter release (Gee et al. 1996). This novel antiepileptic drug is orally active in various animal models of epilepsy (Goa and Sorkin 1993, Gee et al. 1996, Taylor et al. 1998). GBP has also been shown to be effective in decreasing the frequency of seizures in medically refractory patients with partial or generalized epilepsy (Goa and Sorkin 1993, Taylor et al. 1998). Moreover, it displays antinociceptive activity in various animal pain models and, clinically, GBP is indicated as an add-on medication for the treatment of neuropathic pain (Nicholson 2000). Furtermore, this drug could also be beneficial in several other clinical disorders such as anxiety (Pollack et al. 1998), bipolar disorder (Wang et al. 2002) and hot flashes (Loprinzi et al. 2002).

According to Radulovic et al. (1995) GBP was rapidly and extensively absorbed (about 80% of the dose) (Table 2) following oral administration (50 mg/kg). The C_{max} of the drug was reached within 1.0-3.0 h after drug administration (Vollmer et al. 1986, Radulovic et al. 1995, Rhee et al. 2008) and its value was not dependent on either of the formulations used in the experiments (a capsule or tablet). Multiple oral administration compared with single dose did not significantly influence the absolute bioavailability and C_{max} (Vollmer et al. 1986, Radulovic et al. 1995). However, there are reports (Stewart et al. 1993, Radulovic et al. 1995) indicating that the absorption

rate could be dose-dependent. It has been suggested that the decrease in the absorption rate of GBP with increasing the dose could be related to L-amino acid transporter (Stewart et al. 1993, Stevenson 1997). Stevenson et al. (1997) suggested that plasma concentration level could be not only dose but also nutrition dependent. However, studies by Radulovic et al. (1995) indicate that absorption is not dependent on nutrition.

Vollmer et al. (1986) and Radulovic et al. (1995) have shown that GBP has negligible protein binding (less than 3% of gabapentin circulates bound to plasma protein) (Table 2). Moreover, it has been demonstrated that the Vd value of GBP was approximately 1.0 L/kg (Table 2), which suggests easy diffusion of the drug to the tissues (KuKanich et al. 2011). Furthermore, these authors showed GBP concentration in the CNS of rats was nearly half that in the blood (Vollmer et al. 1986, Radulovic et al. 1995).

Studies by Vollmer et al. (1986) and Radulovic et al. (1995) demonstrated that in dogs GBP was metabolized into N-methyl-gabapentin from 30 to 40% of the dose. Furthermore, they also found two other metabolites and their concentration was below 5% for each one.

The major route of elimination of GBP is via the kidney (Vollmer et al. 1986, Radulovic et al. 1995). The authors showed that 24 h after i.v. drug administration (50 mg/kg) almost 60% of GBP was eliminated into the urine as an unchanged form and the rest as N-methyl-gabapentin. Only 0.3-1% of the drug was excreted with feces (Table 2). However, Vollmer et al. (1986) showed that, following oral administration (50 mg/kg), fecal excretion changed from less than 1 to 32% of the dose; in an experiment of Radulovic et al. (1995) following oral administration (100 mg/kg) it was about 21%. Vollmer et al. 1986 also pointed out that the elimination of GBP metabolite was slightly slower than the parent drug. Results of several reports (Vollmer et al. 1986, Radulovic et al. 1995, Rhee et al. 2008, KuKanich et al. 2011) indicate that $t_{1/2kel}$ of GBP ranged from 2.2 to 4.0 h (Table 2) and was independent of GBP dose, number of doses, drug formulation and route of administration. KuKanich et al. (2011) found that the total CL was between 3.5 and 4.0 ml/min/kg after a single oral dose (Table 2), whereas other investigators (Radulovic et al. 1995) established that the value of this parameter was about 2.3 ml/min/kg after i.v. administration.

Levetiracetam

Levetiracetam ((S)-α-ethyl-2-oxo-1-pyrrolidine acetamide; LEV) is an ethyl analogue of the nootropic drug piracetam and it has a different structure from the other second generation antiepileptic drugs (Table 3). This agent proved to be effective in a wide range of animal tests, and the antiepileptogenic effect is reached at doses below those causing neurotoxic side effects (Gower et al. 1993, Löscher and Hönack 1993, Klitgaard et al. 1998, Löscher et al. 1998). LEV is used in the treatment of many types of human seizures including simple partial, complex partial and secondary generalized seizures (Cereghino et al. 2000). Additionally, this drug has minimal effect on the pharmacokinetic disposition of other AEDs, thus it can be used as an adjuvant medication for patients with refractory epilepsy (Klitgaard et al. 1998). LEV has a unique mechanism of action which, however, is not completely understood. This drug antagonizes negative modulators (Zn^{2+}, β-carbolines) of the $GABA_A$ and glycine receptors, thereby increasing Cl^- influx (Rigo et al. 2002). Interestingly, LEV does not directly activate the GABAergic receptor complex (Macdonald and Kelly 1995). Also, this drug penetrates the CNS and attaches itself to synaptic vesicle protein 2A (SV2A) in neurons, probably modulating calcium-dependent exocytosis of neurotransmitters (Xu and Bajjalieh 2001, Lynch et al. 2004). Furthermore, LEV inhibits the high-voltage-activated Ca^{2+} channels (N-type) and moderates inhibition of the K^+ currents in the CNS (Niespodziany et al. 2001, Lukyanetz et al. 2002, Madeja et al. 2003), which may have an influence on its antiepileptic properties. It is not, however, an inhibitor of voltage-gated Na^+ and low-voltage activated Ca^{2+} channels (T-type).

Results obtained by Benedetti et al. (2004) and Patterson et al. (2008) indicated that LEV was rapidly and almost completely (bioavailability was approximately 100%) absorbed after oral (aequous solution, tablets) and intramuscular administration (Table 2). Values of Cmax and AUC were very similar, independent of route of administration; however, t^{max} was reached at 1.3-2.5 h and 0.6 h after a single oral (54 mg/kg in Benedetti et al. experiment and 20 mg/kg in Patterson et al. experiment) and intramuscular dose, respectively (Benedetti et al. 2004, Patterson et al. 2008). It was demonstrated that the multiple oral administration compared with a single dose did not change significantly above pharmacokinetic parameters (Moore et al 2010).

The results of several reports (Doheny et al. 1999, Isoherranen et al. 2001, Benedetti et al. 2004, Patterson et al. 2008) indicate that the Vd of LEV in dogs was between 0.45 to 0.6 L/kg (Table 2), a value close to the volume of intracellular and extracellular water. In studies by Doheny et al. (1999) conducted on rats it was found that LEV easily crossed the BBB to enter both the brain extracellular and cerebrospinal fluid

compartments. The serum free/total serum concentration ratio was approximately 1.0 and was not dependent on time and concentration (Doheny et al. 1999). This finding indicates that this agent is totally dissolved in plasma water and does not attach itself to blood proteins (Table 2). These results were also observed by Benedetti et al. (2004) in experiments conducted on mice, rats, rabbits and dogs.

LEV is relatively poorly metabolized in dogs (Benedetti et al. 2004). Approximately 40% of this agent was subject to hydrolysis and/or oxidation and the rest of the compound was not metabolized. The results of these studies showed that LEV is transformed into acidic and hydroxylated metabolites; however, the main pathway of this pharmacokinetic stage is hydroxylation (Benedetti et al. 2004). However, Benedetti et al. (2004) did not find any qualitative differences in LEV metabolism among four studied species, although the dogs appeared to oxidize levetiracetam more extensively than the rats (Benedetti et al. 2004). These authors also showed that LEV was unlikely to produce clinically relevant interactions through the induction or inhibition of cytochrome P450 enzymes.

The major route of elimination of LEV and its metabolites is via the urine (89% of the dose) (Table 2). More than 60% of the dose was excreted with urine as unchanged LEV, whereas about 25% of the drug was eliminated as metabolites (Benedetti et al. 2004). Data from several reports indicate that the $t_{1/2kel}$ of LEV after oral, i.v. and i.m. administration of the drug ranged from 2.3 to 4.0 h (Table 2) and the value of this parameter was not dose dependent (Doheny et al. 1999, Isoherranen et al. 2001, Benedetti et al. 2004, Patterson et al. 2008, Moore et al. 2010). In the above-mentioned studies the CL was determined to have a value from 1.5 to 2.3 ml/kg/min (Table 2) and its value was not dependent on dose and route of drug administration.

Oxcarbazepine

Oxcarbazepine (10,11-dihydro-10-oxo-carbamazepine; OXC) is a keto analogue of carbamazepine (CBZ) (Table 3), and both oxcarbazepine and its primary metabolite 10,11-dihydro-10-hydroxy-carbamazepine (monohydroxy derivative; MHD) have similar anticonvulsant activity to carbamazepine (McLean et al. 1994). This agent proved to be effective in a wide range of animal tests (McLean et al. 1994) which suggests efficacy in generalized tonic-clonic and partial onset seizures. In humans the efficacy was confirmed in a large randomised, double-blind study (Guerreiro et al. 1997). Also, some data indicate that OXC may be useful in the management of neuropathic pain (Magenta et al. 2005). The mechanism of action of this agent is similar to that of carbamazepine. OXC inhibits voltage-gated Na^+ channels (McLean et al. 1994, Benes et al. 1999), reduces high-voltage activated Ca^{2+} channels (L-type) evoked by membrane depolarization (Stefani et al. 1995) and also inhibits glutamate release from hippocampal nerve terminals (Ambrósio et al. 2001). Moreover, OXC stimulates K^+ channels involved in the generation of burst discharges (McLean et al. 1994) and may also act by an action on adenosine A_1 and A_2 receptors (Fujiwara et al. 1986).

Schicht et al. (1996) showed that in healthy dogs after a single oral dose of OXC (40 mg/kg), t_{max} was achieved in 1.9 h, whereas MHD was achieved after 2.6 h. Bioavailability of this agent in dogs was not studied but in humans absorption was rapid and almost complete (96-99%) with little effect of food on this process (Theisohn and Heimann 1982, Degen et al. 1994).

OXC is a neutral lipophilic agent and is distributed widely. Tecoma (1999) showed that Vd in humans was between 0.7-0.8 L/kg and Volosov et al. (1999) indicated that Vd of MHD in dogs was similar (Table 2). Both OXD and MHD were bound with plasma proteins in 45% (Table 2) and 53% respectively and easily cross the BBB, as indicated by Schicht et al. (1996). Schicht et al. (1996) and Volosov et al. (1999) indicated that cerebrospinal fluid concentrations of OXC and MHD at a steady state corresponded to the concentrations of the free drugs in plasma. Moreover, Jung et al. (1997) demonstrated that MHD, after oral administration of OXD, were bound to red blood cells (RBC). Their results showed that, at all concentrations, profiles for RBC and plasma were similar, which indicates an equal distribution of MHD between erythrocytes and plasma.

In dogs the parent compound (OXC) persists in fairly high concentrations, whereas in humans and other primates this agent is almost immediately converted to the main active metabolite, MHD. This biotransformation is reached in the liver via 2 pathways. The major pathway is conversion of OXC to MHD by reduction of the keto group of parent compound mediated by cytosol arylketone reductase. After this process the MHD is conjugated with glucuronide and eliminated by the kidney. Experiments on humans show that the minor pathway is oxidation of MHD to transdiol/dihydroxy derivative (DHD) which requires microsomal cytochrome P-450 enzymes (Baruzzi et al. 1994, Tecoma 1999). Low hepatic induction indicates that OXC has neglible influence on the metabolism of other drugs (Table 1).

There is no information about OXC excretion in dogs, and in humans this agent is eliminated almost entirely through the kidneys. In humans about 96% of the parent compound or its metabolites are in the urine, 83%, as MHD or its glucuronide conjugate, and another 4-7% as DHD and 0.3-3.0% as unchanged OXC (Tecoma 1999). Schicht et al. (1996) and Volosov et al. (1999) calculated that the $t_{1/2kel}$ of OXC and MHD was 4.6 and 3.7 h respectively and Cl was about 2.0 ml/min/kg for OXC (Table 2) and 1.5-4.0 ml/min/kg for MHD, they indicate that the $t_{1/2kel}$ of MHD were 2-4 times lower than in humans (Dickinson et al. 1989) which indicates a higher rate of metabolism in dogs (Schicht et al. 1996).

Topiramate

Topiramate (2,3:4,5-bis-0-(1-methylethylidene)-β-D-fructopyranose sulfamate; TPM) is structurally different from other antiepileptic agents (Table 3). It is a derivative of the naturally occurring monosaccharide D-fructose and contains a sulfamate functionality. This agent has been tested in the treatment of several rodent models of epilepsy (Gardocki et al. 1986, Nakamura et al. 1994, Edmonds et al. 1996, Wauquier and Zhou 1996) and is commonly used in humans against partial onset and generalized seizures (Sachdeo et al. 1997). TPM has multiple mechanisms of action. It is an inhibitor of the AMPA/kinate subtype of glutamate of receptors (Gibbs et al. 2000) and carbonic anhydrase izoenzymes (CA) II and IV stronger than CA I, CA III, CA V, CA VI (Dodgson et al. 2000). Moreover, TPM changes the activity of some types of voltage-activated Na^+ and Ca^{2+} channels (L-type) (Zona et al. 1996ab, Wu et al. 1998, Taverna et al. 1999, DeLorenzo et al. 2000, McLean et al. 2000, Zhang et al. 2000) and $GABA_A$ receptors (Brown et al. 1993, White et al. 1995, 1997, 2000).

In healthy dogs after a single oral dose of TPM (10, 40 and 150 mg/kg), t_{max} was achieved in 1.6-3.9 h, whereas after a multiple dose (10, 40 and 150 mg/kg for 15 days) this parameter was reached between 1.1 and 2.4 h (Streeter et al. 1995). Value of the AUC after single and multiple oral administration of TPM in a dry-filled capsule formulation was 2 times lower compared with a single oral administration of aqueous solution of this agent (175 vs 343 μg x h/ml) (Streeter et al. 1995). Absolute bioavailability of orally administrated TPM seems to be dependent on the formulation of this substance. The value of this parameter for aqueous solution was about 57% (Table 2), whereas for a dry-filled capsule it was about 29%, which indicates that the aqueous solution was a better formulation of the drug.

It has been demonstrated that the Vd of TPM was approximately 0.63 L/kg (Streeter et al. 1995) (Table 2), indicating that this agent distributes into a volume that approximates to total body water. The high Vd value suggests that the drug easily diffuses to the tissues and BBB (Dodgson et al. 2000). In plasma the unbound fraction of TPM was about 90% (Table 2). Interestingly, Dodgson et al. (2000) showed that RBC were capable of binding a major portion of this drug, which was connected with binding of TPM to carbonic anhydrase isoforms.

The results of Caldwell et al. (2005) indicate that TPM is very poorly metabolized in dogs. They showed that a low percentage only of the total dosage of this agent was metabolized. In phase I of the biotransformation there were three metabolites and in phase II of this process there were four glucuronide conjugates and two sulfate conjugates. Moreover, it was found that the most dominant pathway of metabolism of TPM in dogs was probably hydrolysis at the 2,2-o-isopropylidene group (Caldwell et al. 2005).

Caldwell et al. (2005) found that topiramate was 96% eliminated in unchanged form. About 90% of the drug was eliminated via the urine, while 6% was excreted with feces (Table 2). Moreover, they established that TPM $t_{1/2kel}$ ranged from 2.6 to 3.7 h after a single oral dose, whereas the value of this parameter after multiple doses of the drug was between 2.0 and 3.8 h (Table 2). They thus showed that half-life time was basically independent of the number of doses; however, they also demonstrated that the value of this parameter was not dependent on TPM dose. They showed the total CL to be approximately 2.4-3.6 ml/min/kg after a single oral dose of TPM (Table 2) and 3.0-4.2 ml/min/kg after multiple oral doses (Caldwell et al. 2005). Furthermore, they established that after a single i.v. dose of TPM the value of this parameter was 1.1 ml/min/kg (Streeter et al. 1995).

Zonisamide

Zonisamide (1,2-benzisoxazole-3-methanesulfonamide; ZNS) is a synthetic 1,2-benzisoxazole derivative (Table 3) with antiepileptic activity. This agent showed anticonvulsant properties in several animal models of epilepsy as well as in patients with epilepsy (Uno et al. 1979, Masuda et al. 1980, Hashimoto et al. 2003). ZNS is effective for refractory simple and complex partial seizures, generalized convulsions including tonic-clonic seizures, myoclonic epilepsies, absence, secondary generalized or combined seizures, Lennox – Gastaut and West syndrome, and infantile spasms (Uno et al. 1972, 1979, Masuda et al. 1980, Sackellares et al. 1985, Henry et al. 1988, Suzuki et al.

1997, Hashimoto et al. 2003), and due to its properties the drug may be applied in epilepsy treatment, in mono- as well as in politherapy. Additionally, this agent has a neuroprotective property which is thought to be due to a different mechanism than its antiepileptic action. It prevented cerebral damage after hypoxic-ischemic challenge or a transient global forebrain ischemia (Owen et al. 1997). Moreover, there are some experimental and clinical data suggesting the efficacy of this agent in non-epileptic disorders such as Parkinson's disease (Murata et al. 2001) and mania (Kanba et al. 1994).

ZNS has multiple mechanisms of action. It prevents repetitive neuronal firing by blocking voltage-dependent Na^+ channels and K^+ evoked glutamate-mediated synaptic excitation, reduces voltage-dependent Ca^{2+} channels (T-type), facilitates dopaminergic and serotoninergic transmission, inhibits type-B monoamine oxidase, without affecting the activity of type-A, inhibits lipid peroxidation in the iron-induced epileptic foci of rats and it is a weak inhibitor of carbonic anhydrase (Masuda et al. 1980, Rock et al. 1989, Suzuki et al. 1992, Okada et al. 1995, 1999, Mori et al. 1998, Bialer et al. 2002). Additionally, ZNS has an inhibitory effect on excessive nitric oxide production and free radical generation including hydroxyl and nitric oxide radicals, which consequently leads to neuroprotection by stabilization of the neuron cell membrane (Mori et al. 1998).

In healthy dogs after a single oral dose of ZNS (10 mg/kg), t_{max} was achieved in 2.75 h (Boothe and Perkins 2008), whereas Orito et al. (2008) indicated t_{max} after 6.0-7.0 h (single oral dose of 5 mg/kg of ZNS). Boothe and Perkins (2008) demonstrated that t_{max} was not dependent on dosage value, and oral bioavailability based on plasma drug concentration was about 68% after a single oral dose (Table 2); they also showed that after multiple oral administration (10 mg/kg) AUC for serum, plasma and whole blood at the last dose did not differ from that after the first oral dose. Other research demonstrated that ZNS reached a steady state within 4 days after repeated oral administrations (5, 10, 15, 30 mg/kg) of this agent and also showed that the canine dose-C_{min} (minimal concentration) relationship, after repeated p.o. administration, exhibited linearity at 5-30 mg/kg (Fukunaga et al. 2009).

It has been demonstrated by Boothe and Perkins (2008) that following a single oral dose administration the Vd of ZNS was about 0.72 L/kg (Table 2), a value approximate to total body water (Boothe and Perkins 2008). The value of this parameter indicates facilitated drug passage through the biological barriers, including BBB, as shown by Mimaki et al. (1994) in an experiment on rats; they also showed that plasma protein binding of ZNS was approximately 39.5% (Table 2). After i.v. and p.o. administration the C_{max} was lower in serum and plasma compared to RBC, indicating that erythrocytes were binding a major portion of this drug. This is probably due to binding of ZNS to carbonic anhydrase contained within RBC (Boothe and Perkins 2008).

The results of two reports (Matsumoto et al. 1983, Boothe and Perkins 2008) showed that about 70% of ZNS was metabolized with the participation of cytochrome P-450 enzymes. In dogs the metabolism pathway is not completely understood. In rats the major metabolites were 2-(sulfamoylacety1)-phenol glucuronide (SMAP) and SMAP-glucuronide, N-acetyl-3-(sulfamoylmethyl)-1,2-benzisoxazole (N-acetyl-ZNS), and ZNS-glucuronide. It should also be mentioned that this agent does not induce its own metabolism (Stiff and Zemaitis 1990).

Matsumoto et al. (1983) and Boothe and Perkins (2008) indicated that the major route of elimination of ZNS and its metabolites was 83% via the urine. The rest of drug was eliminated with feces (Table 2). 30% of this agent was excreted as a parent compound and the rest as the above-mentioned metabolites. The $t_{1/2kel}$, as reported in several studies, was between 13.0-17.0 h after a single i.v. and p.o. administration (Table 2) and after multiple oral dose was about 23.5 h (Matsumoto et al. 1983, Boothe and Perkins 2008, Orito et al. 2008); in these studies the CL was determined to have a value from 0.95 to 2.5 ml/kg/min after a single i.v. administration and 0.6 ml/min/kg after a single p.o. administration (Table 2).

Summary

The comparison of pharmacokinetic parameters indicates that the second generation antiepileptic drugs will probably find wider use in canine epilepsy therapy. Unfortunately, one of the reasons for low interest in this group of pharmaceuticals is their relatively high cost in comparison to routinely applied drugs i.e. first generation drugs such as PB or CBZ. In addition, some second generation drug properties cause their administration to be difficult. For instance, only zonisamid allows administration one to two times a day. Other drugs have a short period of $t_{1/2}$ in the elimination phase and they have to be administered much more often. This does not diminish the fact that such drugs are effective, and may be used by veterinarians in adjuvant therapies, especially in epilepsy resistant to standard treatment. Such a regimen may contribute to lowering the dosage of first generation drugs as well as to increasing the percentage of treated seizures induced by epilepsy. It should also be

taken into account that among the second generation drugs there are substances whose pharmacokinetics in the case of dogs have been insufficiently tested or have not been tested at all. These substances are lamotrygine, tiagabine and wigabatrin, which could also be applied in the treatment of animals.

Moreover, in human medicine third generation antiepileptic drugs have been introduced in the last several years, and some of them are used in treatment (eslicarbazepine, fosphenytoin, lacosamide, pregabalin, rufinamide, stiripentol), whilst others are still under clinical tests (brivaracetam, carabersat, elpetrigine, fluorofelbamate, ganaxolone, losigamone, safinamide, seletracetam, soretolide, talampanel, valrocetamide).

References

Adusumalli VE, Gilchrist JR, Wichmann JK, Kucharczyk N, Sofia RD (**1992**) Pharmacokinetics of felbamate in pediatric and adult beagle dogs. Epilepsia 33: 955-960.

Adusumalli VE, Yang JT, Wong KK, Kucharczyk N, Sofia RD (**1991**) Felbamate pharmacokinetics in the rat, rabbit, and dog. Drug Metab Dispos 19: 1116-1125.

Ambrósio AF, Silva AP, Malva JO, Soares-da-Silva P, Carvalho AP, Carvalho CM (**2001**) Inhibition of glutamate release by BIA 2-093 and BIA 2-024, two novel derivatives of carbamazepine, due to blockade of sodium but not calcium channels. Biochem Pharmacol 61: 1271-1275.

Baruzzi A, Albani F, Riva R (**1994**) Oxcarbazepine: pharmacokinetic interactions and their clinical relevance. Epilepsia 35: S14-S19.

Benedetti MS, Coupez R, Whomsley R, Nicolas JM, Collart P, Baltes E (**2004**) Comparative pharmacokinetics and metabolism of levetiracetam, a new anti-epileptic agent, in mouse, rat, rabbit and dog. Xenobiotica 34: 281-300.

Benes J, Parada A, Figueiredo AA, Alves PC, Freitas AP, Learmonth DA, Cunha RA, Garrett J, Soares-da-Silva P (**1999**) Anticonvulsant and sodium channel-blocking properties of novel 10,11-dihydro-5H-dibenz[b,f] azepine-5-carboxamide derivatives. J Med Chem 42: 2582-2587.

Berendt M, Gram L (**1999**) Epilepsy and seizure classification in 63 dogs: a reappraisal of veterinary epilepsy terminology. J Vet Intern Med 13: 14-20.

Bialer M, Johannessen SI, Kupferberg HJ, Levy RH, Loiseau P, Perucca E (**2002**) Progress report on new antiepileptic drugs: a summary of the Sixth Eilat Conference (EILAT VI). Epilepsy Res 51: 31-71.

Boothe DM, Perkins J (**2008**) Disposition and safety of zonisamide after intravenous and oral single dose and oral multiple dosing in normal hound dogs. J Vet Pharmacol Ther 31: 544-553.

Bourgeois B, Leppik IE, Sackellares JC, Laxer K, Lesser R, Messenheimer JA, Kramer LD, Kamin M, Rosenberg A (**1993**) Felbamate: a double-blind controlled trial in patients undergoing presurgical evaluation of partial seizures. Neurology 43: 693-696.

Brown SD, Wolf HH, Swinyard EA, Twyman RE, White HS (**1993**) The novel anticonvulsant topiramate enhances GABA-mediated chloride flux. Epilepsia 34: S122-S123.

Caldwell GW, Wu WN, Masucci JA, Mckown LA, Gauthier D, Jones WJ, Leo GC, Maryanoff BE (**2005**) Metabolism and exretion of the antiepileptic/antimigraine drug. Topiramate in animals and humans. Eur J Drug Metab Pharmacokinet 30: 151-164.

Cereghino JJ, Biton V, Abou-Khalil B, Dreifuss F, Gauer LJ, Leppik I (**2000**) Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. Neurology 55: 236-242.

Chronopoulos A, Stafstrom C, Thurber S, Hyde P, Mikati M, Holmes GL (**1993**) Neuroprotective effect of felbamate after kainic acid-induced status epilepticus. Epilepsia 34: 359-366.

Degen PH, Flesch G, Cardot JM, Czendlik C, Dieterle W (**1994**) The influence of food on the disposition of the antiepileptic oxcarbazepine and its major metabolites in healthy volunteers. Biopharm Drug Dispos 15: 519-526.

DeLorenzo RJ, Sombati S, Coulter DA (**2000**) Effects of topiramate on sustained repetitive firing and spontaneous recurrent seizure discharges in cultured hippocampal neurons. Epilepsia 41: S40-S44.

De Sarro G, Ongini E, Bertorelli R, Aguglia U, De Sarro A (**1994**) Excitatory amino acid neurotransmission through both NMDA and non-NMDA receptors is involved in the anticonvulsant activity of felbamate in DBA/2 mice. Eur J Pharmacol 262: 11-19.

Dewey CW (**2006**) Anticonvulsant therapy in dogs and cats. Vet Clin North Am Small Anim Pract 36: 1107-1127.

Dickinson RG, Hooper WD, Dunstan PR, Eadie MJ (**1989**) First dose and steady-state pharmacokinetics of oxcarbazepine and its 10-hydroxy metabolite. Eur J Clin Pharmacol 37: 69-74.

Dodgson SJ, Shank RP, Maryanoff BE (**2000**) Topiramate as an inhibitor of carbonic anhydrase isoenzymes. Epilepsia 41: S35-S39.

Doheny HC, Ratnaraj N, Whittington MA, Jefferys JG, Patsalos PN (**1999**) Blood and cerebrospinal fluid pharmacokinetics of the novel anticonvulsant levetiracetam (ucbL059) in the rat. Epilepsy Res 34: 161-168.

Ebert U, Reissmüller E, Löscher W (**2000**) The new antiepileptic drugs lamotrigine and felbamate are effective in phenytoin-resistant kindled rats. Neuropharmacology 39: 1893-1903.

Edmonds HL Jr, Jiang YD, Zhang PY, Shank RP (**1996**) Anticonvulsant activity of topiramate and phenytoin in a rat model of ischemia-induced epilepsy. Life Sci 59: PL 27-31.

Fujiwara Y, Sato M, Otsuki S (**1986**) Interaction of carbamazepine and other drugs with adenosine (A1 and A2) receptors. Psychopharmacology 90: 332-335.

Fukunaga K, Saito M, Muto M, Yoshioka R, Mishima K, Fujiwara M, Orito K (**2009**) Steady-state pharmacokinetics of zonisamide in plasma, whole blood, and erythrocytes in dogs. J Vet Pharmacol Ther 33: 103-106.

Gardocki JF, Labinski LS, Brown GL, Maryanoff BE (**1986**) Anticonvulsant activity of McN-4853 (M) 2, 3:4, 5-bis-O-(L-methylethylidene)-β-D-fructopyranose sulfamate in mice and rats Epilepsia 27: 648-649.

Gee NS, Brown JP, Dissanayake VU, Offord J, Thrulow R, Woodruff GN (**1996**) The novel anticonvulsant drug, gabapentin (neurontin), binds to the α2δ subunit of a calcium channel. J Biol Chem 271: 5768-5776.

Gibbs JW 3rd, Sombati S, DeLorenzo RJ, Coulter DA (**2000**) Cellular actions of topiramate: blockade of kainate-evoked inward currents in cultured hippocampal neurons. Epilepsia 41: S10-S16.

Giorgi O, Carboni G, Frau V, Orlandi M, Valentini V, Feldman A, Corda MG (**1996**) Anticonvulsant effect of felbamate in the pentylenetetrazole kindling model of epilepsy in the rat. Naunyn Schmiedebergs Arch Pharmacol 354: 173-178.

Goa KL, Sorkin EM (**1993**) Gabapentin. A review of its pharmacological properties and clinical potential in epilepsy. Drugs 46: 409-427.

Gower AJ, Noyer M, Verloes R, Gobert J, Wülfert E (**1993**) ucb L059, a novel anti-convulsant drug: pharmacological profile in animals. Eur J Pharmacol 222: 193-203.

Guerreiro MM, Vigonius U, Pohlmann H, de Manreza ML, Fejerman N, Antoniuk SA, Moore A (**1997**) A double-blind, controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. Epilepsy Res 27: 205-213.

Harty TP, Rogawski MA (**2000**) Felbamate block of recombinant N-methyl-D-aspartate receptors: selectivity for the NR2B subunit. Epilepsy Res 39: 47-55.

Hashimoto Y, Araki H, Futagami K, Kawasaki H, Gomita Y (**2003**) Effects of valproate, phenytoin, and zonisamide on clonic and tonic seizures induced by acute and repeated exposure of mice to flurothyl. Physiol Behav 78: 465-469.

Henry TR, Leppik IE, Gumnit RJ, Jacobs M (**1988**) Progressive myoclonus epilepsy treated with zonisamide. Neurology 38: 928-931.

Isbell H, Fraser HF (**1950**) Addiction to analgesics and barbiturates. J Pharmacol Exp Ther 99: 355-397.

Isoherranen N, Yagen B, Soback S, Roeder M, Schurig V, Bialer M (**2001**) Pharmacokinetics of levetiracetam and its enantiomer (R)-alpha-ethyl-2-oxo-pyrrolidine acetamide in dogs. Epilepsia 42: 825-830.

Jung H, Noguez A, Mayet L, Fuentes I, Gonzhlez-Esquivel DF (**1997**) The distribution of 10-hydroxy carbazepine in blood compartments. Biopharm Drug Dispos 18: 17-23.

Kanba S, Yagi G, Komijima K, Suzuki T, Tajima O, Otaki J, Arata E, Koshikawa H, Nibuya M, Kinoshita N, Asai M (**1994**) The first open study of zonisamide, a novel anticonvulsant, shows efficacy in mania. Prog Neuropsychopharmacol Biol Psychiatry 18: 707-715.

Kelly KM (**1998**) Gabapentin: Antiepileptic mechanism of action. Neuropsychobiology 38: 139-144.

Klitgaard H, Matagne A, Gobert J, Wulfert E (**1998**) Evidence for a unique profile of levetiracetam in rodent models of seizures and epilepsy. Eur J Pharmacol 353: 191-206.

Kukanich B, Cohen RL (**2011**) Pharmacokinetics of oral gabapentin in greyhound dogs. Vet J 187: 133-135.

Longo LP, Johnson B (**2000**) Addiction: Part I. Benzodiazepines-side effects, abuse risk, and alternatives. Am Fam Physician 61: 2121-2128.

Loprinzi L, Barton DL, Sloan JA, Zahasky KM, Smith DA, Pruthi S, Novotny PJ, Perez EA, Christensen BJ (**2002**) Pilot evaluation of gabapentin for treating hot flashes. Mayo Clin Proc 77: 1159-1163.

Löscher W, Hönack D (**1993**) Profile of ucb L059, a novel anticonvulsant drug, in models of partial and generalized epilepsy in mice and rats. Eur J Pharmacol 232: 147-158.

Löscher W, Hönack D, Rundfeldt C (**1998**) Antiepi-leptogenic effects of the novel anticonvulsant levetiracetam (ucb L059) in the kindling model of temporal lobe epilepsy. J Pharmacol Exp Ther 284: 474-479.

Lukyanetz EA, Shkryl VM, Kostyuk, PG (**2002**) Selective blockade of N-type calcium channels by levetiracetam. Epilepsia 43: 9-18.

Lynch BA, Lambeng N, Nocka K, Kensel-Hammes P, Bajjalieh SM, Matagne A, Fuks B (**2004**) The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. Proc Natl Acad Sci USA 101: 9861-9866.

Macdonald RL, Kelly KM (**1995**) Antiepileptic drug mechanisms of action. Epilepsia 36: S2-S12.

Madeja M, Margineanu DG, Gorji A, Siep E, Boerrigter P, Klitgaard H, Speckmann EJ (**2003**) Reduction of voltage-operated potassium currents by levetiracetam: a novel antiepileptic mechanism of action? Neuropharmacology 45: 661-671.

Magenta P, Arghetti S, Di Palma F, Jann S, Sterlicchio M, Bianconi C, Galimberti V, Osio M, Siciliano G, Cavallotti G, Sterzi R (**2005**) Oxcarbazepine is effective and safe in the treatment of neuropathic pain: pooled analysis of seven clinical studies. Neurol Sci 26: 218-226.

Masuda Y, Karasawa T, Shiraishi Y, Hori M, Yoshida K, Shimizu M (**1980**) 3-Sulfamoylmethyl-1,2-benzisoxazole, a new type of anticonvulsant drug. Pharmacological profile. Arzneimittelforschung 30: 477-483.

Matsumoto K, Miyazaki H, Fujii T, Kagemoto A, Maeda T, Hashimoto M (**1983**) Absorption, distribution and excretion of 3-(sulfamoyl[14C]methyl)-1,2-benziosoxazole (AD-810) in rats, dogs and monkeys and of AD-810 in men. Arzneimittelforschung 33: 961-968.

McLean MJ, Bukhari AA, Wamil AW (**2000**) Effects of topiramate on sodium-dependent action- potential firing by mouse spinal cord neurons in cell culture. Epilepsia 41: S21-S24.

McLean MJ, Schmutz M, Wamil AW, Olpe HR, Portet C, Fedmann KF (**1994**) Oxcarbazepine: mechanisms of action. Epilepsia 35: S5-S9.

Mellick GA (**1995**) Hemifacial spasm: successful treatment with felbamate. J Pain Symptom Manage 10: 392-395.

Mimaki T, Tanoue H, Matsunaga Y, Miyazaki H, Mino M (**1994**) Regional distribution of 14C-zonisamide in rat brain. Epilepsy Res 17: 223-226.

Moore SA, Muñana KR, Papich MG, Nettifee-Osborne J (**2010**) Levetiracetam pharmacokinetics in healthy dogs following oral administration of single and multiple doses. Am J Vet Res 71: 337-341.

Mori A, Noda Y, Packer L (**1998**) The anticonvulsant zonisamide scavenges free radicals. Epilepsy Res 30: 153-158.

Murata M, Horiuchi E, Kanazawa I (**2001**) Zonisamide has beneficial effects on Parkinson's disease patients. Neurosci Res 41: 397-399.

Nakamura J, Tamura S, Kanda T, Ishii A, Ishihara K, Serikawa T, Yamada J, Sasa M (**1994**) Inhibition by topiramate of seizures in spontaneously epileptic rats and DBA/2 mice. Eur J Pharmacol 254: 83-89.

Nicholson B (**2000**) Gabapentin use in neuropathic pain syndromes. Acta Neurol Scand 101: 359-371.

Niespodziany I, Klitgaard H, Margineanu DG (**2001**) Levetiracetam inhibits the high-voltage-activated Ca^{2+} current in pyramidal neurones of rat hippocampal slices. Neurosci Lett 306: 5-8.

Okada M, Hirano T, Kawata Y, Murakami T, Wada K,

Mizuno K, Kondo T, Kaneko S (**1999**) Biphasic effects of zonisamide on serotoninergic system in rat hippocampus. Epilepsy Res 34: 187-197.

Okada M, Kaneko S, Hirano T, Mizuno K, Kondo T, Otani K, Fukushima Y (**1995**) Effects of zonisamide on dopaminergic system. Epilepsy Res 22: 193-205.

Orito K, Saito M, Fukunaga K, Matsuo E, Takikawa S, Muto M, Mishima K, Egashira N, Fujiwara M (**2008**) Pharmacokinetics of zonisamide and drug interaction with phenobarbital in dogs. J Vet Pharmacol Ther 31: 259-264.

Owen AJ, Ijaz S, Miyashita H, Wishart T, Howlett W, Shuaib A (**1997**) Zonisamide as a neuroprotective agent in an adult gerbil model of global forebrain ischemia: a histological, in vivo microdialysis and behavioral study. Brain Res 770: 115-122.

Patterson EE, Goel V, Cloyd JC, O'Brien TD, Fisher JE, Dunn AW, Leppik IE (**2008**) Intramuscular, intravenous and oral levetiracetam in dogs: safety and pharmacokinetics. J Vet Pharmacol Ther 31: 253-258.

Podell M, Fenner WR, Powers JD (**1995**) Seizure classification in dogs from a nonreferral-based population. J Am Vet Med Assoc 206: 1721-1728.

Pollack MH, Matthews J, Scott EL (**1998**) Gabapentin as a potential treatment for anxiety disorders. Am J Psychiatry 155: 992-993.

Radulovic LL, Turck D, von Hodenberg A, Vollmer KO, McNally WP, DeHart PD, Hanson BJ, Bockbrader HN, Chang T (**1995**) Disposition of gabapentin (neurontin) in mice, rats, dogs, and monkeys. Drug Metab Dispos 23: 441-448.

Rhee YS, Park S, Lee TW, Park CW, Nam TY, Oh TO, Jeon JW, Han SB, Lee DS, Park ES (**2008**) In Vitro/in vivo relationship of gabapentin from a sustained-release tablet formulation: a pharmacokinetic study in the beagle dog. Arch Pharm Res 31: 911-917.

Rho JM, Donevan SD, Rogawski MA (**1997**). Barbiturate-like actions of the propanediol dicarbamates felbamate and meprobamate. J Pharmacol Exp Ther 280: 1383-1391.

Rigo JM, Hans G, Nguyen L, Rocher V, Belachew S, Malgrange B, Leprince P, Moonen, G, Selak I, Matagne A, Klitgaard H (**2002**) The anti-epileptic drug levetiracetam reverses the inhibition by negative allosteric modulators of neuronal GABA- and glycine-gated currents. Br J Pharmacol 136: 659-672.

Ritter FJ, Leppik, IE Dreifuss FE, Santilli N, Homzie R, Dodson WE, Glauser TA, Sackellares JC, Olson L, Garafolo EA, Shields WD, French J, Sperling M, Kramer LD, Kamin M, Rosenberg A, Shumaker R, Perhach JL, Dix R (**1993**) Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome). N Engl J Med 328: 29-33.,

Rock DM, Macdonald RL, Taylor CP (**1989**) Blockade of sustained repetitive action potentials in cultured spinal cord neurons by zonisamide (AD810, CI 912), a novel anticonvulsant. Epilepsy Res 3: 138-143.

Rogvi-Hansen B, Gram L (**1995**) Adverse effects of established and new antiepileptic drugs: an attempted comparsion. Pharmacol Ther 68: 425-434.

Sachdeo RC, Reife RA, Lim P, Pledger G (**1997**) Topiramate monotherapy for partial onset seizures. Epilepsia 38: 294-300.

Sackellares JC, Donofrio PD, Wagner JG, Abou-Khalil B, Berent S, Aasved-Hoyt K (**1985**) Pilot study of zonisamide (1,2-benzisoxazole-3-methanesulfonamide) in patients with refractory partial seizures. Epilepsia 26: 206--211.

Schicht S, Wigger D, Frey HH (**1996**) Pharmacokinetics of oxcarbazepine in the dog. J Vet Pharmacol Ther 19: 27-31.

Schwartz-Porsche D, Loscher W, Frey HH (**1985**) Therapeutic efficacy of phenobarbital and primidone in canine epilepsy: a comparison. J Vet Pharmacol Ther 8: 113-119.

Segelman FH, Kelton E, Terzi RM, Kucharczyk N, Sofia RD (**1985**) The comparative potency of phenobarbital and five 1,3-propanediol dicarbamates for hepatic cytochrome P450 induction in rats. Res Commun Chem Pathol Pharmacol 48: 467-470.

Sills GJ (**2006**) The mechanisms of action of gabapentin and pregabalin. Curr Opin Pharmacol 6: 108-113.

Sofia RD, Gordon R, Gels M, Diamantis W (**1993**) Effects of felbamate and other anticonvulsant drugs in two models of status epilepticus in the rat. Res Commun Chem Pathol Pharmacol 79: 335-341.

Stefani A, Calabresi P, Pisani A, Mercuri NB, Siniscalchi A, Bernardi G (**1996**) Felbamate inhibits dihydropyridine-sensitive calcium channels in central neurons. J Pharmacol Exp Ther 277: 121-127.

Stefani A, Pisani A, De Murtas M, Mercuri NB, Marciani MG, Calabresi P (**1995**) Action of GP 47779, the active metabolite of oxcarbazepine, on the corticostriatal system. II. Modulation of high-voltage-activated calcium currents. Epilepsia 36: 997-1002.

Stevenson CM, Radulovic LL, Bockbrader HN, Fleisher D (**1997**) Contrasting nutrient effects on the plasma levels of an amino acid like antiepileptic agent from jejunal administration in dogs. J Pharm Sci 86: 953-957.

Stewart BH, Kugler AR, Thompson PR, Bockbrader HN (**1993**) A saturable transport mechanism in the intestinal absorption of gabapentin is the underlying cause of the lack of proportionality between increasing dose and drug levels in plasma. Pharm Res 10: 276-281.

Stiff DD, Zemaitis MA (**1990**) Metabolism of the anticonvulsant agent zonisamide in the rat. Drug Metab Dispos 18: 888-894.

Streeter AJ, Stahle PL, Holland ML, Pritchard JF, Takacs AR (**1995**) Pharmacokinetics and bioavailability of topiramate in the beagle dog. Drug Metab Dispos 23: 90-93.

Suzuki S, Kawakami K, Nishimura S, Watanabe Y, Yagi K, Seino M, Miyamoto K (**1992**) Zonisamide blocks T-type calcium channel in cultured neurons of rat cerebral cortex. Epilepsy Res 12: 21-27.

Suzuki Y, Nagai T, Ono J, Imai K, Otani K, Tagawa T, Abe J, Shiomi M, Okada S (**1997**) Zonisamide monotherapy in newly diagnosed infantile spasms. Epilepsia 38: 1035--1038.

Swinyard EA, Sofia RD, Kupferberg HJ (**1986**) Comparative anticonvulsant activity and neurotoxicity of felbamate and four prototype antiepileptic drugs in mice and rats. Epilepsia 27: 27-34.

Taglialatela M, Ongini E, Brown AM, Di Renzo G, Annunziato L (**1996**) Felbamate inhibits cloned voltage-dependent Na^+channels from human and rat brain. Eur J Pharmacol 316: 373-377.

Taverna S, Sancini G, Mantegazza M, Franceschetti S, Avan-

zini G (**1999**) Inhibition of transient and persistent Na^+ current fractions by the new anticonvulsant topiramate. J Pharmacol Exp Ther 288: 960-968.

Taylor CP, Gee NS, Su TZ, Kocsis JD, Welty DF, Brown JP, Dooley DJ, Boden P, Singh L (**1998**) A summary of mechanistic hypotheses of gabapentin pharmacology. Epilepsy Res 29: 233-249.

Taylor LA, McQuade RD, Tice MA (**1995**) Felbamate, a novel antiepileptic drug, reverses N-methyl-D-aspartate/glycine-stimulated increases in intracellular Ca^{2+} concentration. Eur J Pharmacol 289: 229-233.

Tecoma ES (**1999**) Oxcarbazepine. Epilepsia 40: S37-S46.

Theisohn M, Heimann G (**1982**) Disposition of the antiepileptic oxcarbazepine and its metabolites in healthy volunteers. Eur J Clin Pharmacol 22: 545-551.

Thomas WB (**2010**) Idiopathic epilepsy in dogs and cats. Vet Clin North Am Small Anim Pract 40: 161-179.

Uno H, Kurokawa M, Masuda Y, Nishimura H (**1979**) Studies on 3-substituted 1,2-benzisoxazole derivates. 6. Syntheses of 3-(sulfamoylmethyl)-1,2-benzisoxazole derivatives and their anticonvulsant activities. J Med Chem 22: 180-183.

Uno H, Kurokawa M, Natsuka K, Yamato Y, Nishimura H (**1972**) Studies on 3-substituted 1,2-benzisoxazole derivatives. Chem Phrmacol Bull 24: 632-643.

Vollmer KO, Von Hodenberg A, Kölle EU (**1986**) Pharmacokinetics and metabolism of gabapentin in rat, dog, and man. Arzneimittelforschung 36: 830-839.

Volosov A, Sintov A, Bialer M (**1999**) Stereoselective pharmacokinetic analysis of the antiepileptic 10-hydroxycarbazepine in dogs. Ther Drug Monit 21: 219-223.

Walker MC, Patsalos PN (**1995**) Clinical pharmacokinetics of new antiepileptic drugs. Pharmacol Ther 67: 351-384.

Wallis RA, Panizzon KL, Fairchild MD, Wasterlain CG (**1992**) Protective effects of felbamate against hypoxia in the rat hippocampal slice. Stroke 23: 547-551.

Wang PW, Santosa C, Schumacher M, Winsberg ME, Strong C, Ketter TA (**2002**) Gabapentin augmentation therapy in bipolar depression. Bipolar Disord 4: 296-301.

Wasterlain CG, Adams LM, Hattori H, Schwartz PH (**1992**) Felbamate reduces hypoxic-ischaemic brain damage in vivo. Eur J Pharmacol 212: 275-278.

Wasterlain CG, Adams LM, Schwartz PH, Hattori H, Sofia RD, Wichmann JK (**1993**) Posthypoxic treatment with felbamate is neuroprotective in a rat model of hypoxia-ischemia. Neurology 43: 2303-2310.

Wauquier A, Zhou S (**1996**) Topiramate: a potent anticonvulsant in the amygdala-kindled rat. Epilepsy Res 24: 73-77.

White HS, Brown SD, Woodhead JH, Skeen GA, Wolf HH (**1997**) Topiramate enhances GABA-mediated chloride flux and GABA-evoked chloride currents in murine brain neurons and increases seizure threshold. Epilepsy Res 28: 167-179.

White HS, Brown SD, Woodhead JH, Skeen GA, Wolf HH (**2000**) Topiramate modulates GABA-evoked currents in murine cortical neurons by a nonbenzodiazepine mechanism. Epilepsia 41: S17-S20.

White HS, Brown D, Skeen GA, Wolf HH, Twyman RE (**1995**) The anticonvulsant topiramate displays a unique ability to potentiate GABA-evoked chloride currents. Epilepsia 36: S39-S40.

White HS, Wolf HH, Swinyard EA, Skeen GA, Sofia RD (**1992**) A neuropharmacological evaluation of felbamate as a novel anticonvulsant. Epilepsia 33: 564-572.

Wlaź P, Löscher W (**1997**) Anticonvulsant activity of felbamate in amygdala kindling model of temporal lobe epilepsy in rats. Epilepsia 38: 1167-1172.

Wu SP, Tsai JJ, Gean PW (**1998**) Frequency-dependent inhibition of neuronal activity by topiramate in rat hippocampal slices. Br J Pharmacol 125: 826-832.

Xu T, Bajjalieh SM (**2001**) SV2 modulates the size of the readily releasable pool of secretory vesicles. Nat Cell Biol 3: 691-698.

Yang JT, Adusumalli VE, Kucharczyk N, Sofia RD (**1991**) Felbamate metabolism in the rat, rabbit, and dog. Drug Metab Dispos 19: 1126-1134.

Yang JT, Morris M, Wong KK, Kucharczyk N, Sofia RD (**1992**) Felbamate metabolism in pediatric and adult beagle dogs. Drug Metab Dispos 20: 84-88.

Zhang X, Velumian AA, Jones OT, Carlen PL (**2000**) Modulation of high-voltage-activated calcium channels in dentate granule cells by topiramate. Epilepsia 41: S52-S60.

Zona C, Barbarosie M, Kawasaki H, Avoli M (**1996a**) Effects induced by the anticonvulsant drug topiramate on voltage-gated sodium currents generated by cerebellar granule cells in tissue culture. Epilepsia 37: S24

Zona C, Ciotti MT, Avoli M (**1996b**) Topiramate attenuates voltage-gated sodium currents in rat cerebellar granule cells. Neurosci Lett 231: 123-126.