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Therapeutic drug monitoring of old and newer anti-epileptic drugs

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Abstract

The aim of the present paper is to provide information concerning the setting up and interpretation of therapeutic drug monitoring (TDM) for anti-epileptic drugs. The potential value of TDM for these drugs (including carbamazepine, clobazam, clonazepam, ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pheneturide, phenobarbital, phenytoin, primidone, tiagabine, topiramate, valproic acid, vigabatrin and zonisamide) is discussed in relation to their mode of action, drug interactions and their pharmacokinetic properties. The review is based upon available literature data and on observations from our clinical practice. Up until approximately 15 years ago anti-epileptic therapeutics were restricted to a very few drugs that were developed in the first half of the 20th century. Unfortunately, many patients were refractory to these drugs and a new generation of drugs has been developed, mostly as add-on therapy. Although the efficacy of the newer drugs is no better, there is an apparent improvement in drug tolerance, combined with a diminished potential for adverse drug interactions. All new anticonvulsant drugs have undergone extensive clinical studies, but information on the relationship between plasma concentrations and effects is scarce for many of these drugs. Wide ranges in concentrations have been published for seizure control and toxicity. Few studies have been undertaken to establish the concentration-effect relationship. This review shows that TDM may be helpful for a number of these newer drugs.

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Introduction

Epilepsy

Epilepsy is a neurological disease affecting an estimated 50 million people worldwide. The annual incidence ranges from 20 to 70 cases per 100,000 and the prevalence is 0.4–0.8% (1, 2). Epilepsy encompasses a number of different syndromes for which the predominant feature is recurrent, periodic, unpredictable and unprovoked seizures. The term seizure refers to a transient alteration of behavior due to a disordered, synchronous, and rhythmic firing of brain neurons. The most frequently encountered clinical features are complex partial seizures and generalized tonic-clonic seizures. The latter form usually begins in both cerebral hemispheres. In contrast, partial epilepsies originate from localized foci and are due to one or more central nervous system (CNS) insults. Seizures are thought to arise from the cerebral cortex and therefore the behavioral manifestations of a seizure are determined by the functions normally served by the cortical site from which they arise.

Generalized epilepsies occur in approximately one-third of patients. Most generalized epilepsies have a strong genetic (non-Mendelian) component (3, 4). Mutations result in changes in ion-channel proteins, such as sodium, potassium and calcium channels (channelopathies). More complex mutations, however, involve mutations of the γ-aminobutyric acid (GABA) receptors. Examples of generalized seizures are tonic-clonic (grand mal, sustained contractions followed by relaxations), absence (petit mal) and myoclonic seizures. These seizures have no aura (i.e., sensations before the seizure). Most generalized epilepsies involve tonic-clonic seizures, for which carbamazepine, phenytoin and valproic acid are effective. Absence epilepsy does not usually provoke tonic-clonic convulsions. During absence seizures, patients stare and cease normal activity for a short period. The precise abnormality has still to be clarified, but some studies (5, 6) link T-type calcium channels to the disease and others suggest altered GABA receptors. Ethosuximide has a unique property in that it is only effective in absences by blockade of T-type calcium currents. Valproic acid, which inhibits the same channel, is also used. Benzodiazepines are also able to treat absences, but work through GABA inhibitor agonism. Myoclonic seizures are mostly very brief shock-like contractions (<1 s) which are either

restricted to part of one extremity or may be generalized. The conventional drug used is valproic acid (7).

Partial epilepsies are seen in the remaining two-thirds of the patients with epilepsy. The mechanisms of partial epilepsy are not as clear. They are most common in adults and stem from local lesions such as head trauma, strokes and tumors. The most prevalent of these seizures arise from the temporal lobe (8, 9) with clearly demonstrated loci in meisal temporal structures such as the hippocampus and adjacent parahippocampal cortex. Hippocampal sclerosis has been extensively studied as a model in partial epilepsy. However, changes at the molecular level may also be important, especially for the expression and composition of $GABA_A$ receptors. Three seizure types are commonly encountered. Simple partial seizures occur without loss of consciousness and are determined by the region of the cortex activated. Complex partial seizures cause impaired consciousness (>2 min) and often purposeless movements. These simple and complex partial seizures can evolve into clonic seizures with loss of consciousness and sustained contractions (tonic) and relaxations (clonic) of muscles also lasting less than 2 min. Here, too, carbamazepine, phenytoin and valproic acid are the drugs of choice for partial epilepsy. Aura is very often present.

Status epilepticus (SE) is a series of tonic-clonic seizures, mostly evolving from generalized partial epilepsy and involving all areas of the cortex. Significant physiological changes accompany SE and many of the systemic responses are thought to result from the catecholamine surge that accompanies SE. SE has a significant mortality rate (20%); death is often related to an underlying cause of brain injury. A myriad of causes can be involved: first onset of seizure disorder; neuropathological conditions such as stroke, tumors or hemorrhage; trauma and more general electrolyte abnormalities; infectious or toxicological (e.g., cocaine) etiologies; or an exacerbation of an idiopathic seizure disorder (10). Treatment consists of supportive care, including airway, breathing and circulation (ABC) maintenance and, if seizure fails to stop within 4–5 min, prompt administration of diazepam is advocated. Since seizures often trigger further seizures, early treatment is more effective. The current consensus in the US recommends lorazepam, when available, as the initial drug to be used. Phenytoin is usually the next drug to be employed (11).

Lennox-Gastaut syndrome is one of the most drug-resistant forms of childhood epilepsy. It usually develops in children between 1 and 8 years old and is characterized by seizures, developmental delay and behavioral disturbances. The incidence is estimated to account for as much as 10% of all childhood epilepsies or for up to 50% of drug-resistant epilepsies. The disorder may be caused by brain injury, or genetic or developmental malformations of the brain. The seizures may be tonic, myoclonic (with sudden jerks) and absences may also be seen. The drugs that should be tried are carbamazepine, valproic acid, vigabatrin, lamotrigine and clobazam.

West's syndrome is composed of infantile spasms, an interictal electroencephalogram (hypsarrhythmia) and mental retardation. It constitutes 2% of childhood epilepsy but 25% of epilepsy, with onset in the first year of life: 1.6–5.0 per 10,000 live births. The anti-epileptic drugs used are vigabratin, benzodiazepines, valproic acid, lamotrigine, topiramate and zonisamide.

Juvenile myoclonic epilepsy (impulsive petit mal epilepsy) is an idiopathic generalized epileptic syndrome characterized by myoclonic jerks, tonic-clonic seizures and sometimes absence seizures. The risk of juvenile myoclonic epilepsy is estimated as 0.5–1 per 1000, representing 5–10% of all epilepsies. It typically begins in adolescence with absence seizures, followed by myoclonic jerks 1–9 years later and generalized tonic-clonic seizures a few years later.

Epileptic syndromes Epilepsy can be classified not only by its seizures, but also by a more complex approach utilizing a cluster of symptoms. The seizure type, age of onset and etiology allow the identification of more than 40 different syndromes. However, once again, they are subdivided into partial and generalized epilepsies. To date, this classification has had more of an impact on the clinical assessment and management of the patient than on the choice of anti-epileptic drug.

Anticonvulsant mechanisms of action

According to current theories, there are three mechanisms involved in the action of drugs used to treat epilepsy. (i) Some anticonvulsants intensify the action of GABA. GABA is an inhibiting neurotransmitter, which opens the chloride channel in the neuronal membrane. This results in a flow of chloride into the cell. Because of this, hyperpolarization of the cell occurs and the neuronal excitability diminishes. This raises the seizure threshold. Barbiturates, benzodiazepines and topiramate bind at the chloride channel and amplify the action of GABA. Tiagabine inhibits the reuptake of GABA and vigabatrine irreversibly inhibits the GABA-transaminase. Valproic acid appears to raise the concentration of GABA in the synaptic connection by enhancing synthesis and inhibiting the breakdown of GABA (12). (ii) Another mechanism involves inhibiting the action of glutamate, an exciting neurotransmitter, e.g., lamotrigine inhibits the release of glutamate. (iii) Anticonvulsants may also influence the voltage-activated Na^+, K^+ and Ca^{2+} channels. These play an important role in the start and multiplication of the action potentials. Calcium channels interfere in the generation of absence seizures. Carbamazepine, phenytoin, lamotrigine, oxcarbazepine, topiramate, valproic acid and zonisamide influence these channels (see Figure 1 for the action of phenytoin on a sodium channel). The mechanisms are not strictly separated. For example,

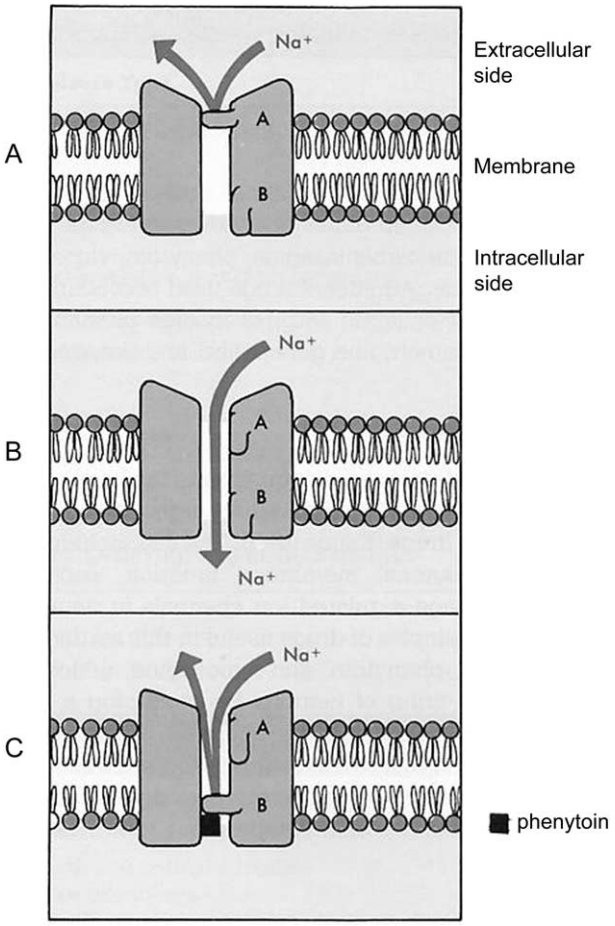


Figure 1 Action of phenytoin on sodium channel. A: Resting state in which sodium-channel gate (A) is closed. B: Arrival of an action potential causes depolarization and opening of activation gate (A), and Na^+ flows into the cell. C: When depolarization continues, an inactivation gate (B) moves in the channel. Phenytoin prolongs the inactivated state of the sodium channel, presumably by preventing reopening of the inactivation gate (B). Reproduced with permission from reference (213).

besides inhibition of the release of glutamate, lamotrigine enhances the concentration of GABA with an action on the Na^+ channels. Many anti-epileptic drugs appear to have more than one mechanism that may contribute to antiseizure activity (12).

In many patients with epilepsy, seizures can be controlled with the established anti-epileptic drugs (13), but 25–30% of patients continue to have seizures despite optimal therapy (14). In addition, some patients experience intolerable side effects from their anticonvulsant therapy. Another problem is that the metabolism of many older drugs is easily influenced by other anti-epileptics and other drugs (see Table 1 for an overview of cytochrome P450 in the metabolism of anti-epileptics). There is clearly a need for additional drugs with greater efficacy, lower toxicity and fewer drug interactions. Most of the newer drugs were approved as add-on drugs on the basis of demonstrating a reduction in the frequency and/or severity of seizures (14). They were only used later in monotherapy.

Arguments for therapeutic drug monitoring of anti-epileptic drugs

The lack of clinical response or a clear physiological marker can be an argument for therapeutic drug monitoring (TDM) of anticonvulsants. TDM is especially indicated when there is an important inter- and/or intra-individual variation in pharmacokinetics, including those due to drug interactions and genetic polymorphism (15). The clinical significance of genetic polymorphism in anti-epileptic drug metabolism has been extensively reviewed (16). Variability in dose-concentration relationships, susceptibility to adverse effects and seizure intractability are indeed often related to cytochrome peroxidase CYP2C9 and CYP2C19 polymorphism (17). Another argument is that for many of these drugs the clinical effect correlates better with blood levels than with doses. The dose-dependent kinetics of phenytoin introduced TDM to epilepsy practice. Since anti-epileptic treatment is prophylactic and often lifelong, potentially toxic drug levels must be avoided. For most anticon-

Table 1 Cytochrome P450 enzymes in the metabolism of anti-epileptics.

	Metabolization	Induction	Inhibition
Carbamazepine	CYP3A4 CYP2C8	CYP2C9 CYP3A4	
Clonazepam	CYP3A4		
Diazepam	CYP2C19 CYP3A		
Ethosuximide	CYP3A4 CYP2E CYP2B CYP2C		
Felbamate	CYP3A4 CYP2E1	CYP3A4	CYP2C19 β-oxidation
Lamotrigine	UGT	UGT (weak)	
Oxcarbazepine		CYP3A4 CYP3A5	CYP2C19
Phenobarbital	CYP2C9 CYP2C19 CYP2E1	CYP2C9 CYP3A4 UGT	
Phenytoin	CYP2C9 CYP2C19	CYP2C9 CYP3A4 UGT	CYP2C9
Primidone		CYP2C9 CYP3A4 UGT	
Tiagabine	CYP3A4		
Topiramate		β-oxidation	CYP2C19
Valproic acid	CYP2C9 CYP2C19 β-oxidation UGT CYP2A6		CYP2C9 UGT
Zonisamide	CYP3A		

UGT, uridine diphosphate glucuronosyltransferase.

vulsants there is a correlation between the concentration of the drug and its therapeutic and/or toxic effect. The therapeutic ranges for the older anti-epileptics were established after many studies with reliable methods. For the newer anti-epileptic drugs, large prospective studies concerning the concentration-effect relationship are often missing. This is partly because these drugs were initially licensed as add-on therapy and in some cases TDM was considered a disadvantage by the pharmaceutical industry (18, 19).

In the course of anticonvulsive TDM, it became clear that the early therapeutic ranges were too wide due to the inclusion of refractory patients in these studies. Patients with less severe forms of epilepsy could be kept seizure-free at lower concentrations (20). The type and severity of epilepsy are important determinants in relating anticonvulsant levels in blood and clinical response.

The inappropriate use of TDM has been discussed extensively in literature. Although TDM is useful in a number of indications, it is not indispensable (21). Others state that it should be reserved for a number of clear-cut indications, such as: (i) phenytoin and multiple-drug treatment due to poor seizure control or to dose-related toxicity; (ii) mentally retarded patients; (iii) patients with renal and/or hepatic impairment; (iv) pregnant patients in whom free drug concentrations should be monitored; and (v) patients with poor compliance (22). Others advocate the use of TDM in the case of newly diagnosed epilepsy to ensure that the drug is in the appropriate target range. Monitoring has also been useful in encouraging compliance with drug therapy. TDM can be helpful in situations where breakthrough seizures occur in patients who are otherwise well controlled and can help the clinician to distinguish between too little and too much medication (13).

What TDM should be available for urgent request? TDM has been primarily dependent on the development of rapid, sensitive and specific analytical techniques, and therefore most drugs can now be determined reasonably quickly. Phenobarbital with its long half-life, marked toxicity and neonatal use, should have TDM available on an emergency basis. As a first-line drug with its unusual pharmacokinetics and a rather long half-life, the TDM of phenytoin should be available in every laboratory with a short turnaround time. Other drugs with short half-lives, which are mainly checked for dosage adjustments and compliance, do not need such a priority, e.g., valproic acid.

Free drug concentrations Most acidic drugs are bound to albumin, while basic drugs are bound to α_1-acid glycoprotein. Depending on its affinity for plasma proteins, a drug may be bound tightly, loosely or not at all. Of the anti-epileptics considered in this review, phenytoin shows the most extensive protein binding, while gabapentin exhibits no protein binding at all. A drug can be displaced from its binding sites by a drug with greater affinity and/or concentration. In the classic example, valproate can displace phenytoin from its binding sites due to its higher concentration, leading to an increased free fraction of the latter. Moreover, free fatty acids may also displace drugs from plasma proteins, and some general disease states can also alter the free drug concentration. In uremic patients the free fraction of phenytoin may be more than doubled (from 10% to 20–30%) leading to serious adverse reactions. It is advisable to quantitate free phenytoin in uremic patients and adjust the dose to maintain the concentration at approximately 2 mg/l (23). This and other causes of hypoalbuminemia may hide intoxications in senile geriatric patients, for whom impairment of cognitive function can be removed by lowering the free concentration. Some drugs exhibit saturation of the binding sites, i.e., valproic acid shows saturation above 100 mg/l, and consequently further increases in the dose raise the free fraction. Free drug concentrations may be determined by measuring drugs in plasma ultrafiltrate, obtained by centrifugation through a 30,000-Da membrane. TDM of oral-fluid anticonvulsant concentrations has been extensively evaluated in the treatment of epilepsy. Carbamazepine, ethosuximide, phenytoin, and primidone are considered good candidates for therapeutic oral-fluid monitoring (24–26). Knowledge of the saliva/plasma ratio is helpful. Since non-ionized drugs can cross biological membranes and because saliva is usually more acidic than plasma, basic drugs concentrate in oral fluid. In fact, drugs not hindered by protein binding are generally quite easily measured in oral fluid.

Time of sampling and specimens In routine monitoring when considering if a patient is within the therapeutic window, the sample should be drawn at steady-state, which is at least 4–5 half-lives after the first dose. Sampling prior to the next dose provides trough levels that are easily comparable. Moreover, the distribution phase is then completed. Serum, solely and without serum separators, should be used as the sample for analysis. Citrate and oxalate anticoagulants should be avoided, since they substantially decrease the total concentration of phenytoin and valproic acid (27, 28); heparin can activate lipoprotein lipases, which can allow free fatty acids to displace drugs from albumin binding sites, and thus affect free drug determinations. The effect of EDTA is not established (29). Care should be taken with serum separators. Although several studies (30–33) indicate that gel-containing tubes are acceptable for TDM, these should be avoided. Prolonged specimen storage with exposure of smaller sample volumes to centrifuged gels increases adsorption to unacceptable levels.

Analytical methods

A large number of drugs are used to treat seizures. In addition, pharmacologically active metabolites that significantly contribute to the effect should be measurable. Although immunoassay is the mainstay method for the well-established drugs, many laboratories use chromatographic procedures: high-performance liquid chromatography (HPLC) and gas chromatogra-

Table 2 Procedure for liquid chromatographic measurement of anti-epileptics.

	General anti-epileptics	Levetiracetam
Sample preparation	Mix 100 µl of serum with 100 µl of IS (hexobarbital) and 400 µl of diethyl ether	Mix 100 µl of serum with 25 µl of 5 M NaOH, 50 µl of IS [2-(2,2-dimethyl-5-oxopyrrolidin-1-yl)-propanamide] and 500 µl of DCM
	Vortex for 1 min and centrifuge (~2000×*g*) for 5 min	Vortex for 30 s and centrifuge (~2000×*g*) for 5 min
	Evaporate to dryness 300 µl of supernatant at RT	Evaporate to dryness 300 µl of the lower phase at 50 °C
	Dissolve the residue in 200 µl of mobile phase	Dissolve the residue in 50 µl of mobile phase
	Vortex and centrifuge (~2000×*g*) for 5 min	Vortex and centrifuge (~2000×*g*) for 5 min
	Inject 10 µl	Inject 10 µl
Mobile phase	20 mM KH_2PO_4, pH 7/acetontrile/methanol (63:27:10)	20 mM KH_2PO_4, pH 7/acetonitrile/methanol (90:5:5)
Chromatography		
Column	Polaris C18-A (Varian) 100×4.6 mm (5 µm)	Polaris C18-A (Varian) 100×4.6 mm (5 µm)
Pre-column	Polaris C18-A guard column 10×3.0 mm (5 µm)	Polaris C18-A guard column 10×3.0 mm (5 µm)
Flow	1 ml/min	1 ml/min
Pressure	~100 bar	~80 bar
Run time	18 min	12 min
UV detection	195 nm	195 nm

General anti-epileptics that can be analyzed are carbamazepine, 10,11-epoxycarbamazepine, ethosuximide, felbamate, 10-hydroxycarbazepine, oxcarbazepine, pheneturide, phenobarbital, phenylethylmalonamide, phenytoin and primidone. Sample preparation is carried out in duplicate. IS, internal standard; DCM, dichloromethane; RT, room temperature.

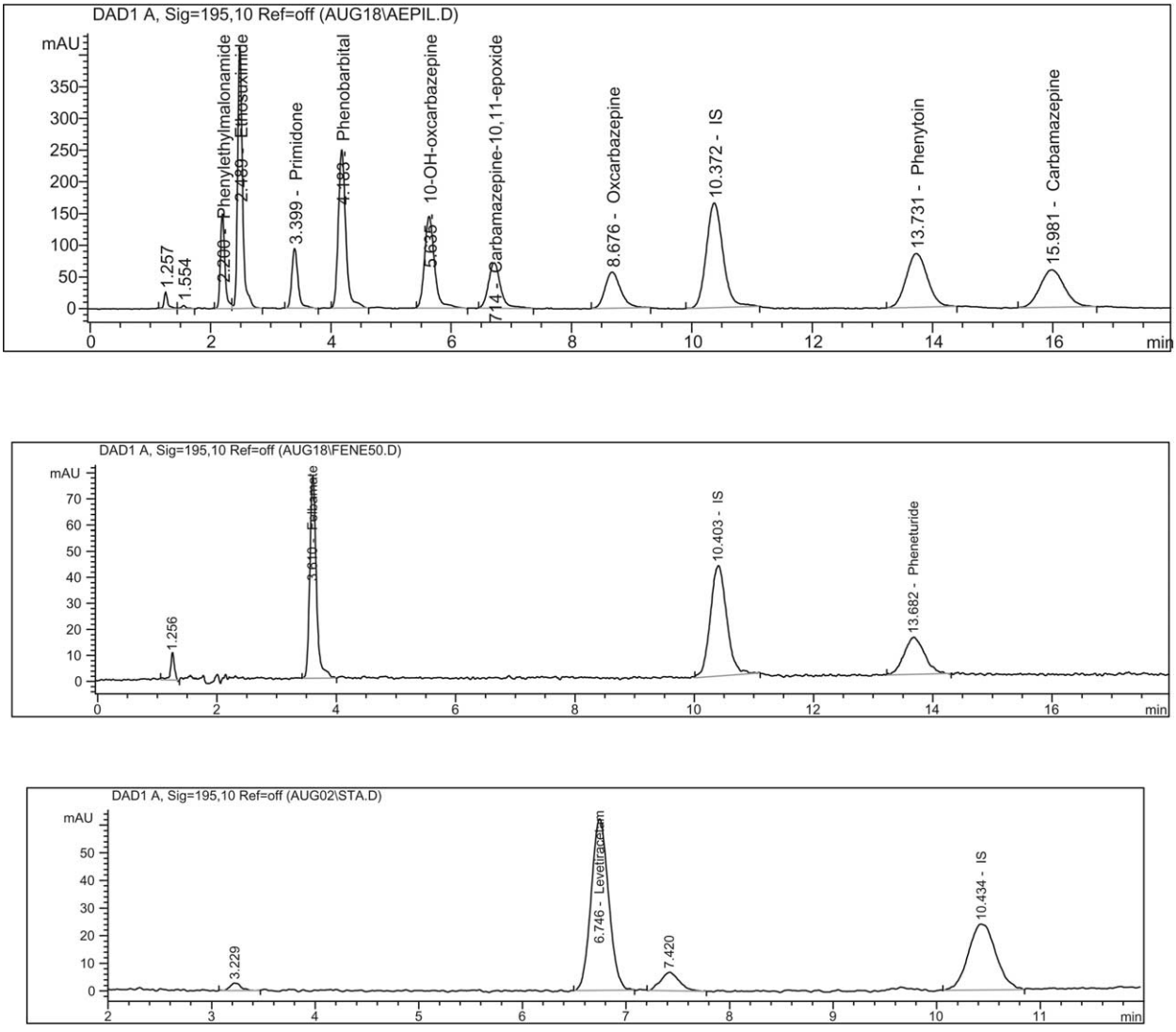


Figure 2 Representative chromatograms of serum extracts spiked with standards. For conditions see Table 2.

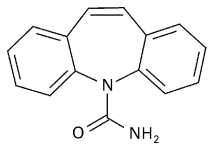
phy (GC). Immunoassays are more expensive from a reagent point of view but are less labor-intensive and faster to execute. Unfortunately they are restricted to single agents and do not provide information about metabolites. In some cases the antibodies utilized may cross-react with biologically active drug metabolites of the drug in question, i.e., carbamazepine-10,11-epoxide in the case of free carbamazepine (34) or p-hydroxy phenytoin in the case of a patient with renal failure (35). Turbidimetric and nephelometric techniques, labeled immunochemical assays and enzyme immunoassay techniques are also in common use. These are either homogeneous or heterogeneous, but are mostly in a competitive format (36). The certification by regulatory bodies should ensure validity of the performance of commercially available assays.

Some of the older established drugs (e.g., phenobarbital and primidone) are being prescribed less frequently and this hinders the use of expensive standard immunoassay procedures with a short shelf life. The earliest references for liquid chromatographic reversed-phase procedures, which allow simultaneous measurement of several of the older drugs, date from 1976 and 1977 (37, 38). Methods commonly in use are mostly HPLC assays based on reversed-phase C18 columns and a mixture of acetonitrile and an aqueous buffer. These assays allow the quantification of thermolabile metabolites. The sample clean up is either carried out using protein precipitation with acetonitrile containing the internal standard (equal parts of serum) and centrifugation, or liquid/liquid extraction using an organic solvent. Fixed wavelength, variable wavelength or diode array detectors are used. To optimize the limits of quantification for a mixture of drugs, the wavelength is best set at a weighed mean of wavelengths considering the different therapeutic concentrations (39). With the newer type of detectors the wavelength can be changed during the run. This allows quantification of more recent drugs, such as oxcarbazepine and its metabolite (40). We successfully adapted the method of Neels et al. (39) for oxcarbazepine and levetiracetam (see Table 2 and Figure 2). An interesting Lichrosphere RP™ reversed-phase C8 column allowed Pragst et al. to successfully identify at least 2682 UV-absorbing drugs (including all common anti-epileptic drugs except valproic acid) in a systematic toxicological analysis (41–43). Quantification of benzodiazepines using this photodiode array method at 235 and 310 nm is carried out daily in our laboratory.

Therapeutic drug monitoring of anti-epileptic drugs

In this review, weight is given to all anti-epileptics in current use and, more particularly, the monographs include information on mechanism of action, pharmacokinetics, drug interactions, drug concentration and clinical effects, and analytical methods. Infrequently used drugs or anti-epileptics for less important epileptic syndromes are summarized in the section Miscellaneous therapeutic agents. Concise Tables concerning CYP isoenzymes (Table 1), pharmacokinetic data (Table 3) and brand names (Table 5) are provided.

Carbamazepine



5H-Dibenz(b,f)azepine-5-carboxamide: mol. wt., 236.27; usual dose, initially 100–400, increasing to 400–1200 mg daily; max. dose, 1800 mg/day; pK_a 7.0; therapeutic concentration, 4–12 mg/l (carbamazepine) and 0.2–6 mg/l (carbamazepine-10,11-epoxide); plasma half-life, 10–30 h (adult long-term use, 10–20 h), 8–19 h (children); plasma protein binding, 70–80%; distribution volume, 1.4 l/kg.

Carbamazepine is effective in the treatment of partial and generalized tonic-clonic seizures (13), but it is not effective in patients with absence or myoclonic seizures. The drug acts by preventing repetitive firing of action potentials in depolarized neurons (44) through voltage- and use-dependent blockade of sodium channels (45), in a manner similar to phenytoin. It has been employed since the 1960s for the treatment of trigeminal neuralgia and is also occasionally used as a prophylactic in manic-depressive patients. Although carbamazepine is considered a primary drug, it is not without problems. Treatment should be initiated at low doses to allow tolerance to the CNS side effects. Diplopia, headache, dizziness and nausea are the most common side effects. Other adverse side effects include nystagmus, vomiting, aplastic anemia and agranulocytosis. Since carbamazepine has antidiuretic effects, retention of water, especially in elderly patients with cardiac disease, occurs as a late complication (13).

Pharmacokinetics Carbamazepine is poorly soluble in water and as a consequence absorption may be slow and irregular. Approximately 70–80% of carbamazepine is bound to plasma proteins. The drug is mainly metabolized in the liver, resulting in the 10,11-epoxide metabolite and glucuronides. Approximately 2% of the dose given is found unchanged in urine. The plasma half-life is approximately 30 h when given as a single dose, but as a strong inducing agent, the plasma half-life shortens to approximately 15 h when given repeatedly. When carbamazepine is given with other inducing agents (phenytoin, phenobarbital, valproic acid and lamotrigine) the plasma half-life can be even further decreased and the concentration of the 10,11-epoxide can rise considerably. Under these conditions, the steady-state trough concentration of the latter increases from the usual 20% to 50% of the parent drug, contributing not only to enhanced anticonvulsant activity, but also to toxic effects (46). The elimination half-life of carbamazepine-10,11-epoxide is 6 h and its plasma protein binding is 50–60%. The

Table 3 Pharmacokinetic data.

Anti-epileptic	Active metabolites	Tentative target range, mg/l	Toxic concentration mg/l	Protein binding, %	$t_{1/2}$, h	t_{max}, h	Bioavailability, %	Distribution volume, l/kg
Carbamazepine	Yes	4–12	>12	70–80	15	4–8	100	1.4
	Epoxycarbamazepine	0.2–9		50	6			
Clobazam	Yes	0.1–0.4		85	30	1–4	87	1
	Desmethylclobazam				46			
Clonazepam	No	0.02–0.07	>0.1	86	20–40	1–4	90	3
Ethosuximide	No	40–100	>160	0	30–60	3–7		0.7
Felbamate	No	30–80	>120	22–36	15–23	2–6	>90	0.8
Gabapentin	No	12–20		0	5–7	2–3	60	0.6–0.8
Lamotrigine	No	3–14		55	13.5	1–3	98	1–1.4
Levetiracetam	No	10–37		<10	6–8	1	100	0.5–0.7
Oxcarbazepine	Yes			67	1–2.5	1–2		3–15
	10-Hydroxycarbazepine	3–40	>45	40	8–14	3–5		0.7
Pheneturide	No	5–20		85–90	30–90		90–95	2.6
Phenobarbital	No	15–40	>50	50	50–150	6–18	70–90	0.5
Phenytoin	No	10–20	>20	90	12–36	4–8	90–100	0.5–1.2
Primidone	Yes	8–12	>15	<20	5–16	0.5–9		0.6
	Phenobarbital	15–40			50–150			
	Phenylethylmalonide	7–10			16–50			
Tiagabine	No	10–100 μg/l		96	7–9	0.5–2	90–95	1–1.3
Topiramate	No	5–25		13–17	20–30	2–3	81–95	0.6–0.8
Valproic acid	No	50–100	>200	90	8–15	1–4	100	0.15–0.4
Vigabatrin	No	1–36		0	5–8	1	80–90	0.8
Zonisamide	No	10–38	>40	40–60	50–70	2–6	100	1.45
Acetazolamide	No	10–15		90–95	13	2–4		0.2
Barbexaclone	Yes						70–80	
	Phenobarbital	10–40						
Diazepam	Yes	0.2–1	>1.5	96	21–37	0.5–1.5		0.7–2.6
	Nordazepam	0.1–2.2	>20		40–100			
	Temazepam							
	Oxazepam							
Fosphenytoin	Yes		>30	95–99	0.13–0.25	0.5	90–100 i.m.	0.6–0.7
	Phenytoin							
Lorazepam	No	0.05–0.24	>0.3	90	9–24		95	1–2
Methsuximide	Yes			0	1–3	1–3		
	N-Desmethyl-mesuximide	10–40	>40		36–45			
Methylphenobarbital	Yes			40–60	50–60		50	2–3
	Phenobarbital	15–40			50–150			
Nitrazepam	No	0.03–0.07	>0.2	85–90	17–48	1.5–2.5	60–90	2–5
Sulthiame	No	0.5–12.5	>12		5.5–12	1–5		
Trimethadione	Yes	19–41		0	16			
	Dimethadione	350–1033	>1000		5–10 days			

rate of metabolism is higher in children than in adults, again resulting in significantly higher 10,11-epoxide levels.

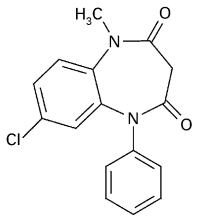
Drug interactions Metabolic reactions, catalyzed by CYP isoenzymes CYP3A4 and CYP2C8 (and to a lesser extent CYP1A2 and CYP2C19) include the formation of the 10,11-epoxide, which has anticonvulsant properties, followed by hydroxylation to the inactive trans-10,11-dihydro-10,11-dihydroxycarbamazepine.
Carbamazepine not only induces its own metabolism, but also accelerates hepatic oxidation and conjugation of other lipid-soluble drugs (47); the effect of the oral anticoagulants, disopyramide and quinidine can be diminished. The concentration of cyclosporin, tacrolimus, protease inhibitors and benzodiazepines can be lowered. The reliability of oral contraceptives can be reduced and most women require an increase in the daily dose of estrogen from 35 to 50 μg or more (13, 48). Carbamazepine also increases the metabolism of valproic acid and ethosuximide. Paradoxically, phenytoin induces the metabolism of carbamazepine, while carbamazepine inhibits the metabolism of phenytoin. Adding phenytoin decreases plasma carbamazepine levels by one third, whereas adding carbamazepine increases plasma phenytoin concentrations by a similar amount. The effect of valproic acid on the concentration of carbamazepine is in fact unpredictable; plasma levels of carbamazepine can increase or decrease. When valproic acid is initiated or stopped, the carbamazepine dosage should be corrected. Plasma concentrations and the effect of carbamazepine can be increased by metabolism-inhibiting drugs such as danazol, isoniazid, cimeti-

dine, fluoxetine, fluvoxamine, erythromycin, dextropropoxyphene, diltiazem, verapamil, nefazodone and protease inhibitors. With the concomitant use of lithium, augmentation of both the therapeutic and toxic effects has been described (12, 13).

Drug concentrations and clinical effects Although it is generally accepted that the therapeutic levels of carbamazepine range between 4 and 12 mg/l, interpretation is quite difficult due to the relative short half-life (long-term use, 10–20 h). It is also possible that some patients with a therapeutic concentration of carbamazepine may present with clinical toxicity due to the presence of high levels of carbamazepine-10,11-epoxide, undetected in most immunoassays (49). In many patients, the dose is adequately titrated by monitoring its clinical effects (50). However, the use of other anticonvulsive agents and compliance problems justify TDM. Peak concentrations in plasma (C_{max}) are observed 4–8 h after oral ingestion, but may be delayed by as much as 24 h, especially following the administration of a large dose. CNS side effects are frequent at concentrations above 9 mg/l. Hyponatremia develops in 1–10% of patients due to the antidiuretic effect of carbamazepine. Symptoms are weight gain and edema. When the plasma sodium concentration falls below 125 mmol/l, there may be confusion and decreasing control of seizures (51).

Analytical methods Immunoassay is the method most used but, with the exception of the Dade Behring assay (52) these detect only carbamazepine (49). Liquid chromatographic assays with low UV detection or specific detection at a maximum of 280 nm are commonly used and allow the quantitation of both carbamazepine and the 10,11-epoxide metabolite (39). GC techniques with flame ionization (FID) or mass spectrometric detection (MSD) are also reported (53, 54). Comparisons with immunoassays have been published (55). With UV detection, the limit of detection can be as low as 0.020 mg/l (56).

Clobazam



7-Chloro-1-methyl-5-phenyl-1H-1, 5-benzodiazepine-2, 4 (3H, 5H)-dione: mol. wt., 300.75; usual dose, 20–30 mg/day; max. dose, 80 mg/day; therapeutic concentration, 0.1–0.4 mg/l; plasma half-life, 30 h (parent drug), 46 h (metabolite); plasma protein binding, 85%; distribution volume, 1 l/kg.

Clobazam, a 1,5-benzodiazepine, has a slightly different chemical structure from that of clonazepam and diazepam, which are 1,4-benzodiazepines, and is less likely to cause psychomotor impairment. Clobazam is effective in partial seizures, but also in patients with typical or atypical absence seizures, in those with myoclonic and secondarily generalized tonic-clonic and atonic seizures, and those with the Lennox-Gastaut syndrome (57). Clobazam can be given intermittently for catamenial epilepsy (where seizures occur around menstruation, probably due to low progesterone levels, or just before ovulation due to high estrogen levels) (57). Clobazam is an inexpensive, safe and well-tolerated adjuvant drug that even controls seizures in 10–30% of patients with refractory epilepsy. Because of its tolerance, it is often used intermittently as an adjuvant when seizures must not occur (i.e., wedding or holiday). Adverse effects include sedation, dizziness, mood changes, depression, aggression and disinhibition (58). Clobazam gives less sedation and tolerance than clonazepam. In a monotherapy study in children the efficacy with regard to tolerance was comparable to phenytoin and carbamazepine (59, 60). Although its use is advocated in numerous publications, it is not on the market in the USA (57).

Mechanism of action Clobazam probably exerts its antiseizure activity by potentiating the inhibitory actions of GABA (61).

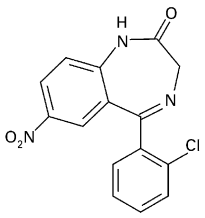
Pharmacokinetics The drug is well absorbed after oral administration. Clobazam is highly lipophilic and rapidly crosses the blood-brain barrier. The protein binding of clobazam is approximately 85%. It is metabolized mainly by dealkylation and hydroxylation to N-desmethyl-clobazam, which is pharmacologically active (20% compared to the parent drug), and 4-hydroxy-clobazam, respectively. The elimination half-lives of clobazam and desmethyl-clobazam are approximately 30 (10–58 h) and 46 h, respectively (62) and are slightly prolonged in the elderly.

Drug interactions The sedative effect of alcohol and other CNS depressive drugs can be potentiated. There is indirect in vivo evidence of CYP2C19 involvement in the metabolism of the main clobazam metabolite (N-desmethyl clobazam) (63).

Drug concentrations For clobazam the therapeutic range is 0.1–0.4 mg/l, while the steady-state concentration of desmethyl clobazam is approximately eightfold higher than that of clobazam (12, 64). The therapeutic range of clobazam is similar to that for other benzodiazepines and lethal intoxications are seldom seen, except for combinations with other CNS-active drugs. TDM is seldom required since the drug is rarely used for long periods.

Analytical methods GC and HPLC are the methods currently used. GC procedures use nitrogen phosphorus (NPD) or electron capture detection (ECD) to achieve limits of detection of 0.003 mg/l (65, 66). HPLC has a much higher limit of detection (67), which can be lowered by concentrating the extracts through solid-phase extraction to reach limits of quantification of 0.002 and 0.001 mg/l (68).

Clonazepam



5-(2-Chlorophenyl)-1, 3-dihydro-7-nitro-2 H-1, 4-benzodiazepin-2-one: mol. wt., 315.72; usual dose, 1–2 mg/day in 2–3 doses; max. dose, 20 mg/day; pK_a 1.5, 10.5; therapeutic concentration, 0.02–0.07 mg/l; plasma half-life, 20–60 h; plasma protein binding, 86%; distribution volume, 3 l/kg.

Clonazepam has a high affinity for central benzodiazepine receptors. Clonazepam is effective in preventing absence seizures, myoclonic jerks and tonic–clonic seizures (69). Adverse effects, as for other benzodiazepines, are sedation, somnolence, muscle weakness, ataxia, headache, dizziness and diplopia. Few patients show a good response, and in nearly 50% of patients the epilepsy is exacerbated when the drug is withdrawn (70). The therapeutic role of clonazepam is therefore limited, and it is used mostly for refractory myoclonic seizures (13).

Mechanism of action Clonazepam is a facilitator of the GABA system and it also increases the central synthesis of serotonin (71).

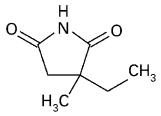
Pharmacokinetics Clonazepam is orally well absorbed. Approximately 86% is bound to plasma proteins. Clonazepam is metabolized in the liver by CYP3A4, mainly to the slightly active 7-amino-metabolite. The elimination half-life ranges from 20 to 60 h; 50–70% of the dose given is excreted in urine and 10–30% in feces as metabolites (12).

Drug interactions The sedative effect of alcohol and other CNS depressive drugs can be potentiated. The metabolism of clonazepam is inhibited by delavirdine and protease inhibitors.

Drug concentrations Tentative therapeutic plasma concentrations range between 0.02 and 0.07 mg/l (12). Toxicity is associated with plasma concentrations >0.1 mg/l.

Analytical methods Many dedicated methods are available. GC methods with ECD (72) and MSD (73) attain a detection limit of 0.001 and 0.0001 mg/l, respectively. UV reversed-phase HPLC often allows the simultaneous measurement of other benzodiazepines. The limits of detection can be as low as 0.002 mg/l, while one method reaches 0.001 mg/l in analyzing post-mortem blood (74). Clonazepam can also be quantified in hair using HPLC with diode array detection (75).

Ethosuximide



3-Ethyl-3-methyl-2,5-pyrrolidinedione: mol. wt., 141.17; usual dose, 250 mg twice a day; max. dose, 1500–2000 mg/day; pK_a 9.5; therapeutic concentration, 40–100 mg/l; plasma half-life, 30–60 h in adults, 20–55 h in children; plasma protein binding, absent; distribution volume, 0.7 l/kg.

Ethosuximide is mainly used for its selective effect on absence seizures. The succinimides evolved from a systematic search to find less toxic products than the oxazolidinediones (i.e., trimethadione, see Miscellaneous therapeutic agents). Methsuximide (also see Miscellaneous therapeutic agents) and phensuximide have phenyl substituents and although more active in some experimental settings, they are no longer commonly used. Possible adverse effects of ethosuximide involve the gastrointestinal tract (nausea, vomiting and abdominal pain) and the CNS (ataxia, dizziness, lethargy and insomnia). Blood dyscrasias, like aplastic anemia, are rarely reported.

Mechanism of action Ethosuximide acts by reducing low-threshold, transient, voltage-dependent calcium currents in thalamic neurons (T-currents) (76). By contrast, ethosuximide does not inhibit sustained repetitive firings or enhance GABA responses at clinically relevant concentrations (46).

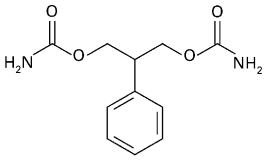
Pharmacokinetics Ethosuximide is well absorbed. Due to its low binding to plasma proteins, concentrations of the drug in plasma, cerebrospinal fluid and saliva are very similar during long-term therapy. The apparent distribution volume is 0.7 l/kg. Ethosuximide is mainly metabolized in the liver to at least three inactive metabolites. Approximately 15–25% is excreted unchanged in the urine. The plasma half-life is longer in adults (30–60 h) than in children (20–55 h).

Drug interactions Although the metabolism of ethosuximide is altered by enzyme inducers, such as phenytoin and carbamazepine, and by enzyme inhibitors such as valproic acid, the effects are minimal.

Drug concentrations During long-term treatment with ethosuximide, the plasma concentration average is 2 mg/l per daily dose of 1 mg/kg. Plasma concentrations between 40 and 100 mg/l are satisfactory for seizure control in 80% of patients. Higher concentrations of up to 160 mg/l have been described without excessive toxicity. Side effects are often not correlated with high plasma concentrations (13). TDM of ethosuximide is not common due to its low protein binding and to the infrequent incidence of absence seizures.

Analytical methods Immunoassays are available, but reversed-phase HPLC with UV detection is commonly used (37, 38, 77). GC techniques with ECD or FID have been published (78, 79). More recently, MSD has also been used (80).

Felbamate



2-Phenyl-1,3-propanediol dicarbamate: mol. wt., 238.24; usual dose, 600–1200 mg/day; max. dose, 3600 mg/day; therapeutic concentration, 30–80 mg/l; plasma half-life, 15–23 h; plasma protein binding, 22–36%; distribution volume, 0.8 l/kg.

Felbamate is a dicarbamate related to meprobamate. In animals it is effective against multiple types of seizures at doses considerably lower than toxic doses (81). It has been used as add-on therapy and as monotherapy for partial seizures with and without generalization in adults. It is also used in children with partial and generalized seizures associated with the Lennox-Gastaut syndrome. Although felbamate was well tolerated in clinical trials, it was withdrawn for all indications except for seizures associated with the Lennox-Gastaut syndrome and for refractory epilepsy, due to several fatalities (aplastic anemia and hepatotoxic reactions). Frequent blood counts and measurements of liver enzyme activity are recommended, although it is not known whether early detection of either reaction will prevent the most serious outcomes. Other possible adverse affects are irritability, fatigue, headache, dizziness, somnolence, rash and dyspepsia (57).

Mechanism of action The mechanism of action is not completely known, but felbamate reduces the repetitive firing of action potentials through inhibition of sodium channels. It enhances the inhibitory actions of GABA and blocks N-methyl-D-aspartate receptors (82).

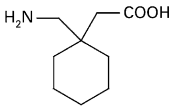
Pharmacokinetics Felbamate is well absorbed from the gastrointestinal tract (83). It has a half-life of 15–23 h in healthy volunteers (84). Felbamate is minimally metabolized (15% through CYP3A4 and CYP2E1). Approximately 90% of felbamate is excreted in the urine (almost 50% unchanged) and less than 5% in the feces. Approximately 25% is bound to plasma proteins.

Drug interactions Compounds with cytochrome enzyme-inducing activity increase felbamate clearance, possibly through the induction of CYP3A4 activity (85). Felbamate itself alters the serum concentration of many other anti-epileptic drugs. For example, it increases the serum concentration of phenytoin, phenobarbital, valproic acid, N-desmethylclobazam and carbamazepine-10,11-epoxide, while it decreases serum levels of carbamazepine (83).

Drug concentrations Although there is an overall lack of data from prospective studies, seizure control seems to be related to serum concentration. Monitoring felbamate concentrations may be particularly useful since levels are not easily predicted from administered dosages, and felbamate appears to have a narrow therapeutic window (83). A tentative target range for optimal treatment varies from 30 to 80 mg/l (86). Others (87) suggest higher intervals (50–110 mg/l), while Hachad et al. (85) suggest a lower range (18–52 mg/l).

Analytical methods No immunoassays are available. Given the restricted use of felbamate, it is unlikely that efforts will be made to develop such assays. GC methods using capillary columns and NPD or FID detectors are available (88, 89). Reversed-phase HPLC is also available and a similar method is used in our laboratory (see Table 2). Felbamate can also be quantified with the HPLC method of Pragst and colleagues (41).

Gabapentin



1-(Aminomethyl)cyclohexaneacectic acid: mol. wt., 171.24; usual dose, 1200 mg/day; max. dose, 3600 mg/day; pK_a 3.68, 10.7; therapeutic concentration, 12–20 mg/l; plasma half-life, 5–7 h; plasma protein binding, none; distribution volume, 0.6–0.8 l/kg.

Gabapentin is currently approved for adjunctive management of partial seizures with or without secondary generalization, in patients older than 12 years and for children aged between 6 and 12 years (83). The pharmaceutical company Pfizer was able to broaden its indication largely to neuropathic pain after spinal cord injury, post-traumatic stress disorder, post-stroke pain syndrome, alcohol withdrawal, migraine therapy, hot flashes associated with prostate cancer therapy, postoperative pain after cancer surgery (90) and nausea induced by chemotherapy (91). Long-term use can lead to somnolence, fatigue, dizziness, ataxia, nystagmus and weight gain; however, overall, it is well tolerated.

Mechanism of action Gabapentin is structurally related to the neurotransmitter GABA. However, gabapentin is not metabolized to GABA nor is it an agonist of GABA receptors. It binds to a unique receptor in the brain and gabapentin has also been demonstrated to increase brain GABA concentrations in humans (92).

Pharmacokinetics Gabapentin is orally absorbed. Absorption kinetics may be dose-dependent, with decreasing bioavailability at increasing dosages, possibly due to a saturable transport system (93). Gabapentin is not metabolized nor bound to plasma proteins. The elimination half-life is not dose-dependent and lies between 5 and 7 h (93). Gabapentin is only excreted in the urine.

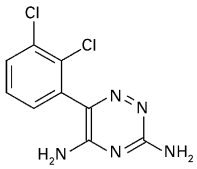
Drug interactions Gabapentin does not induce hepatic microsomal enzymes and therefore it does not interact with other anti-epileptic drugs. Thus, gabapentin

may be very useful in patients who are taking other medications, especially the elderly (57).

Drug concentrations A tentative target range of 12–20 mg/l is suggested (57, 83). Some studies report a wider range (2–61 mg/l) (94), while others set a smaller range (2–10 mg/l) (95). Over the therapeutically effective dose range, there is an approximately linear relationship between dose and plasma concentration, although gabapentin dose increments may result in decreased oral bioavailability. Hence, TDM is used to clarify whether a poor response is caused by impaired absorption (93). An imperative for TDM is drug accumulation due to worsening renal function (95). However, the lack of pharmacokinetic interactions due to the absence of metabolism, the short half-life and the absence of protein binding reduce the need for TDM of gabapentin. Furthermore, the short half-life results in a wide fluctuation of serum levels during the dosage interval, complicating the establishment of a target range (93). In treating chronic pain and addictions, higher trough concentrations of 15–30 mg/l are usually maintained (90).

Analytical methods Capillary GC methods are available with either MSD (96) or FID (97). Derivatization of the amino acid character of gabapentin with either dansyl chloride (98) or trinitrobenzene sulfonic acid (23, 90) allows HPLC with either fluorimetric or UV detection. The method described in the latest version of the Tietz textbook of clinical chemistry (23) is quite easy to carry out.

Lamotrigine



6-(2,3-Dichlorophenyl)-1,2,4-triazine-3,5-diamine: mol. wt., 256.1; usual dose, 100–200 mg/day; max. dose, 850 mg/day; pK_a 5.7; therapeutic concentration, 3–14 mg/l; plasma half-life, 13.5 h (adults); plasma protein binding, 55%; distribution volume, 1–1.4 l/kg.

Lamotrigine is a synthetic anticonvulsant phenyltriazine, unrelated to other agents. This drug is effective in partial seizures, primary and secondary generalized tonic-clonic seizures, absence seizures, and drop attacks associated with Lennox-Gastaut syndrome (99). Adverse effects include dizziness, diplopia, blurred vision, somnolence, headache, ataxia, asthenia, nausea, vomiting, rash and depression.

Mechanism of action Lamotrigine acts mainly by inhibiting excitatory amino acid (glutamate) release. It stabilizes the neuronal membrane through blockade of voltage-sensitive sodium channels and possibly via calcium channels (12).

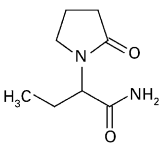
Pharmacokinetics Lamotrigine is completely absorbed from the gastrointestinal tract. The average plasma half-life is 25 ± 10 h for healthy volunteers, 13.5 h for adults with epilepsy and 36 h under conditions of renal insufficiency. Lamotrigine undergoes extensive metabolism, primarily by conjugation, to form the inactive N-2 and N-5 glucuronides. The metabolism of lamotrigine is slightly reduced by frequent administration (100). Approximately 55% of lamotrigine is bound to plasma proteins. The drug is mainly (94%) excreted in the urine (primarily as *N*-glucuronide, 10% unchanged), with 2% in the feces. Steady-state serum lamotrigine concentrations increase linearly with dose (83).

Drug interactions Because of the extensive metabolism of lamotrigine, significant drug interaction can be observed. Co-medication with hepatic enzyme-inducing anti-epileptic drugs enhances the metabolic clearance of lamotrigine and higher doses are needed when given concurrently with phenytoin, carbamazepine, primidone and phenobarbital (101, 102). Valproic acid down-regulates the metabolism of lamotrigine, thereby extending its half-life to 60 h and necessitating a reduced dose (101, 102). The plasma concentration of lamotrigine in patients taking oral contraceptive drugs can be significantly lower (approx. 50%) (103).

Drug concentrations For lamotrigine, there is a clinical need to individualize patient therapy (19). There are large variations between individuals in dose versus serum concentrations in patients on monotherapy. Furthermore, pharmacokinetic variability, which depends on other anti-epileptic medication, complicates dosing (83, 104). A therapeutic serum concentration range of 1–4 mg/l was originally proposed based on preclinical data (105). Morris et al. concluded that an appropriate range of optimal lamotrigine concentrations would be 3–14 mg/l (106).

Analytical methods No immunoassay is currently available. Of the newer anti-epileptic drugs, lamotrigine has attracted the most interest in relation to TDM. Many methods have been described, most of them based on reversed-phase HPLC with UV detection. Of the specific methods, the one reported by George et al. is the most practical (107). The method of Lensmeyer et al. (108) and others (109) has the advantage of simultaneous determination of phenytoin, carbamazepine and carbamazepine-10,11-epoxide, albeit substantially slower. We use a capillary GC NPD method, exploiting the five nitrogen atoms contained in the molecule; despite being a NPD method the precision is good (110).

Levetiracetam



(αS)-α-Ethyl-2-oxo-1-pyrrolidineacetamide: mol. wt., 170.21; usual dose, 500 mg/day; max. dose, 1500 mg/day; therapeutic concentration, 10–37 mg/l; plasma half-life, 6–8 h; plasma protein binding, <10%; distribution volume, 0.5–0.7 l/kg.

Levetiracetam is the *S*-enantiomer of racemic pyrrolidine acetamide (111). Levetiracetam is effective for use as adjunctive therapy in the management of partial onset seizures in adults with epilepsy. It is also efficacious in children with partial seizures, and there is a suggestion that it may be effective for the management of generalized seizures (83). Adverse effects of levetiracetam are mainly somnolence, fatigue and dizziness. Other side effects, such as headache, gastrointestinal disturbances, rash and diplopia, have also been reported. Levetiracetam is also a potential cause of weight loss (112).

Mechanism of action Levetiracetam appears to act through a specific binding site in the brain, but with an unknown mechanism (113).

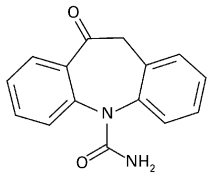
Pharmacokinetics Levetiracetam is well absorbed after oral ingestion and undergoes minimal metabolism to inactive metabolites. The pharmacokinetic profile of levetiracetam has been described as closely approximating the ideal characteristics expected of an anti-epileptic drug (114). Less than 10% of the drug is bound to plasma proteins and its elimination half-life ranges from 6 to 8 h (114). Approximately 66% of the dose is excreted unchanged and 27% as an inactive hydrolysis product (on the acetamide group) (115). Its elimination is decreased in patients with renal dysfunction.

Drug interactions Levetiracetam is not metabolized by the hepatic CYP450 system and thus interactions with other inducing anti-epileptic drugs are unlikely. This has been demonstrated in vitro (116), as well during placebo-controlled clinical studies and analysis of the levetiracetam half-life (117). However, this large, recent study pointed out that the serum level/dose ratio of levetiracetam decreased in co-medication with phenytoin, carbamazepine and oxcarbazepine compared to monotherapy, whereas valproate, phenobarbital and lamotrigine did not show any influence.

Drug concentrations A tentative target range for levetiracetam of 6–20 mg/l is suggested by the manufacturer (83). Others (118) reported peak plasma levels between 10 and 37 mg/l with doses of between 5.4 and 32.2 mg/kg. A large study designed to investigate the influence of the levetiracetam dose, age, and co-medication on the serum concentration showed levels of 16.2 ± 9.7 mg/l (median 14.2, range 1.5–48 mg/l) (119). The relationship between levetiracetam serum concentrations and clinical effect has not been ascertained, and consequently the value of serum concentration measurements has not been established. Because of its favorable therapeutic index, low plasma protein binding and minimal side-effect profile, routine monitoring of levetiracetam drug concentrations appears to be unnecessary for safe use of the drug, and dosing can be readily guided by the therapeutic response (83). Since phenytoin, carbamazepine and carbamazepine-10,11-epoxide can decrease levetiracetam levels by 20–30% (119), monitoring levetiracetam levels might be justified under these circumstances.

Analytical methods Megabore GC and reversed-phase HPLC methods have been described for the determination of levetiracetam in biological fluids (119–121). In our laboratory the common reversed phase methodology described in Table 2 and Figure 2 is in use.

Oxcarbazepine



10,11-Dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide: mol. wt., 252.27; usual dose, 600–2400 mg/day; max. dose, 46 mg/kg daily; therapeutic concentration, 3–40 mg/l (metabolite of prodrug oxcarbamazepine, 10-hydroxy-carbazepine); plasma half-life, 1–2.5 h (oxcarbazepine), 8–14 h (10-hydroxy-carbazepine); plasma protein binding, 40%, distribution volume, 0.7 l/kg (10-hydroxy-carbazepine).

Oxcarbazepine is the 10-keto analog of carbamazepine. Oxcarbazepine is used as monotherapy and as adjunctive treatment for partial seizures and generalized tonic-clonic seizures in children and adults (122). It is not effective against absence seizures (57). The adverse effects for oxcarbazepine are similar to those for carbazepine. In humans oxcarbazepine is rapidly metabolized to the pharmacologically active 10-hydroxy-carbazepine.

Mechanism of action 10-Hydroxy-carbazepine was found to have similar pharmacological effects to oxcarbazepine and carbamazepine. It acts mainly by blocking the voltage-dependent sodium channels. In addition 10-hydroxy-carbazepine has the ability to reduce voltage-activated calcium currents (122–124).

Pharmacokinetics Oxcarbazepine is well absorbed after oral administration. Oxcarbazepine is rapidly reduced by non-inducible ketoreductases to two pharmacologically active, equally potent enantiomers (10-hydroxy-carbazepine) with an accumulation of the S-enantiomer (125). This transformation is not CYP450-mediated. The R- and S-enantiomers are further metabolized to form the 10,11-diol and glucuronides. The elimination half-life of both enantiomers is approximately 12 h, while the half-life of the parent drug is approximately 1–2.5 h. The protein binding of oxcarbazepine is approximately 67% and of the mono-hydroxy metabolites is 40% (126). More than 95% of a dose is recovered in the urine as follows: less than 1% and 27% as unchanged oxcarbazepine and 10-hydroxy-carbazepine, and 9% and 49% as inactive glucuronide conjugates of oxcarbazepine and 10-hydroxy-carbazepine, respectively (127).

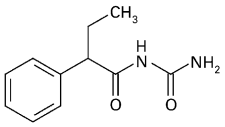
Drug interactions Since the biotransformation of oxcarbazepine to 10-hydroxy-carbazepine is not CYP450-mediated, the potential for interactions with

other anti-epileptic drugs that interfere with CYP450 isoenzymes is reduced. Nevertheless, the concentration of 10-hydroxy-carbazepine is reduced by co-administration of carbamazepine, phenytoin, phenobarbital and valproic acid. The metabolite inhibits CYP2C19 (85), increasing serum phenytoin concentration by up to 40% in patients taking both (128). 10-Hydroxy-carbazepine lowers the concentrations of carbamazepine, while increasing those of carbamazepine-10,11-epoxide. Oxcarbazepine is a weak and selective hepatic enzyme inducer (CYP3A4 and CYP3A5) (129, 130). Oxcarbazepine has an inducing effect on the metabolism of lamotrigine (131). When oxcarbazepine was given with an oral contraceptive, 4 out of 6 women developed breakthrough bleeding (132).

Drug concentrations There is a need for more systematic studies exploring the concentration-effect relationships for oxcarbazepine. In a retrospective analysis the safety and efficacy responses could adequately be explained by oxcarbazepine dose alone. The plasma concentration of the metabolite provided limited additional information (93). A reduction in the clearance of 10-hydroxy-carbazepine was reported in elderly patients (133) and in patients with impaired renal function (134).

Analytical methods Several methods are available for the measurement of oxcarbazepine and its main metabolite (135–137). In general, the common reversed-phase HPLC methods used to determine anti-epileptic drugs such as phenytoin, phenobarbital, ethosuximide, primidone and carbamazepine are able of quantifying oxcarbazepine and its active metabolite with minor modifications (see Table 2).

Pheneturide



N-(Aminocarbonyl)-α-ethylbenzeneacetamide: mol. wt., 206.24; usual dose, 300–600 mg/day; max. dose, 1.2 g/day or 20 mg/kg daily; therapeutic concentration, 5–20 mg/l; plasma half-life, 30–90 h; plasma protein binding, 85–90%; distribution volume, 2.6 l/kg.

Pheneturide is an old anti-epileptic for which Bayer received a patent back in 1912. It is still in use in some countries and is indicated for the treatment of partial seizures with and without secondary generalization. Pheneturide is a non-sedative anti-epileptic with a slight CNS stimulating effect. Adverse effects include ataxia, rash, leucopenia and aplastic anemia. Plasma folate and calcium levels can be lowered. Probably due to the latter, elevation of alkaline phosphatase is not uncommon.

Mechanism of action The anticonvulsive activity of pheneturide can be compared to phenylacetylureum, a straight-chain analog of 5-phenylhydantoin, which is no longer in use due to its toxicity. More details are not available.

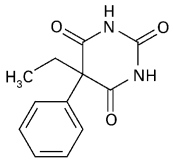
Pharmacokinetics Pheneturide is well (90–95%) but slowly (8 h) absorbed. The binding to plasma proteins ranges between 85% and 90%. The plasma half-life is long, with an average of 54 h (31–90 h). When used chronically the half-life diminishes to 40 h. It is mainly metabolized in the liver to inactive metabolites that are excreted in the urine.

Drug interactions Pheneturide is an inducing agent and therefore it lowers the serum concentration of several other drugs, e.g., nortriptyline, chlorpromazine, doxycycline, digitoxin, oral anticoagulants and oral contraceptives (138). It also enhances its own metabolism. Pheneturide inhibits the metabolism of phenytoin and phenobarbital, and can raise the plasma concentrations of phenytoin to toxic levels. Increased levels of phenobarbital have also been observed.

Drug concentrations There is very little information on pheneturide. In the registration file it is stated that the optimal plasma concentration lies between 5 and 20 mg/l, which is in accordance with values observed in our laboratory.

Analytical methods Very few methods are published, but the conventional reversed-phase HPLC methods for simultaneous measurement of anti-epileptic drugs allow separation and quantification of pheneturide (39).

Phenobarbital



(±)-5-Ethyl-5-phenyl-2,4,6(1H,3H,5H)-pyrimidinetrione: mol. wt., 232.23; usual dose, 60–250 mg/day; pK_a 7.4; therapeutic concentration, 15–40 mg/l; plasma half-life, 50–150 h; plasma protein binding, 50%; distribution volume, 0.5 l/kg.

Phenobarbital was the first effective organic anti-epileptic agent (139). Clinically, phenobarbital is useful, as it is effective against various forms of partial and generalized seizures, but not against absence seizures. Phenobarbital is as effective as carbamazepine and phenytoin, though it is not the first choice because of sedation. Its propensity to alter mood and behavior, the occurrence of insomnia, hyperactivity and aggression (in children) limits its use. Long-term use of barbiturates has a negative effect on cognitive functions, especially in children.

Mechanism of action Phenobarbital prolongs inhibitory postsynaptic potentials by increasing the mean chloride channel opening time and hence the duration of GABA-induced bursts of neuronal activity (140).

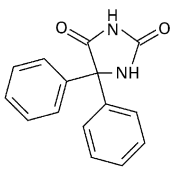
Pharmacokinetics Phenobarbital is well absorbed and approximately 50% of the drug in blood is bound to plasma albumin. The distribution volume is approximately 0.5 l/kg of body weight. The plasma half-life is 50–150 h in adults, longer than that of other anti-epileptics. In neonates the half-life is somewhat longer, while in children it is shorter and more variable. However, once-daily dosing is possible with this drug (1–5 mg/kg for adults and 3–6 mg/kg for children). Approximately 25% is excreted unchanged in the urine. The remaining 75% is metabolized by oxidation and conjugation by the hepatic microsomal enzymes, mostly *para*hydroxylation of the phenyl ring (CYP2C9). The pK_a of phenobarbital is 7.4, which means that the tissue distribution and renal excretion is partly pH-dependent.

Drug interactions Phenobarbital accelerates not only its own metabolism, but also that of many other lipid-soluble drugs. The enzymes induced are mostly CYP3A4 and CYP2C. There is a drug interaction with valproic acid (see valproic acid) and pheneturide.

Drug concentrations The generally accepted target concentration lies between 15 and 40 mg/l. The plasma level at which 50% of patients respond well is approximately 20 mg/l (141). During long-term therapy in adults, the plasma concentration averages 10 mg/l per daily dose of 1 mg/kg; in children the value is 5–7 mg/l per 1 mg/kg. The relationship between the plasma concentration of phenobarbital and its adverse effects varies with the development of tolerance. Sedation, nystagmus and ataxia are usually absent at concentrations below 30 mg/l during long-term therapy, but adverse effects may be apparent for several days at lower concentrations when therapy is initiated or whenever the dosage is increased. Plasma concentrations above 50 mg/l may cause coma, while 80 mg/l may be lethal in the non-tolerant individual.

Analytical methods Immunoassay is or was the mainstay. Many different manufacturers provide assays, but since phenobarbital is not a first line of therapy, these can be relatively expensive since the kits are rarely fully used prior to their expiration. Numerous liquid chromatographic assays are available. As mentioned in the Introduction, most methods use reversed-phase columns with acetonitrile/aqueous buffer and UV absorption at 210 nm or lower, or with filter photometry at 254 nm. Limits of quantitation are approximately 1 mg/l and limits of detection approximately 0.6 mg/l. GC techniques with NPD or FID are also used (142) and have lower limits of detection (0.1 mg/l).

Phenytoin



5,5-Diphenyl-2,4-imidazolidinedione: mol. wt., 252.27; usual dose, 200–500 mg daily; pK_a 8.3; therapeutic concentration, 10–20 mg/l; plasma half-life, 12–36 h; plasma protein binding, approximately 90%; distribution volume, 0.5–1.2 l/kg.

Phenytoin remains a first-line drug for all types of epilepsy except for absence seizures. It was first synthesized in 1908, but its anticonvulsant activity was not discovered until 1938 when a search for non-sedative structural relatives of phenobarbital was carried out (143, 144). Clinically, in spite of its many side effects and unpredictable pharmacokinetic behavior, phenytoin remains a useful anti-epileptic drug, as it is effective against various forms of partial and generalized seizures. As mentioned above it is not effective against absence seizures, which may even worsen with phenytoin intake. Phenytoin can cause a range of dose-related and idiosyncratic adverse effects. Reversible changes such as acne and hirsutism are often mild. Fosphenytoin is a water-soluble phenytoin pro-drug that can be given by intramuscular or intravenous injection and appears to be less irritating than the parent drug (see Miscellaneous therapeutic agents below) (57). Its faster rate of i.v. administration is its main advantage over phenytoin.

Mechanism of action Phenytoin exerts a stabilizing effect on excitable membranes of a variety of cells, including neurons and cardiac myocytes. It appears to act by inducing a voltage- and use-dependent blockade of sodium channels (145, 146).

Pharmacokinetics The pharmacokinetic characteristics of phenytoin are markedly influenced by its limited aqueous solubility and by its dose-dependent elimination. Phenytoin is slowly but well absorbed when given orally, and in plasma approximately 80–90% is bound to albumin. A greater fraction remains unbound in the neonate, in patients with hypoalbuminemia and in uremic patients. The distribution volume is approximately 0.6 l/kg. Phenytoin is approximately 90% metabolized in the liver by CYP2C9 and CYP2C19 (the mixed-function oxidase system) and subsequently excreted, mainly as the glucuronide. Less than 2% is excreted unchanged in the urine. The rate of metabolism is correlated with the plasma concentration when the concentration is low. Metabolism can be saturated above 10 mg/l and then a small increase in the amount of phenytoin administered can cause a substantial rise in the plasma level and result in symptoms of intoxication. Phenytoin causes enzyme induction, and thus increases the rate of metabolism of other drugs. The plasma half-life is very variable from patient to patient and lies between 12 and 36 h.

Drug interactions Phenytoin can induce the oxidative metabolism of many lipid-soluble drugs, including carbamazepine, valproic acid, ethosuximide, anticoagulant agents, corticosteroids, benzodiazepines, cyclosporin, tacrolimus and oral contraceptives containing ethinyl estradiol and progestagens. Rifampicin and ritonavir can diminish phenytoin concentrations

by increasing its hepatic clearance. Because the metabolism of phenytoin is saturable, inhibitory interactions are very likely to have neurotoxic effects. Drugs that inhibit the metabolism of phenytoin include allopurinol, amiodarone, chloramphenicol, cimetidine, co-trimoxazole, disulfiram, fluconazole, isoniazid, itraconazole, omeprazole, oral anticoagulants, warfarin and some sulfonamides (12, 13). Interactions involving protein-binding displacement are not clinically important unless the displacement is accompanied by enzyme inhibition, producing a significant rise in plasma phenytoin concentrations, as is the case with valproic acid (47).

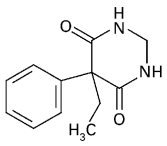
Drug concentrations Approximately 50% of patients exhibit a favorable therapeutic effect with drug concentrations of 8–10 mg/l. Concentrations exceeding 20 mg/l are often accompanied by neurotoxic symptoms (drowsiness, dysarthria, tremor and cognitive difficulties). At concentrations above 25 mg/l, nystagmus, ataxia and diplopia develop; at 30 mg/l, somnolescence, lethargy and asterixis; and at 50 mg/l, extreme lethargy and sometimes coma (12, 23, 46). With hypoalbuminemia (<3 g/dl) signs of toxicity appear at lower concentrations due to a free fraction increase with a 1% per 0.1 g albumin decrease (12). To evaluate this, a method, named after Sheiner and Tozer was developed to evaluate an apparent total phenytoin concentration as a function of the albumin concentration (147):

$$C_n = \frac{C_0}{0.2\mathrm{Alb} + 0.1}$$

where C_0 is the total phenytoin concentration measured (mg/l), Alb is the albumin concentration (g/dl), and C_n is the total phenytoin concentration that would have been observed with normal albumin concentrations and, therefore, 90% of the drug bound to protein. This empirical adjustment is widely adopted (148).

Analytical methods Various immunoassays are employed since phenytoin is an often-used drug that has critical pharmacokinetics. Fluorescence polarization immunoassay, nephelometric or turbidimetric inhibition, linked enzyme-catalyzed reactions and other techniques offer quick, sensitive and reproducible results (55). However, p-hydroxy-phenytoin, an inactive metabolite when accumulated in renal failure, can be recognized by the antibodies, thereby falsifying the true concentration. Numerous HPLC methods for phenytoin have been published (37, 38). Treatments for refractory epilepsy with a second drug or a combination of drugs indicate the need for simultaneous chromatographic measurement (39, 40, 42).

Primidone



5-Ethyldihydro-5-phenyl-4,6(1H,5H)-pyrimidinedione: mol. wt., 218.25; usual dose, 750–1500 mg/day; max. dose, 2000 mg/day; therapeutic concentration, 8–12 mg/l (primidone), 15–40 mg/l (phenobarbital); plasma half-life, 5–16 h (primidone), 50–150 h (phenobarbital); plasma protein binding, <20%, distribution volume, 0.6 l/kg (primidone).

The anti-epileptic activity of primidone is achieved by three molecules, primidone and its two metabolites, phenobarbital and phenylethylmalonamide (PEMA). Primidone resembles phenobarbital in its antiseizure effects in many laboratory in vitro models on isolated brain slices, but is less potent. The usual daily dose (750–1500 mg/day) is higher than that for phenobarbital (60–250 mg/day). Like phenobarbital, primidone is effective against generalized tonic-clonic and both simple and complex partial seizures. It is ineffective against absence seizures, but is sometimes useful in treating myoclonic seizures in children. Adverse effects and symptoms of toxicity may include sedation, vertigo, dizziness, nausea, vomiting, ataxia, diplopia and nystagmus.

Primidone was withdrawn from sale in January 2004 in most western European countries. If primidone treatment is discontinued too quickly, withdrawal seizures may appear, some of which may be severe. If a simple and quick substitution is essential, primidone may be replaced by its main metabolite, phenobarbital. Conversion can take place by increasing the daily phenobarbital dose by 25 mg/week while reducing primidone by 250 mg/week. The concentration of phenobarbital in the blood should remain in the therapeutic range of 15–40 mg/l. In patients who have not suffered an epileptic seizure for many years, gradually discontinuing primidone medication, as for any anticonvulsant, may be considered (149).

Pharmacokinetics Primidone is well absorbed from the gastrointestinal tract and is an inducing agent of liver enzymes. It is mainly metabolized in the liver to its two active metabolites, phenobarbital and PEMA. As mentioned earlier, approximately 50% of phenobarbital is bound to plasma proteins, whereas only a small fraction of primidone and PEMA is bound. The plasma half-life of primidone varies between 5 and 16 h, and that of PEMA, between 16 and 50 h. During long-term therapy, both PEMA and phenobarbital (half-life in adults approx. 100 h) accumulate. Approximately 92% of the daily dose of primidone is excreted in the urine in 24 h, of which 15–65% is unchanged drug, 16–65% is PEMA and 1–8% is phenobarbital or its hydroxylated metabolites and conjugates (150).

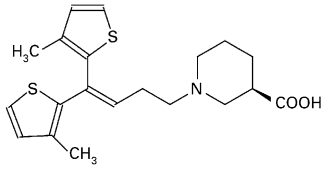
Drug interactions See phenobarbital.

Drug concentrations The relationship between primidone dose and the concentration of the drug and its metabolites is subject to great individual variability. During long-term monotherapy, the plasma concentrations of primidone and phenobarbital average 1 and 2 mg/l, respectively, per daily dose of 1 mg/kg of primidone (46). The plasma concentration of PEMA lies somewhere in between. The ratio of phenobar-

bital/primidone increases in combination therapies with other anticonvulsant drugs or while treating children (141). The optimal plasma concentration of primidone lies between 8 and 12 mg/l, that for PEMA, between 7 and 10 mg/l, and for phenobarbital the concentration is optimal between 15 and 40 mg/l.

Analytical methods Since phenobarbital is the major metabolite, the latter immunoassay can be used. The usual method is, however, HPLC. Simultaneous measurement of primidone and its active metabolites is possible in one run (see Table 2). Since primidone is to be withdrawn from the market, it is not worth investing research and development time in the validation of a technique to monitor it.

Tiagabine



(3R)- 1 -[4, 4-Bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic acid: mol. wt., 375.56; usual dose, 30–50 mg/day; pK_a 3.3, 9.4; therapeutic concentration, 10–100 μg/l; plasma half-life, 7–9 h (adults); plasma protein binding, 96%; distribution volume, 1–1.3 l/kg.

Tiagabine is indicated for adjunctive treatment of adults and children aged above 12 years with partial epilepsy. Adverse effects of tiagabine include dizziness, fatigue, somnolence and gastrointestinal upset.

Mechanism of action Tiagabine is a lipophilic derivative of nipecotic acid that can cross the blood-brain barrier. It is a strong and selective inhibitor of the reuptake of GABA, the most important inhibiting neurotransmitter. Activation of the $GABA_A$ receptor effects inhibition of the postsynaptic cell by increasing the flow of chloride ions into the cell, which tends to hyperpolarize the neuron (151, 152).

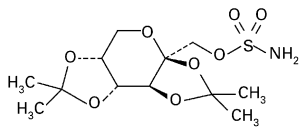
Pharmacokinetics Tiagabine is completely absorbed from the gastrointestinal tract. Approximately 96% of tiagabine is bound to plasma proteins and the drug can be displaced from its binding sites by valproate, (104), salicylates and naproxene (153). It is mainly metabolized in the liver by the CYP3A system. Less than 1% is excreted unchanged in the urine and 14% as inactive metabolites. Approximately 63% is excreted in the feces (154). The drug has no inducing or inhibiting effects on liver enzymes. The elimination half-life is quite variable and ranges from 4 to 13 h with an average of approximately 7 h (155, 156).

Drug interactions Whereas tiagabine is neither an enzyme inducer nor an inhibitor, other drugs can induce its metabolism. Because the metabolism of tiagabine depends on CYP3A4, concurrently administered enzyme-inducers such as phenytoin, carbamazepine and phenobarbital considerably reduce tiagabine half-life and accelerate its clearance (151, 156). Low tiagabine doses (<8 mg/day) did not alter the plasma concentrations of ethinyl estradiol, levonorgestrel or desogestrel (157).

Drug concentrations The short half-life, low plasma concentration and extensive plasma protein binding (with consequent variability in the fraction of unbound, pharmacologically active drug) complicates TDM for this drug (104). Although trough concentrations >40 μg/l were reported to be associated with improved seizure control in one study (158), further investigations are clearly indicated (104).

Analytical methods Concentrations of tiagabine are in the μg/l range, whereas most other anti-epileptic drugs are in the mg/l range. Consequently, its determination is demanding (83). Only a few methods have been published: GC with MSD (159) and a HPLC method with electrochemical detection (160). A stereoselective method has also been published (161).

Topiramate



2, 3: 4, 5-Bis-O-methylethylidine-β-D-fructopyranose sulfamate: mol. wt., 339.36; usual dose, 200–400 mg/day; max. dose, 1000 mg/day; therapeutic concentration, 5–25 mg/l; plasma half-life, 20–30 h; plasma protein binding, 13–17%; distribution volume, 0.6–0.8 l/kg.

Topiramate, a sulfamate derivative of a naturally occurring monosaccharide, is used for the adjunctive treatment of partial seizures, with or without secondary generalization, in adults and children (aged 2–16 years) (83). It is also used for the treatment of Lennox-Gastaut syndrome. Possible adverse effects of topiramate are fatigue, tremor, ataxia, dizziness, headache and weight loss. Probably due to its weak carbonic anhydrase activity and the consequent mild renal tubular acidosis, the risk of calcium nefrolithiasis is two–four-fold higher than expected in the general population (162).

Mechanism of action Topiramate modulates voltage-dependent sodium channels and potentiates the GABA-ergic inhibition at a novel site on the $GABA_A$ receptor (163). Like zonisamide (see below) and acetazolamide (see Miscellaneous therapeutic agents) it is also a weak inhibitor of carbonic anhydrase.

Pharmacokinetics Topiramate is orally well absorbed. Although the drug is not significantly bound to plasma proteins (13–17%), it binds extensively to erythrocytes. Because of the saturable nature of red cell binding, the plasma/whole blood concentration ratio is concentration-dependent (104). Only 20% of topiramate is metabolized by oxidation. At least 80% is excreted in the urine (mainly in an unchanged form and some inactive metabolites). The elimination half-

Table 4 Procedure for gas chromatographic measurement of topiramate.

Sample preparation	Mix 50 μl of sample, 20 μl of internal standard, 150 μl of phosphate buffer (20 mmol/l, pH 7.4) and 2500 μl of hexane; shake for 10 min, then centrifuge (2000×*g*) for 5 min. Add to 200 μl of the underlying phase 200 μl of $NH_4H_2PO_4$ (100 mmol/l, pH 4), vortex mix for 15 s, then add 1500 μl of MTBE, shake for 10 min, then centrifuge (2000×*g*) for 5 min. Collect the ether phase in a new tube and re-extract the aqueous phase with 1500 μl of MTBE, shake for 10 min, then centrifuge (2000×*g*) for 5 min. Combine the ether phases and evaporate to dryness at 40°C; dissolve the residue in 50 μl of 10:90 methanol/toluene. Inject 1 μl.
Chromatography	
Column	HP-5MS fused silica, 12.5 m×0.2 mm i.d., 0.33 μm film thickness.
Flow	He 0.8 ml/min.
Injection	Splitless at 250°C.
Oven	Initial 95°C for 1 min; 40°C/min to 240°C for 2 min; 20°C/min to 310°C for 4 min.
NP detector	310°C, H_2 flow 2 ml/min, air flow 50 ml/min.

MTBE, methyl-*tert*-butylether.

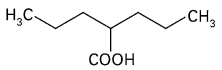
life of topiramate in healthy volunteers is 20–30 h (93).

Drug interactions Other enzyme-inducing anti-epileptic drugs such as phenytoin, phenobarbital and carbamazepine can enhance the metabolism of topiramate. Concurrent use of valproate and topiramate may result in a slight decrease (15%) in the concentration of the latter (164). Topiramate itself is a weak inducer of CYP enzymes and, as such, it can decrease ethinyl estradiol concentrations by approximately 30% (165). When phenytoin metabolism is at or near saturation, topiramate can cause an increase in phenytoin serum concentrations, probably by inhibiting CYP2C19 (166, 167).

Drug concentrations There is a linear relationship between topiramate dose and serum concentration (83). Topiramate has been extensively studied and several reports indicate that seizure-free duration was significantly correlated with topiramate concentration (168–170). Side effects and encephalopathic features become prominent at concentrations >20 mg/l.

Analytical methods A fluorescence polarization immunoassay (FPIA) from Oxis International can be used on Abbott instruments, allowing easy measurement of topiramate in plasma or serum. Several capillary GC procedures are described using either FID (171) or NPD (172, 173). HPLC MSD methods are also described (174, 175). See Table 4 for the GC procedure used in our laboratory.

Valproic acid



2-Propyl-pentanoic acid: mol. wt., 144.21; usual dose, 10–35 mg/kg per day (adult), 15–60 mg/kg per day (children); pK_a 4.6; therapeutic concentration, 50–100 mg/l; plasma half-life, 8–15 h (adults), 6–10 h (children 2–10 years); plasma protein binding, 90%; distribution volume, 0.15–0.4 l/kg.

Valproic acid is a simple branched-chain monocarboxylic acid. It is effective in patients with all types of seizures, and especially in those with idiopathic generalized epilepsy (176). It has many effects and probably works by different mechanisms (177, 178). Valproic acid can take several weeks to become fully effective. In some countries it is marketed as a prophylaxis for migraine. Another use is in the treatment of the manic phase of bipolar disorders. Common side effects include dose-related tremor, weight gain due to appetite stimulation, thinning of the hair and menstrual irregularities (13). Sedation is unusual, although stupor and encephalopathy occur in rare cases, possibly as a consequence of an underlying deficiency of carnitine (179). The incidence of hepatotoxicity as microvesicular steatosis is less than 1 in 20,000 (180) but its relevance is limited to children (<3 years) in several anti-epileptics (181).

Mechanism of action The drug acts by limiting sustained repetitive neuronal firing through voltage- and use-dependent blockade of sodium channels (177). It also causes a significant increase in the GABA content of the brain by inhibition of enzymes that inactivate GABA, and it probably enhances the action of GABA by a postsynaptic action. Because valproic acid can take several weeks to become fully active, the dose should not be increased sooner (182).

Pharmacokinetics Valproic acid is well absorbed orally. It is mainly metabolized in the liver by β-oxidation (30%) by CYP2C9, CYP2C19 and CYP2A6 and glucuronidation (40%). There are many known metabolites, none of which are pharmacologically active. The apparent distribution volume is 0.15–0.4 l/kg. The plasma half-life lies between 8 and 15 h for adults and is somewhat shorter in infants (6–10 h). The binding by plasma proteins is dose-dependent (approx. 90%). The free fraction of valproic acid ranges from 5 to 15%. Valproic acid is mainly excreted in the urine, 70% as glucuronide and approximately 7% as unchanged valproic acid. Since valproic acid is metabolized to several ketone bodies, urine testing for the latter can be positive (183).

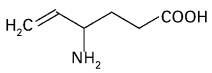
Drug interactions Valproic acid does not induce hepatic microsomal enzymes. Therefore, it enhances neither its own metabolism nor that of other drugs.

However, valproic acid can inhibit hepatic metabolic processes, including oxidation, conjugation and epoxidation (47). Targets include other anti-epileptic drugs, particularly phenytoin, phenobarbital, carbamazepine-10,11-epoxide and lamotrigine. This is probably due to the greater affinity of carboxylic acids for microsomal liver enzymes. However, enzyme induction by other anti-epileptics can enhance the metabolism of sodium valproate and shorten its half-life. Valproic acid can displace other drugs from its binding sites on albumin, as is the case with phenytoin. A metabolite of aspirin, however, displaces valproic acid from its binding sites (141, 184).

Drug concentrations Although plasma concentrations of valproic acid vary widely due to a rather short half-life, routine monitoring is only helpful when correlated with clinical effects. The protein binding of valproic acid is high (~95% at a plasma level of 80 mg/l) and the relative free fraction increases at higher dosages. Due to a pK_a value of 4.6, acidosis provokes a longer half-life. Approximately 50% of patients show good therapeutic effect at a concentration of 80 mg/l. Only 20% of patients respond well to a concentration of 50 mg/l, which in monotherapy is the equivalent to a dosage of 15 mg/kg per 24 h. Generally, in monotherapy, the ratio between the plasma level (mg/l) and the dose expressed in mg/kg per day is approximately 3.5 (141).

Analytical methods Various immunoassays are available and since valproic acid lacks UV absorption it cannot be assayed with common HPLC simultaneous anticonvulsant procedures. However, it can be derivatized to form a UV-active product (185, 186) to allow HPLC determination. GC methods with FID (187) have attained limits of detection of 0.2–1 mg/l (150). GC with MSD allows limits of detection of between 0.0028 and 0.018 mg/l (188).

Vigabatrin



4-Amino-5-hexenoic acid (γ-vinyl-γ-aminobutyric acid): mol. wt., 129.16; max. dose, 3 g/day (adults); pK_a 4.02, 9.72; expected concentration, 1–36 mg/l; plasma half-life, 6–8 h (adults); plasma protein binding, absent; distribution volume, 0.8 l/kg.

Vigabatrin appears to be most effective in partial seizures and in numerous difficult-to-treat syndromic epilepsies. Adverse effects may include drowsiness, headache, fatigue, irritability, depression, dizziness, confusion and weight gain. Recently, irreversible visual-field defects have been reported in approximately one-third of treated patients (189–191) which limits the use of this drug.

Mechanism of action Vigabatrin, a structural analogue of γ-vinyl GABA, selectively inhibits and irreversibly binds to GABA-transaminase and thereby elevates cerebral GABA levels. The drug is a racemate mixture of S(+) and R(−) isomers. However, the pharmacological activity and toxic effects of vigabatrin are associated only with the S(+) enantiomer.

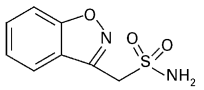
Pharmacokinetics Vigabatrin is well absorbed orally. It does not bind to plasma proteins. From 70 to 100% is excreted unchanged in the urine and minor urinary metabolites have been detected. The elimination half-life of vigabatrin in serum is 6–8 h. The effect of vigabatrin is related to the synthesis of GABA.

Drug interactions Vigabatrin does not induce liver enzymes. Because it is neither metabolized nor bound to serum proteins, pharmacokinetic interactions with concurrently administered drugs are minimal. However, a decrease in the plasma levels of phenytoin of 16–33% has been reported (192).

Drug concentrations Plasma vigabatrin concentrations are linearly related to vigabatrin dosage. Despite earlier reports of a relationship between serum GABA concentrations and the clinical response, a recent study has failed to confirm these findings (83). However, serum vigabatrin concentrations as a check on compliance may be useful. For doses between 1000 and 3000 mg/day, the expected serum level of vigabatrin is 1–36 mg/l (19, 193).

Analytical methods Because vigabatrin irreversibly inhibits GABA-transaminase, there is no correlation between its effect and the plasma concentration. The action of the drug is clearly dependent on the synthesis of GABA and inversely on the regeneration of the GABA-transaminase. Since the future use of vigabatrin is doubtful, stereo-selective methods for differentiating between R(−) and S(+) enantiomers will not be developed. Current assay methods do not differentiate between the active and inactive isomers. HPLC procedures with derivatization that allow the simultaneous quantification of vigabatrin and gabapentin have been published (194, 195). Several selective HPLC methods with fluorescence detection are also available (196, 197).

Zonisamide



1,2-Benzisoxazole-3-methanesulfonamide: mol. wt., 212.23; max. dose, 600 mg/day; pK_a 10.2; therapeutic concentration, 10–38 mg/l; plasma half-life, 50–70 h; plasma protein binding, 40–60%; distribution volume, 1.45 l/kg.

Zonisamide is licensed for the adjunctive treatment of partial seizures with or without generalization in adults with epilepsy. It is also effective in West's and Lennox-Gastaut syndromes. Side effects include somnolence, astheny, tremor, ataxia, tinnitus, nausea, faryngitis, vomiting, pruritus, cough, diminished visual capacity and coordination problems.

Table 5 Brand names of anti-epileptic drugs in Europe.

Drug	Brand name
Carbamazepine	Carba AbZ (D)
	Carba von ct (D)
	Carbabeta (D)
	Carbadura (D)
	Carbaflux (D)
	Carbagamma (D)
	Carbagen (UK)
	Carbamazepina Alter (E)
	Carbamazepina Farmabion (E)
	Carbamazepina Mundogen (E)
	Carbamazepina Normon (E)
	Carbamazepina Ratiopharm (IT)
	Carbamazepina Teva (IT)
	Carbamazepina MG Alter (P)
	Carbamazepina MG Merck (P)
	Carbamazepine A (NL)
	Carbamazepine CF (NL)
	Carbamazepine Dumex (NL)
	Carbamazepine Gf (NL)
	Carbamazepine Katwijk (NL)
	Carbamazepine Merck (B, NL)
	Carbamazepine PHC (NL)
	Carbamazepin AZU (D)
	Carbamazepin AL (D)
	Carbamazepin Heumann (D)
	Carbamazepin neuraxpharm (D)
	Carbamazepin Stada (D)
	Carbamazepine Alpharma (UK)
	Carbamazepne Generics (UK)
	Carbamazepin-ratiopharm (D)
	Carbamazepin-RPh (D)
	Carbamazepin-TEVA (D)
	Carbarun Arun (UK)
	Carbium (D)
	Depletin (A)
	Epimaz (UK)
	Espa-lepsin (D)
	Finlepsin (D)
	Fokalepsin (D)
	Gericarb (IRL)
	Hermolepsin (S)
	Karbamazepin Nycomed Pharma (DK, N)
	MP Carbamazepine (NL)
	Neurotol (FIN)
	Neurotop (A)
	Sirtal (A, D)
	Tegretal (D)
	Tegretol (A, B, DK, FIN, F, GR, IRL, IT, NL, N, P, E, S, CH, UK)
	Tegretol Paranova (DK)
	Temporal (IRL)
	Teril (UK)
	Timonil (D, NL, CH, UK)
	Trimonil (DK, FIN, N, S)
Clobazam	Castilium (P)
	Frisium (A, B, DK, FIN, D, IRL, IT, NL, UK)
	Noiafren (E)
	Urbanil (P)
	Urbanyl (F, CH)
Clonazepam	Antelepsin (D)
	Iktorivil (S)
	Rivotril (A, B, DK, FIN, F, D, GR, IRL, IT, NL, N, P, E, CH, UK)
	Rivotril Orifarm (DK)
	Rivotril Paranova (DK)
Ethosuximide	Emeside (UK)
	Ethymal (NL)
	Etosuximida Faes (E)
	Petinimid (A, CH)
	Petnidan (D)
	Suxilep (D)
	Suxinutin (A, FIN, D, S, CH)
	Zarondan (DK, N)
	Zarondan Paranova (DK)
	Zarontin (B, F, GR, IRL, IT, NL, E, UK)
Felbamate	Taloxa (A, B, F, D, IT, NL, N, P, E, S, CH)
Gabapentin	Aclonium (IT)
	Equipax (E)
	Gabapentin 1A Farm (DK)
	Gabapentin DuraScan (DK)
	Gabapentin Pfizer (DK)
	Gabapentin Pliva (DK, N)
	Gabapentin UNP (DK)
	Gabapentina Alter (E)
	Gabapentina Amicomb (E)
	Gabapentina Bexal (E)
	Gabapentina Combaxona (E)
	Gabapentina Combidox (E)
	Gabapentina Combino Pharm (E)
	Gabapentina Combuxim (E)
	Gabapentina Fluoxcomb (E)
	Gabapentina Kern (E)
	Gabapentina Merck (E)
	Gabapentina Pharmagenus (E)
	Gabapentina Ratiopharm (E)
	Gabapentina Rubio (E)
	Gabapentina Vegal (E)
	Gabatur (E)
	Neuril (DK)
	Neurontin (A, B, FIN, F, D, GR, IRL, IT, NL, N, P, E, S, CH, UK)
Lamotrigine	Crisomet (E)
	Labileno (E)
	Labileno Orifarm (DK)
	Lamictal (A, B, DK, FIN, F, D, GR, IRL, IT, NL, N, P, E, S, CH, UK)
	Lamictal Orifarm (DK)
	Lamictal Paranova (DK)
	Lamotrigine GW (NL)
Levetiracetam	Keppra (A, B, DK, F, D, GR, IRL, IT, NL, N, P, E, S, CH, UK)
Oxcarbazepine	Apydan (DK, FIN)
	Elipsine (E)
	Timox (D)
	Tolep (IT)
	Trileptal (A, B, DK, FIN, F, D, GR, IRL, IT, NL, N, E, S, CH, UK)
Pheneturide	Benurinde (CH)
	Laburide (B)
Phenobarbital	Alepsal (F)
	Aparoxal (F)
	Aphenylbarbit (CH)
	Barbitan (GR)
	Bialminal (P)
	Comizial (IT)
	Epanal (F)
	Fenemal (B, S)
	Fenemal Apotek (N)
	Fenemal Nycomed Pharma (DK, N)
	Fenobarbital Gf (NL)
	Fenobarbital PCH (NL)
	Fenobarbital-Natrium NAF Apotek (N)
	Gardenal (B, F, GR, IT, E, UK)
	Kaneuron (F)
	Lenterules de phenobarbital (F)
	Lepinal (D)

Drug	Brand name
	Lepinaletten (D)
	Lumidrops (GR)
	Luminal (D, IT, P, E, CH)
	Luminaletas (P, E)
	Luminaletten (D, IT, P)
	Phenaemal (D)
	Phenaemaletten (D)
	Phenobarbital Thornton & Ross (UK)
	Phenobarbitone Alpharma (UK)
	Phenobarbitone Boots (UK)
Phenytoin	Aurantin (IT)
Phenytoin sodium	Epanutin (A, B, D, GR, IRL, NL, E, S, CH, UK)
	Epilan (A)
	Di-Hydan (F)
	Dilantin (F)
	Dintoina (IT)
	Diphantoine (B, NL)
	Epilantine (CH)
	Epinat Nycomed Pharma (N)
	Fenatoin Recip (S)
	Fenitoina Combino Pharm (E)
	Fenytoin Apotek (N)
	Fenytoin Nycomed Pharma (DK)
	Hidantina (P)
	Hydantin (FIN)
	Lehydan (S)
	Neosidantoina (E)
	Phenhydan (A, D, CH)
	Phenytoin AWD (D)
	Phénytoine-Gerot (CH)
	Prodilantin (F)
	Sinergina (E)
	Zentropil (D)
Primidone	Cyral (A)
	Liskantin (D)
	Mylepsinum (D)
	Mysoline (B, FIN, F, GR, IRL, IT, NL, N, P, E, S, CH, UK)
	Mysoloine (A)
	Primidon Holsten (D)
	Primidon Era (DK)
	Resimatil (D)
Tiagabine	Gabitril (A, B, DK, FIN, F, D, GR, IRL, IT, P, E, CH, UK)
Topiramate	Epitomax (F, NL)
	Epitomax Orifarm (DK)
	Topamac (GR)
	Topamax (A, B, D, IRL, IT, NL, P, E, CH, UK)
	Topimax (DK, N, FIN, S)
	Topiramat Paranova (DK)
Valproic acid	Absenor (FIN, S)
	Aurantin (IT)
	Convulex (A, B, D, NL, CH, UK)
	Convulsofin (D)
	Delepsine (DK)
	Depakine (A, B, DK, F, GR, IT, NL, N, P, E, CH)
	Depakine Paranova (DK)
	Depakote (F)
	Depamag (IT)
	Depamide (F, GR, IT, E)
	Deprakine (DK, FIN, N)
	Diplexil (P)
	Epilim (IRL, UK)
	Epival (D, UK)
	Epsa-valept (D)
	Ergenyl (D, S)
	Leptilan (D)
	Leptilanil (A)
	Micropakine (F)
	Milzone (E)
	MP Na valproaat (NL)
	Mylproin (D)
	Na valproaat Cf (NL)
	Na valproaat Chrono (NL)
	Na valproaat Cumex (NL)
	Na valproaat Gf (NL)
	Na valproaat PCH (NL)
	Orfiril (DK, FIN, D, NL, N, S, CH)
	Orlept (UK)
	Propymal (NL)
	Sodium valproate Alpharma (UK)
	Sodium valproate Generics (UK)
	Valpro beta (D)
	Valproat AZU (D)
	Valproat-neuraxpharm (D)
	Valproat-RPh (D)
	Valprodura (D)
	Valproflux (D)
	Valproinsäure von ct (D)
	Valproinsäure-ratiopharm (D)
	Valprolept (D)
	ValproNa-TEVA (D)
	Sabril (A, B, F, D, GR, IRL, IT, NL, P, CH, UK)
Vigabatrin	Sabrilex (DK, FIN, NL, N, E, S)
	Sabrilex Orifarm (DK)
Zonisamide	Zonegran

Mechanism of action Zonisamide prevents repetitive neuronal firing by blocking voltage-sensitive sodium and T-type calcium channels. It does not potentiate the synaptic activity of GABA (198). Its spectrum of activity appears to be similar to that of phenytoin and carbamazepine. Several open studies in Japan have shown that the drug is effective in patients who have partial seizures alone or with secondarily generalized seizures (199). It is also a weak inhibitor of carbonic anhydrase, similar to topiramate and acetazolamide (see Miscellaneous therapeutic agents). Carbonic anhydrase inhibitors induce mild systemic renal tubular acidosis and increase the risk of calcium nephrolithiasis (162). In the USA, eligible patients have to be screened for a predisposition to renal calculi (57).

Pharmacokinetics Following oral ingestion, zonisamide is rapidly and almost completely absorbed. The protein binding is between 40 and 60% and the drug is preferentially taken up by erythrocytes, resulting in an eight-fold higher concentration than in plasma. The elimination half-life varies between 50 and 70 h in plasma and 105 h in red blood cells (RBCs). Like topiramate, zonisamide binding to RBCs is saturable. The drug exhibits linear pharmacokinetics up to daily doses of 10–15 mg/kg and is extensively metabolized

by acetylation and conjugation. Auto-induced metabolism of zonisamide is mediated by CYP3A (200, 201).

Drug interactions Zonisamide is initially reported not to induce CYP450 isoenzymes, except for CYP3A. Other enzyme-inducing anti-epileptic drugs, such as phenytoin and carbamazepine, shorten its elimination half-life (202). Controversial results have been reported concerning the effect of zonisamide on the ratio of carbamazepine and its 10,11-epoxide metabolite when the two drugs are concomitantly administered (85).

Drug concentrations Plasma concentrations of 10–38 mg/l have been associated with seizure control (203). Several other studies have proposed narrower therapeutic ranges (204, 205) and in a preliminary study it was suggested that concentrations >30 mg/l provoked cognitive dysfunction. There is a considerable overlap of serum concentrations between seizure-free patients, non-responders and those associated with side effects (203, 205, 206). Clear correlation between the concentration of the drug and its therapeutic and toxic effects is still lacking.

Analytical methods The conjugated double bond of zonisamide allows HPLC with UV detection. Several conventional methods for simultaneous measurement of anti-epileptic drugs including zonisamide have been published (207). Dedicated methods with a lower limit of quantitation and using solid-phase extraction are also available (208–210). There is also a method described based on capillary electrophoresis, also called micellar electrokinetic capillary chromatography (211).

Miscellaneous therapeutic agents

The drugs reviewed here are either infrequently used or are indicated for less important epileptic syndromes or for refractory epilepsy (10, 12, 14, 46, 57, 150, 212).

Acetazolamide

Mol. wt., 222.3; max. dose, 1000 mg/day; pK_a 7.2, 9.0; therapeutic concentration, 10–15 mg/l; plasma half-life, 13 h; plasma protein binding, 90–95%; distribution volume, 0.2 l/kg.

This non-bacteriostatic sulfonamide, which is best known as a carbonic anhydrase inhibitor, is well absorbed from the gastrointestinal tract after oral administration. It increases the blood levels of both carbamazepine and phenobarbital. It is used in partial, myoclonic, absence and primary generalized tonic–clonic seizures not responding to other anticonvulsants; as a second-line drug in juvenile myoclonic epilepsy; and in combination with other anti-epileptics when resistance occurs. Its adverse effects include appetite loss, paresthesias, diarrhea, nausea, vomiting, polyuria, headache and dizziness.

Barbexaclone

Mol. wt., 387.5; max. dose, 400 mg/day; therapeutic concentration, 10–40 mg/l (phenobarbital).

A combination of phenobarbital and L-propylhexedrine, a central stimulant, added to inhibit the sedative effect of phenobarbital. For use and adverse effects, see phenobarbital.

Diazepam

Mol. wt., 284.7; pK_a 3.4; plasma half-life, 21–37 h (diazepam), 40–100 h (desmethyldiazepam); plasma protein binding, 96%; distribution volume, 0.7–2.6 l/kg.

Diazepam is a long-acting 1,4-benzodiazepine, metabolized by CYP2C19 and CYP3A. Its active metabolites are desmethyldiazepam [nord(i)azepam], temazepam, and oxazepam. It is used in status epilepticus and febrile convulsions. Adverse effects include fatigue, drowsiness and ataxia.

Ethadione

Mol. wt., 157.2; max. dose, 2 g/day.

Ethadione is an oxazolidinedione anti-epileptic agent, metabolized to dimethadione. It is used for absence seizures resistant to other therapy.

Fosphenytoin

Mol. wt., 362.3; plasma half-life, 8 min (i.v.), 33 min (i.m.); plasma protein binding, 95–99%.

Fosphenytoin is a phenytoin pro-drug that is given intramuscularly or intravenously. It is less irritating and safer intravenously than the parent drug. It is used in emergency treatment of status epilepticus, prevention and treatment of post-traumatic seizures associated with neurosurgery or head trauma and as a parenteral substitute for oral phenytoin. The plasma protein binding is saturable and fosphenytoin displaces phenytoin from binding sites, so that the free phenytoin fraction increases by approximately 30% while fosphenytoin is hydrolyzed to phenytoin (half-life, 8 min, i.v.). This hydrolysis progresses faster in patients with hypoalbuminemia. For adverse effects, see phenytoin; paresthesias and pruritus are more commonly observed. In overdosage, hypocalcemia and metabolic acidosis occur due to excess phosphate and formaldehyde liberated, respectively.

Lorazepam

Mol. wt., 321.2; pK_a 1.3, 11.5; plasma half-life, 9–24 h; therapeutic concentration, 0.05–0.24 mg/l; plasma protein binding, 90%; distribution volume, 1–2 l/kg.

Lorazepam is an intermediate-acting 1,4-benzodiazepine. It is a sedative hypnotic with a short onset of effects and is more effective than diazepam (longer distribution half-life and shorter elimination half-life). Its metabolites are inactive glucuronides, which tend to accumulate in plasma. It is used in the USA as initial therapy for status epilepticus at a dose of 4 mg/kg for adults and 0.05–0.1 mg/kg for children. It is also

used for sedation in intensive care departments and as a tranquilizer.

Methsuximide (mesuximide)

Mol. wt., 203.2; max. dose, 1.2 g/day; therapeutic concentration, 10–40 mg/l (N-desmethylmethsuximide); plasma half-life, 1–3 h (methsuximide) 36–45 h (N-desmethylsuximide); plasma protein binding, absent.

Methsuximide is a succinimide with similar properties to ethosuximide, but is less potent. It is almost completely absorbed from the gastrointestinal tract and is metabolized in the liver to the N-desmethyl derivative (active metabolite). It shows no interaction with other anti-epileptic drugs. It is used in absence and complex partial seizures and for patients not responding to other anti-epileptics. Adverse effects include gastrointestinal disturbance, drowsiness, fatigue, porphyria and headache.

Methylphenobarbital

Mol. wt., 246.3; max. dose, 600 mg/day; pK_a 7.8; plasma half-life, 50–60 h (methylphenobarbital) 50–150 h (phenobarbital); plasma protein binding, 40–60%; distribution volume, 2–3 l/kg.

Methylphenobarbital is metabolized in the liver to phenobarbital, but has a lower sedative effect. For use and adverse effects see phenobarbital.

Nitrazepam

Mol. wt., 281.3; max. dose, 30 mg/day; pK_a 3.2, 10.8; therapeutic concentration, 0.03–0.07 mg/l; plasma half-life, 17–48 h; plasma protein binding, 85–90%; distribution volume, 2–5 l/kg.

Nitrazepam is an intermediate-acting 1,4-benzodiazepine that is metabolized in the liver to inactive metabolites; its elimination is biphasic. It is used for a variety of seizures occurring in different forms of epilepsy, in the treatment of infantile spasms with hypsarrhythmia (West's syndrome) and infantile myoclonic seizures (Lennox-Gastaut syndrome). Adverse effects include fatigue, drowsiness and ataxia.

Sulthiame

Mol. wt., 290.4; max. dose, 600 mg/day; pK_a 10; therapeutic concentration, 0.5–12.5 mg/l; plasma half-life, 5.5–12 h.

Sulthiame is a carbonic anhydrase inhibitor that can be used for most forms of epilepsy, except absences, as an adjunct to other anti-epileptics. Adverse effects include paresthesias, hyperpnea, gastric disturbances, headache and vertigo. Primidone enhances the adverse effects of sulthiame.

Trimethadione

Mol. wt., 143.1; max. dose, 2.4 g/day; therapeutic concentration, 19–41 mg/l (trimethadione) 350–1033 mg/l (dimethadione, active metabolite; ~20-fold higher and guide for dose adjustment); plasma half-life, 16 h (trimethadione) 5–10 days (dimethadione); plasma protein binding, absent.

Trimethadione is an oxazolidinedione anti-epileptic agent. It is used in absences when other anticonvulsants fail. Adverse effects include drowsiness, photophobia, hemeralopia, nephrotic syndrome, hepatitis, blood disorders, sedation, alopecia, nausea and dizziness.

Conclusions

Due to the nature of epilepsy, it is difficult to monitor its treatment by close observation of the individual patient. In many cases TDM facilitates drug treatment by increasing the effectiveness and safety, as well as reducing treatment costs. TDM allows physicians to monitor the compliance and the consequences of dosage adjustments. Since anti-epileptic treatment is usually prophylactic and lifelong, TDM is justified to avoid the risks of acute and chronic adverse effects.

Although all new anti-epileptic drugs have undergone extensive studies prior to their introduction, in many instances prospective studies are lacking. Accurate therapeutic concentration data can only be obtained from specifically designed studies that investigate the concentration-effect relationship in epileptic patients. In many cases there are no generally accepted target plasma levels and even a considerable overlap of drug levels among responders and non-responders. However, from the data in Table 3 the value of TDM for these newer drugs can be appreciated. The interpretation of trials facilitating TDM should allow improved dosage regimens of mono- and combination therapies for a disabling disease with the potential for disastrous medical and psychological consequences.

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