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Contents

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New Antiepileptic Drugs

A Review of Their Current Status and Clinical Potential

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Contents

Summary

Approximately 20 to 30% of patients with newly diagnosed epilepsy do not have their seizures controlled with currently available antiepileptic drugs. The clinical need for new antiepileptic drugs is therefore clear.

In recent years, as our understanding of the molecular basis of epilepsy has unfolded, several novel candidate antiepileptic drugs have become available for clinical evaluation. The major emphasis has been on the development of more potent and effective antiepileptic drugs, and also drugs with fewer adverse effects than existing therapies. This has resulted in 7 new drugs being licenced around the world in the last 5 years (felbamate, gabapentin, lamotrigine, oxcarbazepine, piracetam, vigabatrin and zonisamide). In addition, 7 other promising drugs are in various stages of development [eterobarb, fosphenytoin, levetiracetam (ubc L059), remacemide, stiripentol, tiagabine and topiramate].

Numerous advantages over existing antiepileptic drugs can be identified for some of these new drugs. A mechanism of action has been determined for lamotrigine, tiagabine and vigabatrin. This may prove particularly useful thera-

peutically since it allows a more rational treatment strategy. Eterobarb, fosphenytoin, oxcarbazepine and remacemide are prodrugs. This is a particular advantage for fosphenytoin, which is metabolised to phenytoin. Gabapentin, piracetam and topiramate are not metabolised and vigabatrin is minimally metabolised. These drugs do not exhibit significant binding to blood proteins. Therefore, these drugs are not susceptible to significant pharmacokinetic drug interactions. Oxcarbazepine also exhibits minimal drug interactions. This is in contrast to felbamate, lamotrigine and stiripentol, drugs with which pharmacokinetic interactions can be clinically problematic.

All drugs, with the exception of piracetam, are effective treatments for partial or secondarily generalised seizures. Piracetam and zonisamide are effective in myoclonus, and felbamate has been licenced for use in children with Lennox-Gastaut syndrome. All 14 drugs have the potential to induce adverse effects, mostly CNS-related. Whilst treatment recommendations can be made for some of the drugs, these cannot be considered definitive since they are based largely on data from controlled clinical studies in highly selected patients. Further treatment recommendations for different seizure types and epilepsy syndromes will inevitably develop as clinical experience with the drugs increases.

1. Why are New Antiepileptic Drugs Needed?

Epilepsy affects approximately 1% of the world population at any one time (about 50 million people worldwide) and is the most common serious neurological condition. In the UK, 30 000 to 35 000 new cases of epilepsy are diagnosed per year, resulting in a prevalence of 300 000 patients nationwide.[1,2] The word 'epilepsy' is derived from the Greek word 'επιλεψια' which means 'to throw oneself'. However, early descriptions of epilepsy included 'the dread disease', 'the sacred disease' and 'the falling sickness', and often the victims were thought to be 'bewitched', 'inflicted by the Gods' or 'possessed'.[3,4] Early treatments included powdered human skull, dragon's blood, liver of wolf, stones of swallows and the gall of a boar dried with urine.

The first effective antiepileptic drugs were potassium bromide and phenobarbital (phenobarbitone).[5,6] The next major advance in the treatment of epilepsy was the introduction of phenytoin in 1938.[7] Following the discovery of phenytoin, there was an impetus for testing the efficacy of putative antiepileptic drugs in animal models of epilepsy. Despite this, only 6 new antiepileptic drugs became widely available between 1938 and 1982 (table I).

Whilst these standard drugs are invaluable in the management of epilepsy, only approximately 70 to 80% of newly diagnosed patients become seizure-free when prescribed these drugs as monotherapy regimens.[8-10] In these patients, acute and chronic CNS adverse effects and idiosyncratic reactions to the drugs are not uncommon. The remaining 20 to 30% of patients who are refractory to these drugs, are usually treated using polytherapy (2 or more antiepileptic drugs) regimens. Although this is

Table I. Major antiepileptic drugs marketed in the UK

Drug	Year introduced
Phenobarbital (phenobarbitone)	1912
Phenytoin	1938
Primidone	1952
Ethosuximide	1960
Carbamazepine	1963
Clonazepam	1974
Valproic acid (sodium valproate)	1974
Clobazam	1982
Vigabatrin	1989
Lamotrigine	1991
Gabapentin	1993
Piracetam	1993

helpful to some patients, it can result in problematic pharmacokinetic and pharmacodynamic drug interactions.[11] In the UK, approximately 80 000 patients have severe treatment-refractory epilepsy, and these patients obtain little benefit from traditional antiepileptic drugs.[2]

In recent years, the ready availability of therapeutic drug monitoring[12,13] has allowed a better understanding of antiepileptic drug pharmacokinetics and how this relates to adverse effects and efficacy. In addition, it has been possible to identify further problems with these drugs. These include common metabolic pathways that can be readily inhibited or induced, saturation kinetics, the development of tolerance, and narrow therapeutic indexes (i.e. the dose required to produce a desirable antiepileptic effect is close to that which may cause toxicity).

The need for new antiepileptic drugs, and preferably for an 'ideal' antiepileptic drug, was recognised in the late-1970s and early-1980s. However, the lack of understanding of the basic neuropathology, neuropharmacology and neurophysiology of epilepsy greatly hindered the development of such ideal drugs. Instead, research was directed towards developing new formulations of the traditional antiepileptic drugs in an attempt to alleviate some of the problematic pharmacokinetic properties of these drugs.[14] Advances in this respect have been the introduction of: (i) 25 and 50mg capsules of phenytoin, which allow progressively smaller incremental doses of the drug appropriate to the plasma concentration increases and saturation elimination; (ii) enteric-coated valproic acid (valproate sodium) tablets to alleviate drug-induced gastrointestinal distress; and (iii) slow release (retard) formulations of carbamazepine, designed to reduce the significant diurnal variation in plasma carbamazepine concentrations. This is required because high peak plasma concentrations of the drug are associated with intermittent toxicity. The avoidance of high peak plasma concentrations also means that higher dosages can be used, with resulting better seizure control.[14]

During the last 20 years, studies of the basic mechanisms of epilepsy have revealed both specific neuronal relationships and many of the neurotransmitters and neuromodulators that are considered important in the control of neuronal excitability. Essentially, 2 major hypotheses of epileptogenesis of partial seizures and generalised convulsions have evolved. First, a hypofunction of the major inhibitory neurotransmitter of the brain, γ-aminobutyric acid (GABA).[15] Secondly, a hyperfunction of the amino acids, glutamate and aspartate, which are the major excitatory neurotransmitters in the brain. These latter neurotransmitters can activate *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and metabotropic receptors.[16] Although both hypotheses have been substantiated experimentally, the clinical translation of these theories has only recently become realised.[17] Typical absences, in contrast, are provoked by GABA acting at $GABA_A$ and $GABA_B$ receptors in the thalamus to activate low threshold calcium currents resulting in thalamo cortical oscillations.[18]

These hypotheses have opened up a new era of molecular design of antiepileptic drugs (the so called 'designer drugs') and several have recently been licenced or are undergoing clinical evaluation. In addition, various designer drugs are presently undergoing preclinical development, and include competitive and noncompetitive NMDA receptor antagonists and modulators of the various allosteric sites of the NMDA receptor complex.[19]

The goal of treatment for patients with epilepsy is to achieve complete seizure control without adverse effects. Also, a good quality-of-life outcome is highly desirable.[20-22] Therefore, an ideal new antiepileptic drug should achieve this, and in addition be effective against all seizure types and require once or twice daily administration. With such a profile polytherapy with other antiepileptic drugs would be unnecessary and, therefore, metabolism and distribution would be minimal considerations. However, for good measure, and because patients with epilepsy would be expected in their lifetime

Table II. Target characteristics of a new antiepileptic drug

- As effective as existing antiepileptic drugs
- Improved therapeutic ratio compared with existing agents (i.e. less toxic in proportion to observed benefit)
- A half-life of 12 to 24 hours, to allow once- or twice-daily administration
- Should not cause drug interactions as a result of inhibition or induction of liver enzymes
- Absence of tolerance or withdrawal problems

to be treated with a variety of drugs for unrelated conditions, the ideal drug should not undergo metabolic degradation and should not bind to blood proteins. This would minimise the possibility of clinically significant pharmacokinetic drug interactions. Unfortunately, such an ideal drug is not a realistic attainment in the foreseeable future. Thus, current drug development is based on the target characteristics listed in table II. Also, as the majority of patients with intractable epilepsy have partial seizures, antiepileptic drug development has been targeted towards this seizure type.

2. New Antiepileptic Drugs

In the last decade, there has been an increase in the availability of putative drugs for clinical evaluation, and clinical trial methodologies have been standardised on a worldwide basis. As a result, since 1989, 6 new antiepileptic drugs have been licenced in Europe (vigabatrin, lamotrigine, gabapentin, oxcarbazepine, felbamate and piracetam), 2 in the US (felbamate and gabapentin) and 1 in Japan (zonisamide).

In this review, 14 new antiepileptic drugs are considered, and these are discussed in alphabetical order. For each drug we briefly describe: (a) its anticonvulsant profile in animal seizure models and, where known, the mechanism of action; (b) the clinical pharmacokinetics, including metabolism and drug interactions; (c) the therapeutic efficacy (including adverse effects); and (d) indications and administration strategy, where known. The possible use of rational polytherapy, where drugs of known but different mechanisms of action are combined, is also discussed.

2.1 Eterobarb

2.1.1 Mechanism of Action

Eterobarb (dimethoxymethylphenobarbital; fig. 1) is a barbiturate that does not enter the brain, but is rapidly converted to phenobarbital and a *N*-monomethoxymethylphenobarbital metabolite (NMMP). As such, eterobarb can be considered a phenobarbital prodrug.[23,24]

The anticonvulsant profile of eterobarb is somewhat different to phenobarbital, being more effective in the maximal electroshock seizure model than in the pentetrazol (pentylenetetrazol)-induced seizure model.[24,25] Also, eterobarb exhibits an attenuated sedative and hypnotic activity in rats compared with phenobarbital. These differences are considered to be the result of the presence of NMMP and to reflect a receptor-mediated pharmacodynamic interaction between the metabolite and phenobarbital. Thus, functional tolerance to the hypnotic but not the anticonvulsant effects of the 2 metabolites occurs.

The exact mechanism of action of eterobarb per se is not known. However, it is likely to act, like phenobarbital, by postsynaptic modulation of GABA and glutamate neurotransmission.

2.1.2 Pharmacokinetics

After oral administration, absorption of eterobarb is very rapid. Both NMMP and phenobarbital, the 2 primary metabolites of eterobarb, are detectable in plasma within 5 minutes. Eterobarb is not detectable in blood since it is rapidly metabolised in the liver by a first-pass effect.[26] NMMP concentrations peak in plasma approximately 30 minutes after oral ingestion of eterobarb. Phenobarbital exhibits a biphasic peak, with an additional peak appearing 3 to 5 hours after eterobarb ingestion. This is probably due to the formation of phenobarbital from 2 pathways; directly from eterobarb (first peak) and from NMMP (second peak).[27]

The elimination half-life of NMMP is 4 to 6 hours and that of phenobarbital 4 to 6 days. Be-

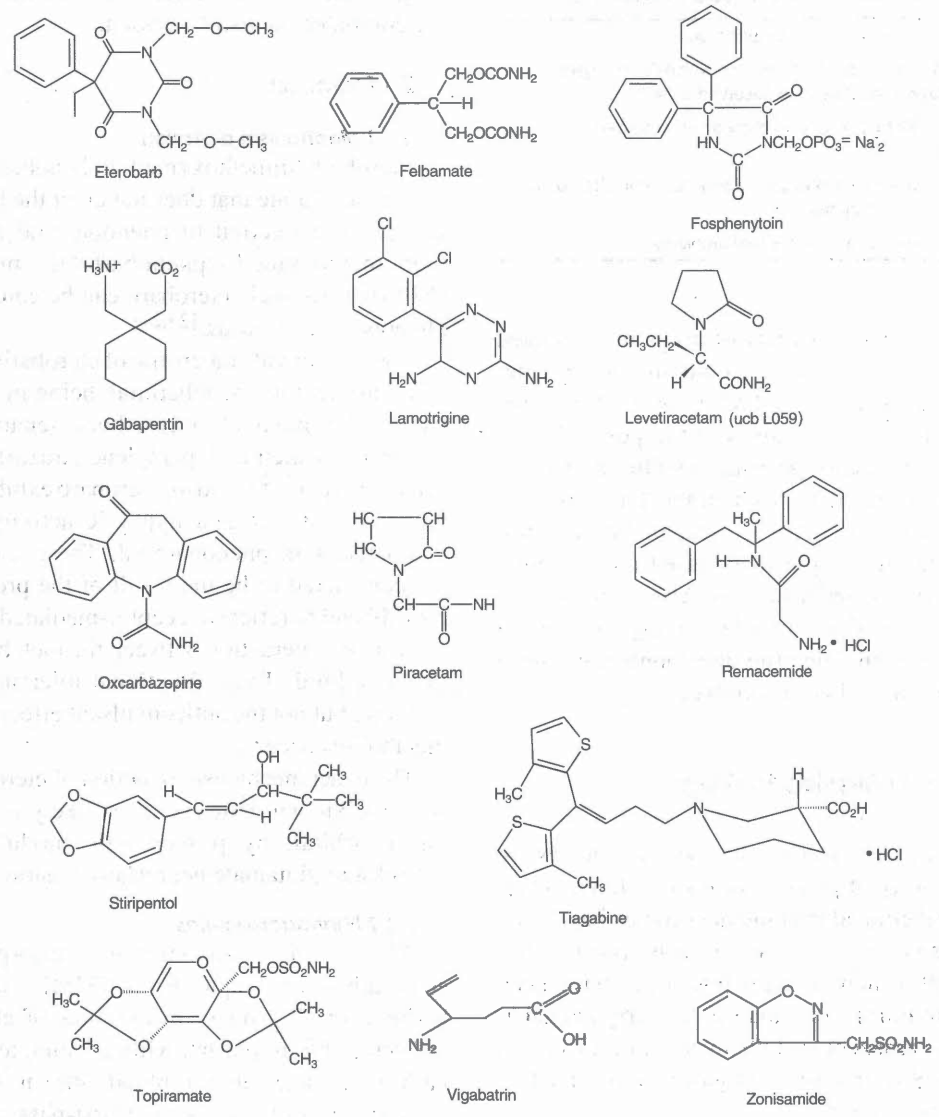

Fig. 1. Structural formulae of a number of new antiepileptic drugs.

cause of limited clinical experience with eterobarb, significant pharmacokinetic interactions with eterobarb *per se* have not been identified. However, interactions commonly encountered with phenobarbital may be anticipated (tables III and IV).

2.1.3 Therapeutic Efficacy and Adverse Effects

Eterobarb has been undergoing clinical evaluation as add-on therapy for treatment-refractory patients for almost 20 years. Of 130 patients studied, 83 patients have been studied in randomised, open label protocols and 47 patients have been studied

using randomised, double-blind, crossover study designs.[28-31] All studies involved a comparison with phenobarbital. 94 of 130 patients (72%) had fewer seizures (generalised tonic-clonic and partial seizures with and without secondary generalisation) during eterobarb treatment than with phenobarbital treatment, with a mean reduction of 50% (range 36 to 70%). Furthermore, overall seizure intensity was significantly lower during treatment with eterobarb than with phenobarbital. Comparing the open label studies with the double-blind studies, 62 of 83 (75%) and 32 of 47 patients (68%), respectively, exhibited significant improvement in seizure control compared with phenobarbital.

High plasma phenobarbital concentrations were better tolerated by patients if the phenobarbital was derived from eterobarb as opposed to phenobarbital *per se*. A recent randomised, double-blind study of 40 male volunteers compared the sedative and hypnotic effects of eterobarb and phenobarbital. Patients receiving eterobarb tolerated much higher plasma phenobarbital concentrations.[32] The reason for this better tolerability is not known, but may be the result of NMMP binding to phenobarbital receptors.

A particular problematic adverse effect of phenobarbital in children is hyperactivity. Of the children studied to date, in those presenting with hyperactive behaviour during phenobarbital treatment, symptoms resolved or were markedly attenuated during eterobarb treatment.[33] These changes were also associated with a marked improvement in school performance. Sedation and dizziness are the most frequently observed adverse effects of eterobarb treatment, in both adults and children. Three cases of status epilepticus has been reported.[30] In all 3 cases, status epilepticus developed when patients were taken off eterobarb and placed on phenobarbital. As plasma phenobarbital concentrations did not change during the switchover it is tempting to hypothesise that NMMP has additive or synergistic antiepileptic properties.

Table III. Effect of new antiepileptic drugs on plasma concentrations of generally available antiepileptic drugs

Drug added	Existing drug					
	CBZ	ESM	PB	PHT	PRM	VPA
ETB	CBZ↓	ESM↓	–	PHT↑↓	–	VPA↓
FBM	CBZ↓ CBZ-E↑	?	?	PHT↑	?	VPA↑
FPHT	CBZ↓	ESM↓	PB↑	–	PRM↑↓ PB↑	VPA↓
GPT	NA	NA	NA	NA	NA	NA
LTG	CBZ-E↑	NA	NA	NA	NA	NA
LTM	NA	?	NA	PHT↑	NA	NA
OXC	NA	NA	NA	NA	NA	NA
PTM	NA	?	NA	NA	?	NA
RMC	?	?	?	?	?	?
STP	CBZ↑ CBZ-E↓	?	PB↑	PHT↑	PRM↑ PB↑	NA
TGB	NA	NA	NA	NA	NA	NA
TPM	NA	?	?	NA	?	NA
VGT	NA	NA	PB↓	PHT↓	PRM↓ PB↓	NA
ZNS	CBZ↑	?	NA	NA	NA	NA

Abbreviations and symbols: CBZ = carbamazepine; CBZ-E = carbamazepine epoxide; ESM = ethosuximide; ETB = eterobarb; FBM = felbamate; FPHT = fosphenytoin; GPT = gabapentin; LTG = lamotrigine; LTM = levetiracetam (ucb L059); NA = no change anticipated; OXC = oxcarbazepine; PB = phenobarbital (phenobarbitone); PHT = phenytoin; PRM = primidone; PTM = piracetam; RMC = remacemide; STP = stiripentol; TGB = tiagabine; TPM = topiramate; VGT = vigabatrin; VPA = valproic acid (valproate sodium); ZNS = zonisamide; – indicates that the combination is unlikely to be prescribed; ? indicates an unknown effect; ↑ indicates an increase in plasma concentration; ↓ indicates a decrease in plasma concentration; ↑↓ indicates that an increase and a decrease in plasma concentration can occur, depending on the relative dose of the interacting drugs.

2.1.4 Current Treatment Recommendations and Therapeutic Status

Eterobarb appears to be a superior antiepileptic drug to phenobarbital and therefore is an attractive alternative to the older agent. It is effective in the management of generalised tonic-clonic and partial seizures, with or without secondary generalisation, in both adults and children. Furthermore, it has significantly fewer adverse effects than phenobarbital. It is not clear to what extent these characteristics are the result of the presence of NMMP.

The attenuated sedative effect in comparison with phenobarbital makes eterobarb a particularly

Table IV. Effect of generally available antiepileptic drugs on plasma concentrations of new antiepileptic drugs

Drug added	Existing Drug													
	ETB	FBM	FPHT	GPT	LTG	LTM	OXC	PTM	RMC	STP	TGB	TPM	VGT	ZNS
CBZ	ETB↓ PB↑	FBM↓	PHT ↑↓	NA	LTG↓	?	10-OH-OXC↓	NA	RMC↓ DGL↑	STP↓	TGB↓	TPM↓	NA	ZNS↓
ESM	NA	?	PHT↑	NA	NA	?	?	?	?	?	?	?	NA	?
PB	–	FBM↓	PHT↑↓	NA	LTG↓	?	OXC↓ 10-OH-OXC↓	NA	RMC↓ DGL↑	STP↓	TGB↓	?	NA	ZNS↓
PHT	ETB↓ PB↑	FBM↓	–	NA	LTG↓	?	OXC↓ 10-oH-OXC↓	NA	RMC↓ DGL↑	STP↓	TGB↓	TPM↓	NA	ZNS↓
PRM	ETB↓ PB↑	FBM↓	PHT↑↓	NA	LTG↓	?	?	?	RMC↓ DGL↑	STP↓	TGB↓	?	NA	ZNS↓
VPA	ETB↑ PB↑	NA	PHT↑↓	NA	LTG↑	?	NA	NA	?	NA	?	TPM↓	NA	?

Abbreviations and symbols: CBZ = carbamazepine; DGL = deglycinated metabolite of remacemide; ESM = ethosuximide; ETB = eterobarb; FBM = felbamate; FPHT = fosphenytoin; GPT = gabapentin; LTG = lamotrigine; LTM = levetiracetam; NA = no change anticipated; 10-OH-OXC = 10,11-dihydroxy-carbazepine; OXC = oxcarbazepine; PB = phenobarbital (phenobarbitone); PHT = phenytoin; PRM = primidone; PTM = piracetam; RMC = remacemide; STP = stiripentol; TGB = tiagabine; TPM = topiramate; VGT = vigabatrin; VPA = valproic acid (valproate sodium); ZNS = zonisamide; – indicates that the combination is unlikely to be prescribed; ? indicates an unknown effect; ↑ indicates an increase in plasma concentration; ↓ indicates a decrease in plasma concentration; ↑↓ indicates that an increase and a decrease in plasma concentration can occur, depending on the dose.

attractive option for children. Also, it would be useful in children whose school performance may be impaired by hyperactivity that is associated with treatment with phenobarbital. Based on the clinical studies to date, it is possible for phenobarbital to be substituted with eterobarb on a basis of 1 to 3. Thus, a typical dose for eterobarb might be 420 mg/day in adults.

2.2 Felbamate

2.2.1 Mechanism of Action

The exact mechanism of action of felbamate (2-phenyl-1,3-propanediol dicarbonate; fig. 1) is not known, but it appears to increase seizure threshold and inhibit seizure spread.[34,35] Felbamate blocks sustained repetitive firing of neurons by affecting voltage-dependent sodium channels.[36,37] It also blocks convulsions secondary to the voltage-dependent potassium channel antagonist 4-aminopyridine. Ligand binding studies have failed to demonstrate any effect of felbamate on GABA or benzodiazepine receptors. Felbamate inhibits NMDA- and quisqualate-induced seizures, suggesting an effect on excitatory amino acid neurotransmission. More recently, it has been proposed that the drug acts via a dual mechanism affecting both excitatory (NMDA) and inhibitory (GABA) mechanisms.[38]

Felbamate exhibits a unique profile of anticonvulsant action in animal models. It is effective in maximal electroshock and pentetrazol- and picrotoxin-induced models of epilepsy, but confers no protection against bicuculline- and strychnine-induced seizures.[34,35,39] Based on these models, which are predictive of partial seizures, felbamate has a broader spectrum of activity than carbamazepine or phenytoin. Furthermore, felbamate exhibits particularly low toxicity in these models and may also be a neuroprotectant.[40-43]

2.2.2 Pharmacokinetics

Approximately 90% of orally administered felbamate is absorbed, with maximum blood concentrations occurring within 1 to 4 hours.[44] Felbamate is approximately 30% bound to plasma proteins, and after hepatic hydroxylation and conjugation the major route of elimination is via the urine.[36] The 3 major metabolites of felbamate, the oxidative derivatives 2-hydroxy-felbamate and *p*-phenyl-hydroxy-felbamate and the hydrolytic metabolite 2-phenyl-1,3-propanediol-monocarbonate, have not been shown to possess any significant

anticonvulsant or neurotoxic activity in animals.[45] The mean elimination half-life of felbamate is approximately 20 hours, and no change in elimination half-life has been observed after repeated administration to healthy volunteers.[46] In animals, the pharmacokinetics of felbamate appear linear up to a dose of 3600 mg/kg. In patients with epilepsy already receiving phenytoin or carbamazepine, the median half-life of felbamate is reduced to approximately 13 hours.[44] This can be attributed to the hepatic enzyme–inducing characteristics of phenytoin and carbamazepine (table IV).

Felbamate exhibits significant pharmacokinetic interactions with phenytoin, carbamazepine and valproic acid (table III). Plasma phenytoin and carbamazepine concentrations have been reported to increase and decrease by 20%, respectively, in some patients on introduction of polytherapy with felbamate.[47-50] The reduction in plasma carbamazepine concentrations has been associated with concurrent increases in the pharmacologically active metabolite of carbamazepine, carbamazepine epoxide.[47,48,51,52] The exact mechanism of these interactions is unknown.

In patients taking valproic acid, plasma valproic acid concentrations have been increased by approximately 28 to 54% during comedication with felbamate.[53] This is the first known interaction with valproic acid whereby plasma valproic acid concentrations are increased. The mechanism of this interaction is unknown, but is most likely to be inhibitory. If indeed the mechanism of interaction is inhibitory, then its clinical interpretation can be misleading. This is because, classically, when a plasma drug concentration is increased it is commonly associated with neurotoxicity. However, in the case of valproic acid, if one accepts the hypothesis that one of its many metabolites is responsible for the antiepileptic effect, then this interaction will result in a loss of seizure control not neurotoxicity.

2.2.3 Therapeutic Efficacy and Adverse Effects

Felbamate was assessed in a double-blind, randomised, placebo-controlled study in 56 patients with refractory partial seizures who were receiving stable dosages of carbamazepine or phenytoin as monotherapy. This study showed that addition of felbamate to therapy was associated with a statistically significant 13.2% reduction in seizures compared with placebo.[54] In another 3-period, crossover, double-blind, placebo-controlled trial involving 30 patients with complex partial seizures on carbamazepine monotherapy, felbamate failed on initial analysis to show a significant reduction in seizure frequency compared with placebo.[55] However, plasma carbamazepine concentrations were lower during felbamate therapy (by a mean of 24%). When the data were reanalysed to take this into account, it was estimated that there would have been a seizure frequency reduction of 50% if carbamazepine plasma concentrations had been maintained at the baseline values.

Recently, studies of felbamate using unique designs have been reported. In the first design, felbamate was studied in presurgical patients with partial seizures.[56] In these patients, felbamate or placebo was administered after withdrawal from their normally prescribed antiepileptic drugs as part of the presurgical evaluation. Two end points were used; time to fourth seizure and the number of patients completing 28 days of therapy. 15 of 28 felbamate recipients compared with 4 of 33 patients receiving placebo completed the 28 days, suggesting a significant antiepileptic effect by felbamate.[56] However, as plasma concentrations of concomitant antiepileptic drugs were not reported, it is difficult to ascertain any contribution that drug interactions may have had on seizure control.

The other unique design compared felbamate with valproic acid.[57,58] The studies were randomised, double-blind and parallel in design. After a 56-day baseline period, patients were randomised to felbamate (3600 mg/day) or valproic acid (15 mg/kg/day). During the first 28 days of blinded treatment, concomitant antiepileptic drugs were discontinued while felbamate or valproic acid were added. Patients completed the study either by continuing through to 112 days of evaluation or requir-

ing withdrawal from the study due to unacceptable seizure exacerbation or lack of seizure control. The primary efficacy variable was the number of patients withdrawing from each treatment group. Based on the observation that 56 patients on valproic acid and 21 on felbamate withdrew from the studies, it was concluded that felbamate has antiepileptic activity and that it is also effective as a monotherapy.[57,58]

Felbamate has also been evaluated in 73 children with Lennox-Gastaut syndrome.[59] The study design was double-blind, placebo-controlled, parallel and add-on. Patients were randomised to receive either felbamate or placebo. Patients were either taking phenytoin or valproic acid and, prior to initiation of study, the dose of these drugs was reduced by 20%. Felbamate treatment was associated with a significant decrease in total seizure frequency (by 19%) compared with the placebo group (by 4%), and in particular the frequency of atonic seizures was reduced (by 34% versus 9% in placebo-treated patients). The results achieved in this highly treatment-resistant seizure syndrome are very encouraging and have been substantiated in a follow-on, open label study of these patients.[60] Thus, 62% of children who were switched from placebo to felbamate had >50% reductions in astatic and total seizure frequencies at 1 month, and approximately 50% showed the same effect at 12 months. This has been taken as evidence that tolerance to the antiepileptic effect of felbamate does not develop.[60]

Analysis of adverse effects associated with felbamate has been complicated by the problematic interactions with concomitant antiepileptic drugs. Indeed, many adverse effects ceased after a reduction in the dosage of concomitant antiepileptic drugs or conversion to felbamate monotherapy.[50,54,59]

The most frequently reported adverse effects during felbamate therapy have been diplopia, insomnia, dizziness, blurred vision, headache and ataxia. Gastrointestinal distress, including anorexia, nausea and vomiting, have also been reported. These adverse effects have been typically mild or moderate in severity. A change in felbamate dose has not commonly been required, as the effects have generally spontaneously resolved or resolved on reduction of the dose of concomitant antiepileptic drugs.[54,55,59] With repeated administration, bodyweight loss and insomnia have been reported with increasing frequency. These effects appear to be directly related to felbamate rather than to effects of increased concentrations of concomitantly administered antiepileptic drugs. All of the above adverse effects have been observed in children. Additionally in children, felbamate may be associated with a higher incidence of respiratory tract infection than would normally be expected.

2.2.4 Current Therapeutic Status and Treatment Recommendations

Felbamate has recently been licenced in the US and several European countries. It is indicated, as monotherapy and adjunctive therapy, for the treatment of partial seizures with and without generalisation in adults, and as adjunctive therapy in the treatment of partial and generalised seizures associated with Lennox-Gastaut syndrome in children. It is available as 400 and 600mg tablets, and as a 600 mg/5ml suspension.

As felbamate has not been systematically evaluated as initial monotherapy, patients should be started at a dosage of 1200 mg/day (divided into 3 or 4 daily doses). The dosage should be increased in 600mg increments every 2 weeks, up to 2400 mg/day based on clinical response. If clinically indicated, a maximum dosage of 3600 mg/day is recommended. When converting patients to monotherapy, felbamate 1200 mg/day in 3 or 4 divided doses is initiated and the dosage of concomitant antiepileptic drugs is reduced by one-third. At weeks 2 and 3, felbamate dosage is increased to 2400 and 3600 mg/day, respectively, while the dosage of concomitant antiepileptic drugs is reduced by one-third on each occasion as clinically indicated.

Since felbamate is also recommended as an adjunct to other antiepileptic drugs, the increased incidence of adverse effects during this type of treatment regimen may prove problematic during

widespread clinical use. This aspect is particularly relevant in Europe where new antiepileptic drugs are commonly licenced only as add-on therapy. The magnitude of drug interactions between felbamate and other antiepileptic agents suggests that dosage adjustments will be necessary if seizure control is to be maintained and adverse effects are to be avoided during polytherapy. A potential major problematic interaction is that with valproic acid, since its clinical interpretation may be positively misleading (see section 2.2.2). Additionally, felbamate metabolism is inducible by carbamazepine and phenytoin, and thus higher felbamate doses will be necessary during coadministration with these antiepileptic drugs.[50]

2.3 Fosphenytoin

2.3.1 Mechanism of Action

Fosphenytoin (3-phosphoryloxymethyl phenytoin disodium; fig. 1) is a phenytoin prodrug. The mechanism of action of fosphenytoin is considered to be identical to that of phenytoin. The regulatory effect of phenytoin on sodium transport across neuronal membranes is a major mechanism of action of fosphenytoin that almost certainly underlies most of its clinical effects.[61]

2.3.2 Pharmacokinetics

Fosphenytoin has been developed for intravenously use for the management of status epilepticus. Pharmacokinetic studies have invariably involved comparisons of intramuscular and intravenous administration in both healthy volunteers and patients with epilepsy.[62-65]

Using a single-blind, increasing-dose study with randomised, placebo-control at each dose, fosphenytoin was administered intravenously over 30 minutes to volunteers.[63] Fosphenytoin was rapidly converted to phenytoin with a mean half-life of approximately 8 minutes (range 5.7 to 12.6 minutes). As expected, the maximum plasma phenytoin concentration at all 4 fosphenytoin doses studied (150, 300, 600 and 1200mg) occurred near the end of the infusion and was proportional to dose. Plasma phenytoin concentrations reached 90% of the maxima about 12 minutes after the end of fosphenytoin infusion. Likewise, the area under the plasma concentration-time curve (AUC) was proportionate to dose, whereas the total clearance remained constant and was dose independent.

These data have been generally confirmed in patients with epilepsy. In these patients, the conversion half-life of fosphenytoin to phenytoin after intramuscular administration is approximately 33 minutes.[65] Fosphenytoin is not detectable in the urine, and following single intravenous or intramuscular administration appears to be approximately bioequivalent to oral maintenance doses of phenytoin.[62]

Fosphenytoin binds to the same plasma albumin protein binding site as phenytoin. Therefore, a protein binding interaction can occur, particularly at the end of the infusion period when plasma fosphenytoin concentrations are highest.[64] The clinical significance of this interaction is unknown. Although other interactions with fosphenytoin have not been investigated, all those known to occur with phenytoin can be expected (tables III and IV).

2.3.3 Therapeutic Efficacy and Adverse Effects

Fosphenytoin has been developed in order to alleviate the administration problems associated with the currently available parenteral formulation of phenytoin.[66] Rapid intravenous administration of undiluted phenytoin can be very painful and irritating to the vein, and can also result in cardiovascular collapse.[66-68] Furthermore, the poor aqueous solubility of phenytoin can result in precipitation of the drug if the formulation is diluted.

Fosphenytoin exhibits none of the above described problematic properties, and can be administered intramuscularly as well as intravenously.[69] It therefore represents a formulation that is less problematic and hazardous than the parenteral phenytoin formulation currently available. Although data on the antiepileptic efficacy of fosphenytoin have not been published, a recent preliminary report of a single-dose, uncontrolled, open label study suggests that it may be effective in status epilepticus.[70] The time course of conversion of fosphenytoin to phenytoin results in less

rapid delivery of phenytoin than occurs with the present parenteral formulation. As a result, it is imperative that comparative efficacy studies are undertaken, particularly in patients in status epilepticus.

2.3.4 Current Therapeutic Status and Treatment Recommendations

Since fosphenytoin can be administered both intravenously and intramuscularly with minimal local irritation, it represents a potentially clinically significant and desirable advance. If, in addition, fosphenytoin exhibits rapid onset of antiepileptic properties (as would be essential in the management of status epilepticus) there may be a major therapeutic role for this prodrug. Intravenously administered fosphenytoin is bioequivalent to intravenously administered parenteral phenytoin. As such, a similar administration strategy to that in current clinical practice with phenytoin will probably be needed.

2.4 Gabapentin

2.4.1 Mechanism of Action

Gabapentin [1-(aminomethyl)-cyclohexaneacetic acid] is a cyclic GABA analogue, originally designed to mimic the steric conformation of GABA (fig. 1). However, the agent has no direct GABA-mimetic effect.[71] An effect on GABA synthesis and release may be involved.[72,73] An effect on voltage-activated sodium channels has also been suggested;[74] however, the exact mechanism of action of gabapentin is not known.

The recent discovery of a specific high-affinity binding site for gabapentin may shed some light on its mechanism of action.[75,76] The site is stereoselective for *S*-(+)-3-isobutyl GABA, a gabapentin analogue that is active in animal seizure models.[77] The identification of an endogenous ligand for this receptor may open new avenues of antiepileptic drug development.

The effectiveness of gabapentin in maximal electroshock, pentetrazol-induced and feline trigeminal complex seizure models suggests that the agent will have clinical efficacy similar to carbamazepine and phenytoin in generalised tonic-clonic and partial seizures.[78,79]

2.4.2 Pharmacokinetics

Absorption of gabapentin from the intestine is dependent on an *l*-amino acid active transport system.[80,81] After oral ingestion, maximum plasma gabapentin concentrations occur within 2 to 3 hours, and bioavailability of the drug is approximately 60%.[82]

In contrast to GABA, gabapentin readily enters the brain.[78,83] Active transport across the blood-brain barrier occurs in a similar manner to that that occurs across the intestine. Thus, gabapentin competes with *l*-leucine, *l*-isoleucine, *l*-valine and *l*-phenylalanine for transport.[84] It is possible, therefore, that increased cytosolic gabapentin concentrations and reduced branched-chain amino acid levels [e.g. leucine, isoleucine and valine (precursors of glutamate)] would result in a net decrease in the rate of glutamate synthesis, and possibly a decrease in glutamate levels.[85,86] This may result in a decrease in excitatory amino acid neurotransmission. Such a mechanism could explain the delay between maximal anticonvulsant activity and peak brain tissue and brain interstitial fluid gabapentin concentrations.[87]

Gabapentin is not bound to plasma proteins and is not metabolised, being excreted unchanged in the urine. The elimination half-life of the drug in both volunteers and patients is 5 to 7 hours. This is not altered by increasing dose, although oral bioavailability is reduced at higher doses.[78,82,88,89] As renal clearance is similar to plasma clearance, non-renal elimination of gabapentin is negligible.

To date, no pharmacokinetic interactions between gabapentin and currently available antiepileptic drugs have been reported (tables III and IV).[90-93] As impaired renal function results in higher plasma gabapentin concentrations and an increase in half-life, a smaller dosage would be necessary in patients with impaired renal function.[94] Coadministration of gabapentin with antacids can reduce gabapentin bioavailability by 24%.[91] Cimetidine may decrease gabapentin renal clearance by 12%; however, probenecid (an in-

hibitor of renal tubular secretion) is without effect.[91] An apparently linear relationship exists between therapeutically useful doses of gabapentin and plasma gabapentin concentrations.[95] However, no target therapeutic plasma range is available for gabapentin, and so it is presently unlikely that therapeutic drug monitoring would be helpful.

2.4.3 Therapeutic Efficacy and Adverse Effects

Gabapentin has been evaluated as add-on therapy in patients with refractory partial seizures with and without secondary generalisation. A dose related antiepileptic effect has been shown.[95] Using a multicentre, double-blind, placebo-controlled, parallel group study design, gabapentin was evaluated in 125 patients with refractory partial seizures. Drug treatment reduced seizure frequency by 50% in 25% of patients compared with a similar reduction in only 9.8% of patients treated with placebo.[96]

A subsequent double-blind, placebo-controlled study of 43 patients, confirmed the dose-dependent antiepileptic effect of gabapentin. In this trial, patients receiving 1200 mg/day benefitted more than those receiving 900 mg/day.[97] In an open-label, add-on study of 35 patients with partial seizures, approximately 20% of patients with simple partial seizures experienced a 50% reduction in seizures, and a sustained reduction was observed for up to 24 months.[98] During this time, 5 patients succeeded in achieving gabapentin monotherapy. One patient become seizure-free and a further patient experienced only rare seizures.

A recent multicentre, add-on, placebo-controlled, parallel-group study of gabapentin (600, 1200 or 1800 mg/day) in 308 patients with refractory partial seizures showed that the mean response ratio was significantly better than that of the placebo group.[99] The responder rate for the 3 gabapentin-treated groups ranged from 18% to 26%, compared with 8% for the placebo-treated group. Furthermore, the median percentage reduction in seizure frequency ranged from 24 to 32% in recipients of active drug compared with 6% for patients receiving placebo. Statistical analysis revealed a highly significant dose-response trend.

Most adverse effects associated with gabapentin relate to the CNS, with somnolence being the most frequently reported.[95,96] Other adverse effects include fatigue, tremor, diplopia, dizziness, pharyngitis, dyspepsia and dysarthria. Bodyweight gain is also reported by some patients. Gabapentin treatment has not been associated with hepatic damage or serious allergic reaction. This may be attributed to the fact that the drug does not undergo metabolic degradation. As gabapentin has minimal adverse effects, it may be argued that its full therapeutic potential, using higher dosage regimens, has not been completely realised.

2.4.4 Current Therapeutic Status and Treatment Recommendations

The pharmacokinetic profile of gabapentin is simple, with linear kinetics, no problematic bioavailability characteristics, no induction or inhibition of hepatic enzymes, and no clinically significant pharmacokinetic interactions. Its short half-life is not ideal, but this can probably be addressed by a formulation adjustment. The fact that a new binding site has been identified for gabapentin, suggests that this drug may be the first of a new class of antiepileptic drugs. The relative lack of toxicity associated with gabapentin in clinical studies suggests that its complete efficacy in relation to dose administration has not yet been completely determined. It is effective against simple seizures, complex partial seizures and secondarily generalised seizures. Further, anecdotal evidence suggests that gabapentin may have beneficial psychotropic effects, e.g. a sense of well-being with improved concentration, increased memory function and an improvement in mood.[98,100]

Gabapentin has recently been licenced in the UK and the US. Its indications are as add-on therapy for partial seizures and for partial seizures with secondary generalisation in patients who have not achieved satisfactory control with or who are intolerant of standard antiepileptic drugs. It is available as 100, 300 and 400mg tablets.

The current recommended maintenance dosage is 900 to 1200 mg/day. It has been suggested that this can be titrated rapidly over a few days. Thus,

gabapentin can be administered at a dosage of 300mg once a day on day 1, 300mg twice a day on day 2 and 300mg 3 times a day on day 3, although in clinical outpatient practice a slower introduction may be more prudent. Thereafter, the dosage can be increased to 1200 mg/day given in 3 equally divided doses. If necessary, further titration can occur using increments of 300 mg/day given in 3 equally divided doses up to a maximum of 2400 mg/day. If gabapentin is to be discontinued, it should be done gradually over a week. If administered to elderly patients, smaller dosages would be required because of declining renal function with age. As antacids may reduce the bioavailability of gabapentin, they should not be coadministered.

2.5 Lamotrigine

2.5.1 Mechanism of Action

Lamotrigine, a phenyltriazine derivative (fig. 1), is considered to act via an inhibitory effect on voltage-sensitive sodium channels. This results in a reduction in neuronal firing. At higher concentrations, lamotrigine acts on calcium channels, resulting in stabilisation of neuronal membranes. These effects result in a reduced release of glutamate.[101-103]

Lamotrigine is effective in the maximal electroshock and pentetrazol-induced seizure models. It also abolishes hindlimb extension induced by picrotoxin and bicuculline. Its effect on maximal electroshock is longer lasting than any currently used antiepileptic drug, and it is also effective in the genetically epilepsy-prone rat model.[104] Thus, lamotrigine has an overall profile of a drug that would have a broad spectrum of antiepileptic activity.

2.5.2 Pharmacokinetics

After oral administration, lamotrigine is rapidly and completely absorbed with blood concentrations peaking in 2 to 3 hours.[105-107] The drug is approximately 60% bound to plasma proteins and exhibits linear pharmacokinetics within the currently recommended target range of 4 to 16 μmol/L.[108] Plasma lamotrigine concentrations are linearly related to dosage.[109] Lamotrigine is extensively metabolised by glucuronidation, and following oral or intravenous administration 8% of the dose is excreted unchanged in the urine and 63% as a glucuronide.[105,107] During overdose (lamotrigine 1350mg) the metabolism of lamotrigine does not appear to be saturable.[110] The clinical relevance of a recent study in healthy volunteers suggesting that metabolism of lamotrigine may undergo auto-induction is uncertain.[111]

In healthy adult volunteers, the mean elimination half-life of lamotrigine is approximately 24 hours, whilst in elderly individuals it is 31 hours.[106] However, its half-life is reduced to a mean of 15 hours (range 8 to 33 hours) in patients with epilepsy who are already receiving enzyme-inducing antiepileptic drugs (e.g. phenobarbital, carbamazepine, phenytoin, primidone). In patients taking valproic acid alone, the mean half-life of lamotrigine is increased to approximately 59 hours (range 31 to 89 hours). Finally, in patients receiving a combination of enzyme-inducing antiepileptic drugs and valproic acid, mean half-life values for lamotrigine of approximately 24 hours have been reported.[112,113] Thus, in prescribing lamotrigine a different dosage strategy needs to be used depending on pre-existing antiepileptic drug medication.

Although lamotrigine does not affect the metabolism of commonly prescribed antiepileptic drugs, some studies suggest that the agent inhibits the metabolism of carbamazepine epoxide, the pharmacologically active primary metabolite of carbamazepine (tables III and IV).[114,115]

The usefulness of therapeutic drug monitoring of lamotrigine has not been determined, particularly since the interrelationship between plasma lamotrigine concentrations and efficacy and toxicity have not been definitively ascertained. Nevertheless, a tentative target/therapeutic range (4 to 16 μmol/L) is quoted, which is based on values obtained in patients during the development of the drug. Current clinical practice would suggest that this range is too low.

2.5.3 Therapeutic Efficacy and Adverse Effects

Using interictal spike activity and photosensitivity as efficacy measures, lamotrigine was shown to reduce the former by 78 to 98% and to abolish the latter.[112,116] Subsequently, 4 randomised, double-blind, placebo-controlled studies were undertaken in patients with refractory epilepsy.[117-120] Of the 92 patients studied, 64 (70%) had a lower number of total seizures during lamotrigine treatment than during placebo treatment and 25 patients (27%) had a >50% reduction in seizures compared with placebo. Recently, these data have been confirmed in more than 750 patients.[109,121-125]

The antiepileptic effect of lamotrigine is dose dependent.[121] In a placebo-controlled, double-blind study of 215 patients with refractory partial seizures, median seizure frequency decreased by 8% with placebo, 20% with lamotrigine 300 mg/day and 36% with lamotrigine 500 mg/day during 6 months of treatment. Lamotrigine may have additional favourable effects on seizure severity, mood and perceived internal control.[125]

A more impressive efficacy profile has been observed in the large number of open studies undertaken.[126] Overall, 32% of patients showed at least a 50% reduction in total seizures. When generalised tonic-clonic seizures were analysed separately, 52% of patients showed at least 50% reduction and 22.5% were completely seizure-free. Good efficacy has been demonstrated for lamotrigine in patients with absence, atypical absence, myoclonic and atonic seizures, although data on these seizure types are rather limited. Efficacy in status epilepticus has also been reported.[127] Lamotrigine may additionally be effective as add-on therapy in some forms of primary generalised epilepsy.[128-130] A recent multicentre study of 285 children below the age of 13 years treated for up to 1 year suggests that the efficacy of lamotrigine in children is similar to that seen in adults.[131] Furthermore, in a series of 120 children aged 10 months to 16 years 9 months, lamotrigine was particularly effective in those with absence seizures, Lennox-Gastaut syndrome and other symptomatic generalised seizures.[132]

Adverse experiences commonly associated with lamotrigine therapy are primarily CNS-related. Overall, 8.6% of patients have been withdrawn from therapy because of adverse effects. These have included rash, dizziness, diplopia, somnolence, headache, ataxia, irritability and increases in seizure frequency.[133] The most common cause of withdrawal of lamotrigine therapy is allergic cutaneous rash. Data from open studies demonstrate an overall rash rate of 10.8%.[134] The rash may be severe and is usually generalised maculopapular or erythema multiforme in nature, although there have been 2 reports of Stevens-Johnson syndrome. The rash resolves upon lamotrigine withdrawal.[133,134] Alterations in biochemical and haematological parameters, including plasma and erythrocyte folate levels, have been reported, but are not considered to be clinically significant.[108,135]

2.5.4 Current Therapeutic Status and Treatment Recommendations

Lamotrigine has recently become available in numerous countries. Its indications are as add-on treatment of partial seizures and secondarily generalised tonic-clonic seizures not satisfactorily controlled with standard antiepileptic drugs. Anecdotal evidence suggesting the effectiveness of lamotrigine in patients with absence, primary generalised seizures and the Lennox-Gastaut syndrome needs clarifying. Lamotrigine is available as 25, 50 and 100mg tablets and/or dispersible tablets.

The current recommended maintenance dosage for patients receiving enzyme-inducing antiepileptic drugs is lamotrigine 200 to 400 mg/day in 2 divided doses. However, not many patients tolerate the higher doses. If the patient is not taking enzyme-inducing antiepileptic drugs, a maintenance dosage of 100 to 200 mg/day given in 2 divided doses is recommended. The initial dosage is 50mg once a day for the first 2 weeks. The use of a small initial dosage appears to reduce the risk of lamotrigine-associated cutaneous rash. During

comedication with valproic acid it is important to initiate lamotrigine therapy at an even lower dosage, and 25mg every alternate day for the first 2 weeks, followed by 25 mg/day for 2 weeks is recommended. Thereafter, the usual maintenance dose to achieve optimum response is 100 to 200 mg/day given once daily or in two doses. In the elderly, the clearance of lamotrigine is significantly reduced and thus a lower dosage may be required in this patient group. The tentative plasma target range is presently 4 to 16 μmol/L. However, clinical practice suggests that this range is too low.

2.6 Levetiracetam (ucb L059)

2.6.1 Mechanism of Action

Levetiracetam (ucb L059), (s)-α-ethyl-2-oxo-pyrrolidine acetamide, is the *S*-enantiomer of the ethyl analogue of piracetam (see section 2.8) [fig. 1]. The profile of action of levetiracetam includes features in common with a wide range of currently available antiepileptic drugs. It is effective in audiogenic, maximal electroshock and chemically-induced seizure models.[136,137] Its exact mechanism of action is unknown, but it probably acts indirectly on the GABA-benzodiazepine-chloride ionophore complex and NMDA receptors.[136]

2.6.2 Pharmacokinetics

After oral ingestion, levetiracetam is rapidly absorbed with peak plasma concentrations occurring within 15 to 20 minutes. The elimination half-life is 5 to 8 hours in patients taking enzyme-inducing drugs such as phenytoin or carbamazepine, or in patients receiving valproic acid as monotherapy.[138] Patients comedicated with phenytoin and levetiracetam may experience high plasma phenytoin concentrations due to an inhibitory metabolic interaction (tables III and IV).[139]

2.6.3 Therapeutic Efficacy and Adverse Effects

Levetiracetam is currently undergoing clinical investigation. Preliminary results are encouraging, with significant efficacy observed in patients with refractory complex partial seizures.[140,141] A single-blind, placebo-controlled, increasing dose add-on study has been performed in patients with refractory partial seizures. Six of 17 patients treated with levetiracetam as add-on therapy experienced more than a 50% reduction in seizure frequency and a further 3 showed a 25 to 50% reduction.[139] Levetiracetam was well tolerated with only mild or moderate adverse events reported. These included drowsiness, memory impairment, depression and mood change. No significant changes in laboratory or safety parameters were detected during treatment with levetiracetam.

2.6.4 Current Therapeutic Status and Treatment Recommendations

Double-blind, controlled and long term studies are currently planned to further evaluate the efficacy and safety of this drug.

2.7 Oxcarbazepine

2.7.1 Mechanism of Action

Oxcarbazepine, a keto analogue of carbamazepine (fig. 1), can be considered a prodrug. In man, it is rapidly metabolised to 10,11-dihydroxy-carbazepine, which is pharmacologically active. Oxcarbazepine and its metabolite have similar antiepileptic activity to carbamazepine in maximal electroshock and pentetrazol-induced seizure models.[142,143] The exact mechanism of action of oxcarbazepine in not known, but it is suggested that a blockade of voltage-sensitive sodium channels and an effect on potassium channels may be involved.[144]

2.7.2 Pharmacokinetics

Oxcarbazepine is rapidly and completely absorbed within 1 to 2 hours of oral ingestion.[145] Maximum blood concentrations of oxcarbazepine are reached within 1 hour, and by 3 hours oxcarbazepine is not detectable in the blood. Plasma concentrations of both oxcarbazepine and 10,11-dihydroxy-carbazepine are linearly related to dose.[146,147] 10,11-Dihydroxy-carbazepine has a half-life of 14 to 26 hours in healthy volunteers and approximately 8 hours in patients receiving enzyme-inducing antiepileptic drugs.[148-150] Approximately 40% of 10,11-dihydroxy-carbazepine and 60% of oxcarbazepine is bound to plasma proteins.[151-153]

Oxcarbazepine is metabolised primarily by ketone reductase and glucuronyl transferase.[154] These enzymes are less prone to induction and inhibition than the cytochrome P450–dependent enzymes that are responsible for the metabolism of most antiepileptic drugs, including carbamazepine.[155-157] Indeed, the metabolism of oxcarbazepine exhibits no or only weak potential for induction in humans.[148,158,159]

Recently, it has been reported that carbamazepine, phenytoin and phenobarbital induce the metabolism of 10,11-dihydroxy-carbazepine.[160-162] Whether the magnitude of these interactions is clinically significant needs to be ascertained (tables III and IV). Thus, oxcarbazepine metabolism appears to be heteroinducible, i.e. it is induced by other drugs and autoinduction may occur. Valproic acid does not affect oxcarbazepine or 10,11-dihydroxy-carbazepine metabolism.[161] Since oxcarbazepine has less potential to induce enzyme activity than carbamazepine, substitution of oxcarbazepine for carbamazepine in the early studies of oxcarbazepine resulted in an elevation in plasma concentrations of concomitant antiepileptic drugs and resulted in adverse effects.[163]

Since carbamazepine is known to interact with numerous drugs used in the treatment of other medical conditions,[11] oxcarbazepine has been investigated for possible interactions. Cimetidine, dextropropoxyphene and erythromycin do not affect plasma oxcarbazepine concentrations, and oxcarbazepine has no effect on the anticoagulant activity of warfarin.[164-167] However, like carbamazepine, oxcarbazepine decreases the bioavailability of oral contraceptives containing ethinylestradiol and levonorgestrel.[168,169]

2.7.3 Therapeutic Efficacy and Adverse Effects

Since oxcarbazepine is a derivative of carbamazepine most studies of the efficacy of oxcarbazepine have compared it directly with carbamazepine. In the largest study of 235 newly diagnosed patients with tonic-clonic or partial seizures, monotherapy oxcarbazepine was compared with monotherapy carbamazepine.[170] In both groups, 80% of patients experienced a decrease in seizure frequency of 50%, suggesting that carbamazepine and oxcarbazepine have equal efficacy.

Using a randomised, placebo-controlled study design, Reinikainen et al.[171] substituted carbamazepine or oxcarbazepine in 35 patients that were refractory or intolerant to phenytoin. Seven of 13 (54%) patients receiving oxcarbazepine and 12 of 18 (67%) patients on carbamazepine became seizure-free, thus confirming that the 2 drugs were of equal efficacy.

In 4 further studies, oxcarbazepine was substituted for carbamazepine in patients with partial seizures not adequately controlled by multiple antiepileptic drug regimens. These studies all concluded that the 2 drugs have indistinguishable efficacy.[163,172-174] However, unlike carbamazepine, oxcarbazepine does not cause a clinically significant induction of hepatic enzymes. Therefore, these studies were flawed since blood concentrations of concomitant antiepileptic drugs increased during oxcarbazepine therapy. Nevertheless, a recent multicentre retrospective evaluation of 947 children, adults and elderly patients has confirmed the antiepileptic effects of oxcarbazepine, with 32 to 48% of patients experiencing seizure reduction.[175]

The clinical interest in oxcarbazepine as an alternative to carbamazepine is based on the premise that it would be associated with less severe adverse CNS effects and idiosyncratic reactions. This profile was suggested by the lack of enzyme induction (including autoinduction) and a different metabolic profile (it is not metabolised to an active epoxide metabolite, an effect that has been proposed to be responsible for the adverse effects associated with carbamazepine).[176,177] Indeed, patient studies to date do suggest that oxcarbazepine has improved tolerability compared with carbamazepine. For example, oxcarbazepine is associated with a lower incidence of allergic reactions and less psychomotor impairment.[163,170,171,178] Also, oxcarbazepine may have a slight stimulant effect on memory and psychomotor activity[179] and its cognitive effects are no different to those seen with phenytoin.[180] However, hyponatraemia may be

as common with oxcarbazepine as with carbamazepine.[147,163,172,181-184]

Oxcarbazepine-related adverse effects have been generally mild and transient, and usually related to the CNS (e.g. drowsiness, dizziness, headache, diplopia, ataxia and nystagmus).[171,185,186] The overall incidence rates of adverse effects vary from 10 to 46%. Carbamazepine-associated skin rashes have been reported to resolve on switching to oxcarbazepine,[147,163,187] and to cross-react (with an incidence of 25%) with oxcarbazepine.[187,188]

The clinical experience with oxcarbazepine therapy in pregnant women is minimal and, therefore, its teratogenic potential in humans is essentially unknown. To date, 10 children have been born after exposure to oxcarbazepine *in utero*. Of these, 1 infant had mild facial dysmorphism.[175,189]

2.7.4 Current Therapeutic Status and Treatment Recommendations

The antiepileptic efficacy of oxcarbazepine appears to be similar to carbamazepine, being effective in reducing seizure frequency in patients with generalised tonic-clonic and partial seizures. The lack of total cross-sensitivity with carbamazepine may mean that oxcarbazepine may be useful in 60 to 70% of patients who become hypersensitised to carbamazepine. Oxcarbazepine has recently been marketed in Denmark, The Netherlands, Argentina and Austria as add-on and monotherapy in adults and children with generalised tonic-clonic and partial seizures. It is available as 300 and 600mg tablets.

The current recommended dosage for adults is 600 to 1200 mg/day as monotherapy or 900 to 3000 mg/day as polytherapy, to be taken in 2 or 3 divided doses under both circumstances. The initial recommended dosage is 300 mg/day and thereafter the dosage can be titrated gradually. In children over 3 years of age, 10 mg/kg/day is initially prescribed. Thereafter, dosage can be gradually increased to a maintenance level of approximately 30 mg/kg/day, taken in 2 or 3 doses.

Since the enzyme-inducing effect of oxcarbazepine is less than that of carbamazepine, on changing patient medication from carbamazepine to oxcarbazepine it may be necessary to reduce the dosage of concurrent medication.

2.8 Piracetam

2.8.1 Mechanism of Action

Piracetam, 2-oxo-1 pyrrolidine acetamide (fig. 1), was developed as a cyclic analogue of GABA. However, piracetam does not have a specific GABAergic effect nor does it modify GABA levels in the brain, and so its mechanism of action is essentially unknown.[190,191]

Studies to determine the effect of piracetam on catecholamines have been inconclusive.[192-194] Other possible mechanisms of action include effects on energy metabolism,[195] cholinergic[196-198] or glutaminergic neurotransmission,[199,200] NMDA receptors,[201] and an effect mediated by steroids.[202] The drug is effective in audiogenic and pentetrazol-induced kindling seizure models, but has no effect on electroconvulsive shock or intravenous pentetrazol- or strychnine-induced seizures.[203,204]

2.8.2 Pharmacokinetics

After oral ingestion piracetam is rapidly and almost completely absorbed, with maximum blood concentrations achieved within 1.5 hours.[205] Blood concentrations are directly proportional to administered dose. The drug is not bound to blood proteins, and the elimination half-life of piracetam from blood is approximately 5 hours. Piracetam is excreted without metabolic modification via the urine. Only 1 to 2% of a dose is found in faeces, and drug recovery is almost complete within 30 hours.[206] Clearance of piracetam is therefore highly dependent on renal creatinine clearance and would be expected to decrease in patients with renal insufficiency.

Although piracetam is a very polar compound, and thus would not be expected to cross the blood-brain barrier, it readily enters the brain. In this organ it concentrates in cortical areas.[207,208]

To date, no significant interactions between piracetam and other commonly prescribed antiepileptic drugs have been reported (tables III and IV). Further, there are no known interactions between piracetam and drugs used in the treatment of non-epileptic conditions.

2.8.3 Therapeutic Efficacy and Adverse Effects

Piracetam represents the prototype of a group of drugs known as nootropics. For many years it has been used in some countries to treat learning deficits associated with aging and mild or moderate dementia, although there is a lack of controlled data in these indications.[209-216] Beneficial effects in dyslexic children have also been observed.[217,218]

In 1978, the first report of the use of piracetam as an antiepileptic drug appeared. Terwinghe and colleagues[219] reported a dramatic improvement in a patient with postanoxic action myoclonus during treatment with piracetam. Subsequently, 3 patients with myoclonus were reported to be dramatically improved when administered piracetam.[220-222] Further, 2 open label studies comprising a total of 45 patients with different clinical and electrophysiological types of myoclonus, confirmed the efficacy of piracetam in the management of cortical myoclonus.[223,224]

More recently, piracetam was evaluated in 21 patients using an add-on, double-blind, placebo-controlled, crossover design (2 patients received piracetam as monotherapy).[225] All 21 patients had action myoclonus, 3 had progressive myoclonic epilepsy of unknown aetiology and 1 patient had epilepsia partialis continua of unknown aetiology. In the run-in phase, piracetam was administered in an open label manner in increasing dosages, initially 2.4 g/day up to a maximum of 16.8 g/day or until stable clinical benefit was evident. Whilst 10 of 21 patients had to be rescued prematurely during the placebo phase due to exacerbation of myoclonus, no patient relapsed during treatment with piracetam. Furthermore, patients had more seizures during the placebo phase (8 seizures) than during the piracetam phase (2 seizures). This was despite the fact that the placebo phase was shorter than the piracetam phase (a median of 9 days versus 14 days, respectively).

Whilst substitution of piracetam for other antimyoclonic drugs has been of benefit in some patients, polytherapy has been a more successful therapeutic regimen. Thus, the addition of piracetam to clonazepam, valproic acid and primidone in various combinations has been particularly effective.

Numerous studies have been undertaken recently to investigate the mechanism(s) of this interaction.[203,226-229] Using electroconvulsive shock and tetanus toxin models of epilepsy, piracetam has been observed to strongly potentiate the anticonvulsant action of carbamazepine and weakly, but significantly, potentiate the actions of clonazepam and valproic acid. The actions of phenobarbital and phenytoin were unaffected by coadministration with piracetam in these models. The augmentation of the action of carbamazepine was however associated with a 25% increase in blood carbamazepine concentrations.[228] This pharmacodynamic synergism between carbamazepine and piracetam has recently been confirmed clinically in patients with epilepsy.[230]

Although high doses of piracetam are required to produce a therapeutic effect, it is unusually well tolerated with no major adverse effects reported. Doses of 1.6 to 15 g/day have been associated with a 1 to 3% incidence of hyperkinesia, insomnia, bodyweight gain, somnolence, nervousness and depression. Diarrhoea and rash have been observed occasionally (incidence <1%).

2.8.4 Current Therapeutic Status and Treatment Recommendations

Piracetam was licenced in the UK in 1993 and indicated as add-on therapy for adult patients with myoclonus of cortical origin, irrespective of aetiology. It is available as 800 and 1200mg tablets and as a solution containing 333.3 mg/ml for patients with dysphagia.

Significant interindividual variability in the required dosage regimen occurs. Therefore, an individualised dose-finding approach is recommended. A reasonable protocol would be to intro-

duce piracetam at a dosage of 7.2 g/day, increasing by 4.8 g/day every 3 to 4 days up to a maximum of 20 g/day, given in 2 or 3 divided doses. The dosage of concomitant antimyoclonic drugs should remain unchanged until an optimum piracetam dosage is achieved. Subsequently, and if possible and depending on clinical benefit, an attempt should be made to reduce the dosage of concomitant antimyoclonic drugs.

As piracetam is almost exclusively excreted by the kidneys, caution should be exercised when using the drug in patients with mild-to-moderate renal impairment [creatinine clearance 20 to 50 ml/min (1.2 to 3 L/h)] and in the elderly. Such patients would require approximately 25 to 50% the usual piracetam dosage. Piracetam is contraindicated in patients with severe renal insufficiency [creatinine clearance of less than 20 ml/min (1.2 L/h)].

2.9 Remacemide

2.9.1 Mechanism of Action

Remacemide is a diphenyl-ethyl-acetamide derivative (fig. 1). It can be considered a prodrug since its major metabolite, the deglycinated metabolite, exhibits even greater efficacy than the parent compound in animal seizure models.[231,232] It is effective against maximal electroshock-induced seizures (an action predicting utility in patients with generalised tonic-clonic seizures), but has little activity against chemically-induced seizures.[231-234] Furthermore, the (–)-stereoisomer of remacemide is more potent that either the racemate or the (+)-stereoisomer.[235] Remacemide interacts with the dizocilpine (MK801) and glycine sites of NMDA receptors; however, its exact mechanism of action is unknown.

2.9 2 Pharmacokinetics

Remacemide is rapidly absorbed after oral ingestion, with peak plasma concentrations achieved within 1 to 2 hours. Both the rate and extent of absorption appear to be unaffected by the presence of food in the gastrointestinal tract. Although remacemide has a short half-life (approximately 4 hours), its active deglycine metabolite has an apparent half-life of 12 to 24 hours.

The metabolic fate of remacemide in humans has not been completely determined, but at least 6 metabolites, as glucuronide conjugates, have been identified in the urine.[236] Approximately 90% of an administered remacemide dose is renally excreted. Its metabolism is inducible (tables III and IV), with plasma remacemide concentrations reduced by 70 to 80% and the deglycine metabolite by 18 to 30%. The clinical relevance of this interaction remains to be determined in view of the fact that the deglycine metabolite is the active component and relatively more of it, compared with remacemide, is present in the circulation. Thus, clearance of remacemide is increased in patients receiving phenytoin and carbamazepine compared with clearance in patients receiving valproic acid.[237]

2.9.3 Therapeutic Efficacy and Adverse Effects

Remacemide is currently undergoing early clinical evaluation. Therefore, knowledge of its efficacy and adverse effect profile is rather limited. Nevertheless, preliminary results are very encouraging, with efficacy observed as add-on therapy in patients with refractory partial and secondarily generalised seizures.[238-240] Furthermore, the tolerability profile of the drug also appears to be encouraging. The most common adverse effects are dose-dependent lightheadedness, dizziness and gastrointestinal upset. These effects resolve on drug discontinuation.

2.9.4 Current Therapeutic Status and Treatment Recommendations

The exact therapeutic status of remacemide will become apparent as data from the current trials of this drug become available.

2.10 Stiripentol

2.10.1 Mechanism of Action

Stiripentol, [4,4-dimethyl-1-(3,4 methylenedioxyphenyl)-1-penten-3-ol], is an ethylene alcohol and is thus structurally unrelated to any currently available or investigation antiepileptic drug (fig. 1). Its activity in numerous animal models, such as

the electroshock, pentetrazol infusion and alumina gel monkey models, suggests a broad spectrum of anticonvulsant activity, and efficacy comparable to carbamazepine and phenytoin. Efficacy is also comparable to that of the first line anti-absence drugs, valproic acid and ethosuximide.[241-244]

Stiripentol increases brain GABA levels by inhibiting GABA uptake and/or inhibiting GABA transaminase.[242,245] However, its exact mechanism of action is unknown.

2.10.2 Pharmacokinetics

After oral ingestion, stiripentol is slowly absorbed, resulting in a multiphasic elimination curve.[246,247] In healthy volunteers, oral bioavailability is approximately 30%.[246] The drug is extensively bound to plasma proteins, with a free fraction of 1%. Stiripentol is extensively metabolised. 12 metabolites have been identified, 25% of which are glucuronidated. 85% of a dose of stiripentol is excreted in urine. Steady-state plasma stiripentol concentrations increase disproportionately with increasing dose, indicating saturation non-linear pharmacokinetics of the Michaelis-Menten type.[248,249]

Stiripentol exhibits significant interactions with other antiepileptic drugs (tables III and IV). This can be attributed to stiripentol metabolism being inducible by enzyme-inducing antiepileptic drugs, such as carbamazepine, phenobarbital and phenytoin. Clearance values for stiripentol during comedication with these drugs increases by as much as 30%.[250,251] Further, the metabolism of carbamazepine, phenytoin and phenobarbital is inhibited by stiripentol.[248,252-255] The metabolism of valproic acid, however, is unaffected by stiripentol.[256] A reduction of carbamazepine clearance is detectable within 2 to 3 days of initiation of stiripentol therapy and becomes particularly pronounced by 7 to 10 days.[252] These interactions, which are highly predictable and reproducible, can be attributed to an inhibition of cytochrome P450 enzymes by stiripentol. Dosage adjustments will therefore be necessary during polytherapy.

2.10.3 Therapeutic Efficacy and Adverse Effects

Initial open, add-on trials indicated that stiripentol may have significant efficacy in the management of refractory partial seizures. However, interpretation of the efficacy data from these studies were complicated by drug interactions which were not controlled for.[250,251,257] Nevertheless, a recent study of stiripentol in 10 children (aged 6 to 10 years) with atypical absence seizures has taken drug interactions into account. Doses of concomitant antiepileptic drugs were adjusted in order to keep blood concentrations close to values observed prior to initiation of stiripentol therapy.[258] All patients experienced a decrease in seizures, ranging from 5 to 95% (mean 70%). Stiripentol is generally well tolerated. Dose-related adverse effects so far reported include anorexia, lethargy, nausea and vomiting.

2.10.4 Current Therapeutic Status and Treatment Recommendations

Further trials of stiripentol are warranted. However, such studies need to take into account that during add-on therapy with stiripentol, patients may require dosage reductions of approximately 25, 50 and 40% for phenobarbital, phenytoin and carbamazepine, respectively.[259] The unusual pharmacokinetic characteristics of stiripentol may prove problematic clinically. The fact that it exhibits non-linear saturation kinetics suggests that inter- and intra-patient variability will be significant, and that doses will need to be individualised.

2.11 Tiagabine

2.11.1 Mechanism of Action

Tiagabine, which is composed of the GABA inhibitor nipecotic acid and a lipophilic moiety (fig. 1), is a potent and specific inhibitor of GABA uptake into neurons and glia. As a consequence, the drug increases extracellular GABA levels.[260-262] This mechanism for enhancing inhibitory GABAergic transmission is novel and thus tiagabine represents a new pharmacological approach in the treatment of epilepsy. Tiagabine is effective in inhibiting pentetrazol- but not maximal electro-

shock-induced seizures.[263] It is also effective in audiogenic and photosensitive seizure models.[264]

2.11.2 Pharmacokinetics

After oral ingestion tiagabine is rapidly absorbed, with peak plasma concentrations achieved within 1 hour. The rate and extent of absorption may be affected by concomitant food ingestion. The drug is approximately 96% bound to plasma proteins and exhibits linear pharmacokinetics over the dosage range 40 to 80 mg/day.[265] Tiagabine is extensively metabolised, probably by hepatic cytochrome P450 enzymes, and may also undergo enterohepatic circulation.[266-268] Its elimination half-life in healthy volunteers is 5 to 13 hours and this parameter is not dose-dependent. However, half-life may be reduced in patients receiving concomitant enzyme-inducing antiepileptic drugs.[269] To date, no other drug interactions with tiagabine have been reported (tables III and IV).

2.11.3 Therapeutic Efficacy and Adverse Effects

Tiagabine is currently being evaluated as add-on therapy for the management of partial seizures.[270-274] One study (the European multicentre study) had a novel trial design in that it was a randomised study comprising 2 phases; a screening and a double-blind phase. In the screening phase, patients were administered increasing doses of tiagabine until a clinical response or unacceptable adverse effects were observed. Patients showing a >25% reduction in seizures were then entered into the double-blind phase, which had a placebo-controlled, crossover design. Of 94 patients entered into the trial 47 were randomised, the remaining patients were withdrawn due to either insufficient response to the drug or adverse effects. Compared with placebo, patients receiving tiagabine exhibited a 32% reduction in complex partial seizures and a 58% reduction in secondarily generalised seizures.[274] No adverse effects on cognitive function were found at the dosages used.[273] The median dosage during the screening phase was 32 mg/day, whilst during the double-blind phase the median dosage was 24 mg/day.

A recent multicentre, randomised, double-blind, placebo-controlled, parallel group study investigated the efficacy of 3 dosages of tiagabine (16, 32 and 56 mg/day) as add-on therapy in 257 patients. Tiagabine was effective in controlling complex and simple partial seizures.[275] A significant dose-effect relationship was observed with tiagabine 32 and 56 mg/day being particularly effective. Other controlled and open studies are currently underway, including a monotherapy study.[270]

Dose-dependent CNS-related adverse effects, including sedation, headache, tiredness and dizziness, are commonly observed after administration of tiagabine to healthy volunteers. These resolved upon withdrawal of the drug.[265,276] Multidose studies are currently in progress to determine the safety and tolerability of tiagabine in patients with epilepsy. Data obtained so far have generally confirmed the data from healthy volunteers, except that higher dosages appear to be tolerated (approximately 20 to 30 mg/day in patients compared with 6 to 12 mg/day in healthy volunteers).[275]

2.11.4 Current Therapeutic Status and Treatment Recommendations

Preliminary data on tiagabine suggest that it is effective in patients with partial seizures. Since it acts by increasing GABA levels in the synaptic cleft it may prove to have an antiepileptic drug profile similar to vigabatrin. A possible disadvantage of tiagabine is its relatively short half-life, which may necessitate administration 3 to 4 times per day. However, if tiagabine proves to have less adverse effects than vigabatrin, particularly fewer behavioural effects, it may prove to be more desirable clinically.

2.12 Topiramate

2.12.1 Mechanism of Action

Topiramate, a sulphamate-substituted monosaccharide, is structurally distinct from other antiepileptic drugs (fig. 1). It has a profile of action similar to phenytoin and carbamazepine in animal models of epilepsy.[277,278] It is effective in blocking maximal electroshock-induced seizures in both rats and mice, but is ineffective in blocking chemically-induced seizures. These observations suggest that

topiramate blocks seizure spread rather than increases seizure threshold, and probably acts by limiting sodium-dependent action potentials. Topiramate has been reported to decrease the extracellular level of glutamate and aspartate, but not GABA or taurine, in the hippocampus of spontaneously epileptic rats. Topiramate also potentiates GABA-induced chloride flux into cultured cerebellar granule cells.[279]

2.12.2 Pharmacokinetics

Topiramate is well absorbed after oral ingestion, with peak plasma concentrations achieved within 2 to 4 hours. Bioavailability is ≥75%. While the rate of topiramate absorption is moderately slowed by food, the extend of absorption is unaffected.[280] The drug is primarily excreted unchanged in the urine, with the fraction excreted ranging between 70 and 97% of the dose. The elimination half-life of topiramate ranges from 19 to 23 hours and is independent of dose. However, during repeated administration, topiramate accumulates, resulting in an increase in plasma concentrations of approximately 2-fold compared with those seen after single dose administration. This is consistent with a plasma elimination half-life of 20 to 30 hours. The drug is approximately 15% bound to plasma proteins.

Pharmacokinetic interactions between topiramate and carbamazepine, phenytoin or valproic acid have been investigated.[280] Concomitant administration of topiramate has no effect on phenytoin, carbamazepine and valproic acid concentrations.[281,282] However, these drugs reduce topiramate plasma AUC values for an administration interval by approximately 50, 30 and 15%, respectively (tables III and IV).[283]

2.12 3 Therapeutic Efficacy and Adverse Effects

Topiramate is currently undergoing clinical investigation, with over 1000 patients having been exposed to the drug. Some patients have been taking topiramate for over 4 years. Preliminary results are very encouraging with clear antiepileptic efficacy in patients with partial seizures and also in patients with Lennox-Gastaut syndrome.[284-288]

Adverse effects noted have been generally mild and reversible and include tiredness, diarrhoea, dizziness/ataxia and paraesthesiae. Of 18 patients who entered a 2-year open extension study, 13 patients responded to a mean dosage of 500 mg/day. Four patients achieved >70% seizure reduction and 6 patients experienced a 50 to 70% reduction.[288] At 2 years of follow-up, long term adverse effects have not been detected.[287]

Animal studies suggest that topiramate may have significant teratogenic potential. This may become a major consideration in the clinical use of the drug.

2.12.4 Current Therapeutic Status and Treatment Recommendations

The role of topiramate in the management of epilepsy will be clarified when detailed data from the current clinical studies become available.

2.13 Vigabatrin

2.13.1 Mechanism of Action

Vigabatrin is a structural analogue of GABA (fig. 1). It acts by selectively and irreversibly inhibiting GABA transaminase, the enzyme responsible for the metabolism of GABA.[289] It comprises a racemic mixture of its 2 enantiomers; the *S*-(+)-enantiomer and the *R*-(–)-enantiomer. It is the *S*-(+)-enantiomer that potently inhibits GABA transaminase.[290]

Vigabatrin dose-dependently increases brain GABA levels in animals, and brain and cerebrospinal fluid (CSF) GABA levels in humans.[88,291-296] In rat cortex, vigabatrin increases synaptosomal GABA content more than non-synaptosomal GABA, indicating a preferential inhibition of neuronal GABA transaminase.[297] It is effective against strychnine-, picrotoxin- and isoniazid-induced seizures, and in the electroconvulsant shock rodent and audiogenic and photoepileptic baboon models.[298-300] Vigabatrin also retards the development of kindling.[301]

2.13.2 Pharmacokinetics

Vigabatrin is rapidly and almost completely absorbed following oral administration, and food has little effect on either the rate or extent of absorp-

tion.[302-304] Peak plasma concentrations occur within 2 hours.[305] Protein binding in the blood is negligible. Metabolism in humans is minimal as evidenced by <5% of an administered dose being represented by 2 minor urinary metabolites. Elimination is not dose-dependent and is primarily by renal excretion, with 75 to 95% of a given dose excreted as unchanged drug within 24 hours.[303,306,307] During repeated administration, steady-state concentrations of vigabatrin are achieved by the second day of administration, and drug accumulation is minimal.[308]

In healthy volunteers, the elimination half-life of vigabatrin is 5 to 7 hours, whilst in patients with epilepsy taking enzyme-inducing antiepileptic drugs elimination half-life values of approximately 4 to 6 hours have been observed.[302,303,309-313] This suggests that a fraction of vigabatrin might be metabolised by the liver and therefore subject to induction by concomitant enzyme-inducing antiepileptic drugs.

Clearance of vigabatrin is directly related to creatinine clearance.[314] Therefore, an adjustment in dose or reduction in frequency of vigabatrin administration should be considered in patients with renal impairment. There is no correlation between the pharmacological effect of vigabatrin and its time course and concentration in either the brain or blood.[302] This can be explained by the rate of resynthesis of GABA transaminase. Five to 6 days is required to regain full enzyme activity, which is long after vigabatrin is eliminated.[290] Further, clinical experience in patients with epilepsy indicates that plasma vigabatrin concentrations can vary greatly from patient to patient.[315,316]

Theoretically, interactions between vigabatrin and other drugs should not occur since vigabatrin is essentially not metabolised and it is not bound to blood proteins. However, vigabatrin causes plasma phenytoin concentrations to decrease by about 30% after about 1 month of coadministration.[311,317-320] The mechanism of this interaction has been studied clinically, but remains unresolved.[307,320] Although, a recent study in rats suggested that a delay in phenytoin absorption may be a contributing factor,[321] in humans, the most likely mechanisms (i.e. hepatic enzyme induction and bioavailability) have been excluded.[307,320] Plasma phenobarbital and primidone concentrations may also decrease during comedication with vigabatrin, but these decreases are not usually clinically significant.[311]

2.13.3 Therapeutic Efficacy and Adverse Effects

As vigabatrin was the first of the 'new' antiepileptic drugs to become available for clinical evaluation it has been extensively evaluated as add-on therapy in refractory patients. A variety of study protocols have been used, including double-blind crossover designs.[311,316,318,319,322-335] Meta-analysis of these studies show that vigabatrin treatment (up to 4 g/day) is associated with at least a 25% reduction in complex partial seizures in 72% of patients whether or not the seizures also become generalised. Meta-analysis of all placebo-controlled European trials (n = 487) indicates that vigabatrin is more effective against partial seizures than against generalised seizures.[336,337] However, because experience in other seizure types is limited, these observations may in fact reflect patient selection bias.

Vigabatrin is effective in monotherapy.[317,338] It also appears that vigabatrin is as effective as carbamazepine in newly diagnosed patients receiving carbamazepine as monotherapy and subsequently switched to vigabatrin monotherapy.[339,340] However, successful vigabatrin monotherapy appears to occur in only those newly diagnosed patients with high baseline CSF glutamate levels.[338] Recently, the use of vigabatrin in the management of intractable infantile spasms has been reported[341,342]. Three of 6 children prescribed vigabatrin as monotherapy became seizure-free within 2 weeks.[342] Vigabatrin has also been reported to be effective in 3 patients (a 6-month-old child, a 3-year-old boy and a 31-year-old woman) with Sturge-Weber syndrome.[343,344] Some patients with Landau-Kleffner syndrome, West syndrome and Lennox-Gastaut syndrome have been reported to respond very well to vigabatrin treatment.[345,346]

The antiepileptic effect of vigabatrin is directly related to dosage.[291,347,348] However, there is a suggestion that there is an optimal dose for each patient, above which seizure control is not increased and may even deteriorate. For many patients this appears to be approximately 2 g/day.[349]

In animal studies, tolerance to the antiepileptic effect of vigabatrin has been reported.[301,350] However, although apparent tolerance has been noted in a few patients,[332,339,351] tolerance is not regarded as a clinical problem.[334,352] In long term studies (1 to 5 years), withdrawal rates of 10 to 40% due to decreased efficacy were reported.[334,339,340,353] Interpretation of these studies is difficult because the dose of concomitant antiepileptic drugs had been reduced in some patients and patients who had unsatisfactory seizure control often withdrew from the studies.

Vigabatrin is generally well tolerated, with 5 to 15% of patients treated for between 6 months and 5 years withdrawing due to unacceptable adverse effects.[311,319,328] The most common adverse effects were drowsiness (incidence 13%) and fatigue (13%). Other adverse effects include irritability, dizziness, ataxia, diplopia, depression and insomnia. These effects are usually mild and transient, occurring most frequently in the first 3 months and most are dose-dependent. Bodyweight gain tends to occur in some patients, usually in the first 6 months, with gains of 5 to 15% of bodyweight being reported in 40% of patients.[319] One study found slight slowing of motor function and impairment on a measure of visual memory.[324] Psychotic reactions, including hallucinations and paranoia, were reported in 7 of 45 patients.[354,355] These reversible reactions, which may be dose-dependent and may involve mood disturbances and aggressive behaviour, were less common in other patient series. It has been suggested that patients with a history of psychosis may be particularly predisposed to such adverse effects and that the development of psychosis in vulnerable patients may be, in part, attributable to an effect of vigabatrin on dopaminergic receptors in the basal ganglia.[356]

Meta-analysis of 9 placebo-controlled clinical trials involving 348 patients, showed that depression was reported in 4% of patients and thus making depression the most common adverse effect.[337] Recently, 10 patients with intractable epilepsy who developed a major depressive episode in association with vigabatrin treatment have been reported.[357] Seven patients developed depression within 2 months of starting vigabatrin treatment, during or soon after a dose increase, and 3 patients within 6 weeks of a dose increase. Depression resolved on withdrawal or reduction of vigabatrin dose, and it is suggested that the occurrence of depression is dose-dependent.[357] However, some studies have reported a lack of effect of vigabatrin on cognitive function or mood.[358-360] This can be attributed to the fact that these studies involved a small cohort of patients and, thus, statistically significant depression was not identified.

Four cases of complex partial status epilepticus have been reported on initiation of vigabatrin therapy at dosages of 2 to 4 g/day.[361] In 2 patients, who had had previous episodes of complex partial status epilepticus, the disorder presented 3 and 4 days post-initiation of therapy. In the other 2 patients, who had no previous history of status epilepticus, the disorder occurred 29 and 67 days, respectively, after initiation of vigabatrin therapy. Two of the patients developed acute encephalopathy (one patient was diagnosed as having myoclonus status epilepticus) after starting vigabatrin 2 g/day as add-on to carbamazepine.[362] Both patients recovered after withdrawal of vigabatrin.

Animal toxicological data demonstrate the occurrence of dose- and species-dependent intramyelinic oedema and astrocytosis, identified using magnetic resonance imaging (MRI), with vigabatrin.[363,364] Pathological data from patients exposed to therapeutic doses of vigabatrin for periods of up to 6 years do not support the view that intramyelinic oedema occurs in humans.[334,365-369] Furthermore, serial quantitative MRI studies of patients treated with vigabatrin for up to 18 months have not found evidence suggestive of neuropathological changes[370] and evoked responses

have not been prolonged in patients taking the drug.[340,371]

Finally, the abrupt withdrawal of vigabatrin has been associated with the rapid onset of agitation, hallucinations and delusional thinking and with transient increases in seizure frequency. Therefore, caution is required on discontinuation of vigabatrin.[318,335,372-374]

2.13.4 Current Therapeutic Status and Treatment Recommendations

Vigabatrin has recently been marketed in numerous countries worldwide. Its indications are as add-on treatment for the management of epilepsy that is not satisfactorily controlled by other antiepileptic drugs. Vigabatrin is available as a 500mg tablet and as a sachet containing 500mg of vigabatrin powder. The drug is most effective against partial and secondarily generalised seizures. The role of vigabatrin in primary generalised tonic-clonic seizures is unclear, and absences and myoclonic jerks are likely to be worsened by the drug.

In adults, a suitable starting dosage is 0.5 g/day, increased in 0.5g increments every 1 to 2 weeks up to a maximum dosage of 4 g/day. This rate of introduction is slower than is recommended in the data sheet, and appears to be associated with lower risk of neuropsychiatric complications. If treatment is to be discontinued it is recommended that this is done in 0.5g steps over 2 to 4 weeks.

The maximum recommended starting dosage in children is 40 mg/kg/day, increasing to 80 to 100 mg/kg/day depending on response. Infants with West syndrome may requires doses of 100 mg/kg/day or higher. Vigabatrin should be used with caution in patients with a history of psychosis, affective disorders or behavioural problems.

The recommended plasma target range is presently 40 to 270 μmol/L. However, since the duration of effect of vigabatrin is dependent on the rate of GABA transaminase enzyme resynthesis, there is no direct correlation between plasma concentration and efficacy. Measuring plasma vigabatrin concentration may be useful as a check of resent compliance.

2.14 Zonisamide

2.14.1 Mechanism of Action

Zonisamide is a substituted 1,2-benzisoxazole derivative (fig. 1). The exact mechanism of action of the drug is not known, but it appears to act by blocking sodium channels, suppressing T-type calcium channels and attenuating the propagation of seizure discharge and focal epileptogenic activity.[375-378] It is effective against maximal electroshock seizures and decreases duration of focal seizures with a profile and protective range similar to phenytoin and carbamazepine, but with a wider therapeutic index.[375,379,380] In the kindled model, zonisamide delays the development of generalised kindled seizures.[381] Regional brain distribution of zonisamide is similar to phenytoin.[382]

2.14.2 Pharmacokinetics

Zonisamide exhibits some unusual and rather complex pharmacokinetic characteristics. After oral ingestion, zonisamide is rapidly and almost completely absorbed, with peak blood concentrations achieved within 2 hours in both healthy volunteers and patients with epilepsy.[383,384] Zonisamide is highly concentrated in erythrocytes, with concentrations exceeding those in plasma 4- to 9-fold. This can be attributed to its high affinity binding to carbonic anhydrase and other red cell protein components. Approximately 50% of zonisamide in blood is bound to plasma proteins and binding is a saturable process, decreasing with increasing drug concentration.[385-387]

Zonisamide is excreted partly unchanged and partly as acetylated and glucuronide conjugates in the urine. 29% (unchanged) and 19% (conjugates) of an administered dose are eliminated after 15 days.[385] The elimination half-life of zonisamide is approximately 60 hours in healthy volunteers and 28 hours in patients taking hepatic enzyme-inducing antiepileptic drugs, such as phenytoin and carbamazepine.[388,389] The metabolism of zonisamide is saturable, resulting in a non-linear relationship between plasma zonisamide concentrations and dosage.[390] Further, the effective plasma concentration of zonisamide is rather variable in

both paediatric and adult patients with epilepsy.[391,392] Plasma concentrations of carbamazepine are elevated during comedication with zonisamide, but no other interactions have been reported[393] [table III and IV].

2.14.3 Therapeutic Efficacy and Adverse Effects

Most of the efficacy studies relating to zonisamide have been noncomparative in which the drug was administered alone or in combination with other antiepileptic drugs to patients with various seizure types. These studies have mainly been undertaken in Japan, but some studies have been performed in Europe and the US. Although clinical trials of the drug were suspended in 1988 in Europe and the US, because of the observation of urinary calculi in some patients, plans are now underway to develop zonisamide further.

Antiepileptic efficacy was confirmed in early pilot studies in patients with refractory partial and generalised tonic-clonic seizures.[393-395] Meta-analysis of add-on studies undertaken in Japan involving 605 adults and 403 children who were treatment-resistant also indicates that zonisamide is effective in the management of partial seizures.[396] Furthermore, a double-blind, multicentre study of zonisamide has shown it to be effective in simple and complex partial and secondarily generalised tonic-clonic seizures.[377]

Open studies in children have shown zonisamide to be effective in a variety of seizure types, including atypical absences, atonic seizures and myoclonic seizures.[397-401] Zonisamide is also effective in adult myoclonus epilepsy.[402]

Recently, 2 multicentre studies of zonisamide have been reported.[403,404] The first, a noncomparative study undertaken in the US and involving 167 patients, reported responder rates of approximately 41% for complex partial seizures, 68% for generalised tonic-clonic seizures and 41% for combined partial and generalised tonic-clonic seizures.[403] The second study was a European multicentre, parallel group, double-blind trial of zonisamide as add-on treatment in 139 patients with refractory partial seizures. This demonstrated that in approximately 30% of patients there was a statistically significant and clinically relevant reduction in seizures compared with placebo.[404]

Pooled data from the comparative and noncomparative clinical trials (n = 1008) suggest that 18% of patients withdrew from treatment due to adverse effects.[377,396] During polytherapy the most frequently noted adverse effects were drowsiness (24% of patients), ataxia (13%), loss of appetite (11%), gastrointestinal distress (7%) and memory loss (5%). Among 55 patients treated with zonisamide monotherapy the principal adverse effects were drowsiness and loss of appetite. During initial therapy with zonisamide cognitive deficits occurred, but resolved with time (usually by 24 weeks).[405] Recently, zonisamide has been implicated in behavioural disorders in 2 children; a girl aged 13 months and a boy aged 35 months.[406] Their behaviour disorders resolved after discontinuing zonisamide. The apparent increased incidence of renal calculi in European and American patients (0.2%) compared with Japanese patients is curious and needs to be resolved. Possible differences may be attributable to diet, environment or genetic constitution.

2.14.4 Current Therapeutic Status and Treatment Recommendations

Zonisamide has been marketed as an antiepileptic drug in Japan since 1989. It appears to have a broad spectrum of activity and is particularly effective in the management of simple and complex partial seizures and secondarily generalised tonic-clonic seizures. It is also effective in myoclonus. To date, no severe adverse effects have been reported and drug interactions are negligible. However, the possible association with renal calculi needs to be resolved and this is being addressed currently in clinical trials in Europe and the US. The recommended plasma target range is presently 30 to 190 μmol/L. However, adverse effects have been noted in some patients at plasma concentration in excess of 140 μmol/L.

3. Combination Therapy

In recent years, monotherapy with antiepileptic agents has been advocated. For approximately 80

to 85% of newly diagnosed patients, complete seizure control can be achieved with this therapeutic approach. However, for 10 to 15% of patients with epilepsy, satisfactory seizure control cannot be achieved with a single drug. In these patients, antiepileptic drug duotherapy often may provide better seizure control.

Although additive or synergistic pharmacodynamic interactions with antiepileptic agents have been well documented in animal studies, the exact mechanism of these interactions is not known.[39,254,407-410] Possible mechanisms include interaction with a common receptor or a common enzyme system.

In contrast, there are few data on the occurrence or magnitude of such interactions in humans. Nevertheless, some antiepileptic drug combinations are widely used. For example, the combination of ethosuximide plus valproic acid is considered to be more effective in controlling typical absences refractory to either treatment alone.[411] Other beneficial synergistic combinations that have been described include carbamazepine plus valproic acid,[412,413] clonazepam plus valproic acid,[414] and valproic acid plus lamotrigine.[415,416] Furthermore, in patients with poorly controlled generalised and/or partial seizures, the combination of carbamazepine plus phenobarbital plus phenytoin has been shown to be more effective than any drug alone or a combination of any two of the drugs.[417]

With the availability of new antiepileptic drugs with known mechanisms of action (e.g. vigabatrin, tiagabine and lamotrigine), it may be possible for a rational polypharmacy approach to be contemplated. In such a regimen, additive or synergistic and pharmacologically favourable drug combinations could be used. Thus, polytherapy with vigabatrin or tiagabine (which enhance GABAergic transmission) and lamotrigine (which reduces the release of glutamate) may be a rational combination.

Anecdotal clinical experience with vigabatrin plus lamotrigine and valproic acid plus lamotrigine has been encouraging. A recent single-blind followed by an open phase study of vigabatrin as add-on therapy in 17 patients (8 patients were receiving carbamazepine monotherapy) showed that 74% of patients had a >50% reduction in seizure frequency.[418] Since these results are better than those of most studies of vigabatrin, the authors suggest that this is evidence of the feasibility of rational polytherapy. Controlled clinical studies are clearly needed to investigate the feasibility of such a therapeutic approach. These studies will need to assess the efficacy of the combinations and to ensure that such therapy does not result in a significant increase in adverse effects.

4. Conclusions

Overall, approximately 80% of newly diagnosed patients go into remission during treatment with currently available antiepileptic drugs. For the remaining 20%, who are not well controlled or who experience adverse effects from these standard drugs, new drugs offer the chance of an improved quality of life.

In recent years, as a result of better understanding of the molecular basis of epilepsy, major advances in antiepileptic drug development have occurred. Since 1989, seven new drugs have been licenced around the world (felbamate, gabapentin, lamotrigine, oxcarbazepine, piracetam, vigabatrin and zonisamide) and more can be anticipated within the next few years. Many patients have already benefitted and many more will benefit from their use. Much has been discovered about the mechanism of action of the new antiepileptic drugs and presently some have unique mechanisms. In the future, it may be possible to choose rational combinations of drugs that have complementary mechanisms of action.

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