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Señora

JEFE DE DIVISIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E.

S.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Tr: 2 PATENTES Eje 1 REGDEPOSITO
A-444 DEBEN ESTABLECER Eje 2 39

Respuesta a Oficio No. 2346 del 02 de marzo de 2006

REF: Expediente No. 00 091 771 – solicitud de patente de invención
a favor de UCB, S.A.

JUAN PABLO CADENÁ SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado sustituto de la sociedad UCB, S.A., domiciliada en Bruselas, Bélgica, según lo acredita el documento de sustitución de poder a mi favor anexo, me permito dar respuesta a las observaciones de carácter técnico y jurídico, relacionadas con la patentabilidad, para la concesión de la patente de acuerdo con la Decisión 486 según el concepto técnico No. 262 notificado por fijación en lista de fecha 02 de marzo de 2006.

Atendiendo las observaciones del señor Examinador, en relación con el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito anexar al presente escrito los siguientes documentos:

- 1) PROUS. "Levetiracetam". Drugs of the future. Barcelona (España). 1994.
19(2) pages 111-113.
- 2) WILSON E. A. ET AL. "New antiepileptic drugs". Baillière's Clinical Neurology.
Londres (GB). 1996. 5(4) pages 723-747.
- 3) WIESSER H. G. "Behandlung der epilepsien: Wo Stehen wir heute?".
Schweizerische Rundschau für Medizin/Praxis. 196. 85(4) pages 74-79.

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Expediente No. 00 091 771

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Con lo anterior hemos dado total cumplimiento a los requerimientos del señor examinador, consideramos por lo tanto que la solicitud se encuentra en condiciones de ser permitida.

De la Señora Jefe,

Atentamente,



JUAN PABLO CADENA SARMIENTO

T.P. No. 57.492 del C.SJ.

C.C. 80.410.337 de Usaquén

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Bogotá, 05 de marzo de 2006

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Anexos

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

REF.: Expediente No. 00 091.771
Solicitante: UCB, S.A.

HECTOR GOMEZ MEJIA, mayor de edad y vecino de esta ciudad, identificado como aparece al pie de mi firma, en mi calidad de Apoderado General de UCB, S.A.

Manifiesto por el presente que SUSTITUYO el Poder conferido en el abogado JUAN PABLO CADENA SARMIENTO, también mayor de edad y vecino de esta ciudad, identificado como aparece al pie de su firma, para que actúe ante esa División en las diligencias que se adelantan dentro del expediente de la referencia.

El apoderado sustituto queda ampliamente facultado para intervenir ante esa División; presentar solicitudes, modificaciones, y afectaciones; presentar oposiciones; presentar objeciones; presentar demandas de cancelación; interponer y presentar recursos; pagar; notificarse; desistir; conciliar y transigir; renunciar; sustituir y reasumir este Poder; y en general adelantar todas las actuaciones requeridas para la defensa y efectividad de los intereses de mi representada.

Ruego se le reconozca personería en los términos de esta sustitución.

Respetuosamente,


HECTOR GOMEZ MEJIA
C.C. No. 22720 de Bogotá
T.P. 19436 del C.S.J.

ACEPTO:

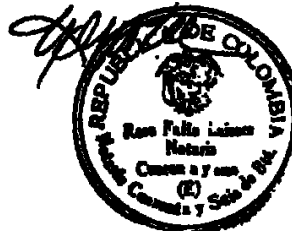

JUAN PABLO CADENA SARMIENTO
C.C. No. 80.410.337 de Usaquén
T.P. 57492 del C.S.J.

ALIDENCIA DE PRESENTACION PERSONAL Y
X REUNION DE CONTENIDO Y FIRMA

El anterior escrito dirigido al _____

Fue presentado personalmente ante el suscrito
Notario Cuarenta y Seis de Bogotá por
HERNAN GOMEZ MEJIA
quien se identificó con la §. C 22720
Bogotá y T. P. 19436
C.S.J. y además declaró que el contenido
del anterior documento es cierto y que la firma
que lo autoriza fue puesta por él, en constancia
la firma en Bogotá, 30 DIC 2005

Hernán Gómez Mejía 



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Drugs of the Future 1994, 18(2): 111-113
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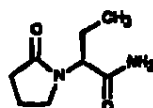
L vetiracetam

Rev 001

Anticonvulsant

Ucb-L059
SIB-S1

(S)- α -Ethyl-2-oxo-1-pyrrolidineacetamide
2-(S)-(2-Oxopyrrolidin-1-yl)butyramide



$C_9H_{14}N_2O_2$

Mol wt 170.21

CAS: 102787-28-2

EN: 113836

Syntheses

Reaction of (S)-2-aminobutyramide (I) with ethyl 4-bromobutyrate (II) in the presence of triethylamine in toluene gives ethyl (S)-4-[1-(carbamoyl)propylamino]butyrate (III), which is cyclized in toluene by means of 2-hydroxypyridine. Compound (I) can also be condensed with 4-chlorobutyryl chloride (IV) either directly in the presence of tetrabutylammonium bromide (TBAB) in dichloromethane, followed by *in situ* treatment with potassium hydroxide, or via the isolation of intermediate (S)-N-[1-(carbamoyl)propyl]-4-chlorobutyramide (V) (1). Scheme 1.

An alternative procedure involves hydrolysis of racemic ethyl 2-(2-oxopyrrolidin-1-yl)butyrate (VI) with sodium hydroxide to give racemic 2-(2-oxopyrrolidin-1-yl)butyric acid (VII), which is resolved by fractional crystallization with (R)-(+)- α -methylbenzylamine in benzene, followed by acid-base treatment to give (S)-2-(2-oxopyrrolidin-1-yl)butyric acid (VIII). Compound (VIII) is finally treated with ethyl chloroformate and ammonia in dichloromethane (1). Scheme 1.

A third procedure involves Ni-Raney desulfurization of (S)-4-(methylthio)-2-(2-oxopyrrolidin-1-yl)butyramide (XI),

prepared from (S)-2-amino-4-(methylthio)butyramide (IX) by reaction with 4-chlorobutyryl chloride (IV). Compound (XI) can also be obtained by treatment of (IX) with ethyl 4-bromobutyrate (II) to give ethyl (S)-4-[1-(carbamoyl)-3-(methylthio)propylamino]butyrate (X), which is cyclized in toluene by means of 2-hydroxypyridine (2). Scheme 1.

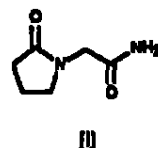
Description

Solid, m.p. 115-8 °C; $[\alpha]_D^{25}$ -89.7° (c 1, acetone) (1); m.p. 117 °C; $[\alpha]_D^{25}$ -90.0° (c 1, acetone) (1); m.p. 117 °C; $[\alpha]_D^{25}$ -91.3° (c 1, acetone) (1); m.p. 116.7 °C; $[\alpha]_D^{25}$ -90.1° (c 1, acetone) (1); m.p. 112-5 °C; $[\alpha]_D^{25}$ -90.0° (c 1, acetone) (2).

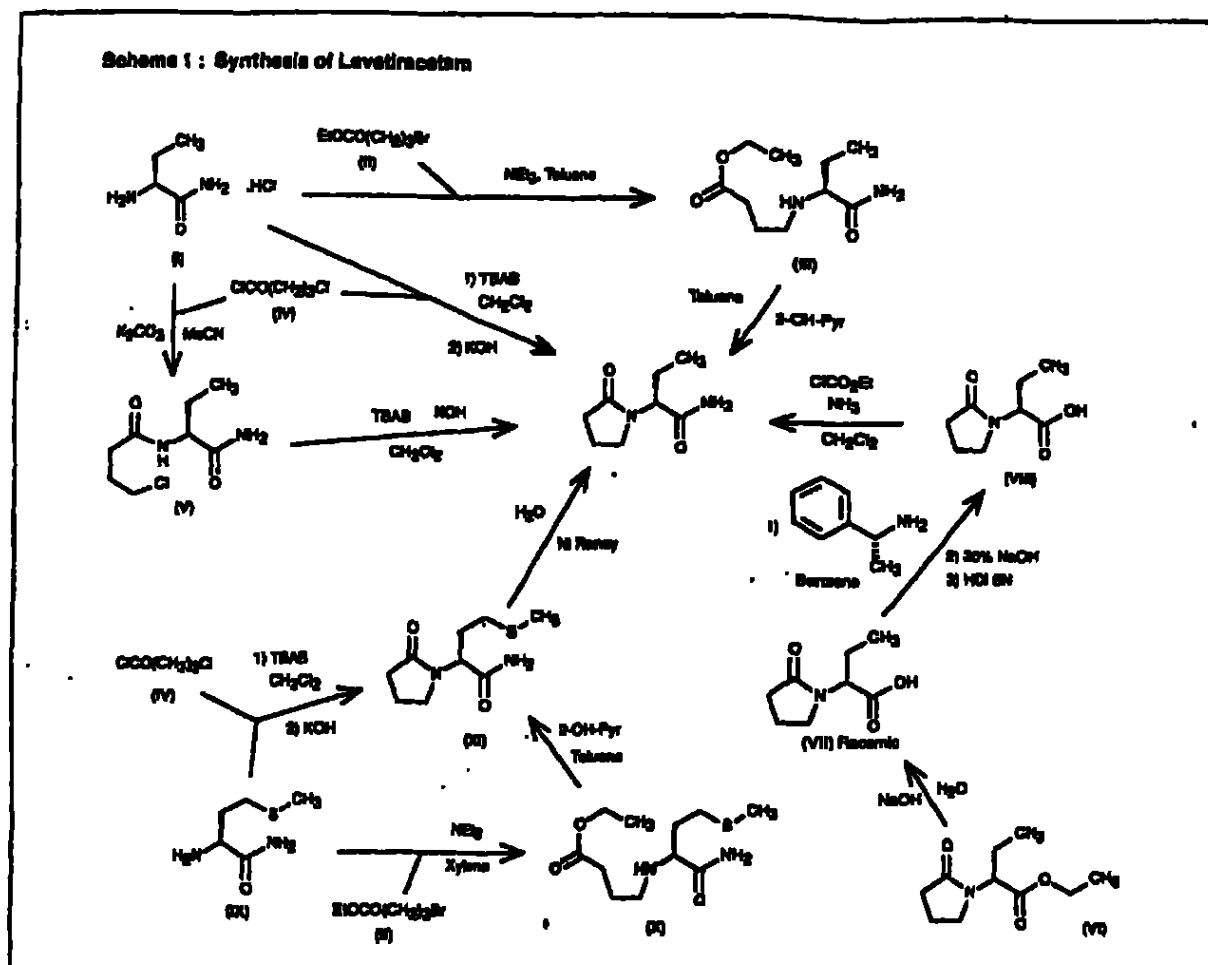
Introduction

Piracetam (UCB) (I), the prototype of the nootropic agents, has been used clinically since 1972 as a cognition-enhancing agent in the elderly. The mechanism of action of these drugs is unknown, but some evidence suggests that effects on energy metabolism and neuronal excitability may be involved (3, 4). Recently, piracetam and other nootropic drugs have been reported to exert anticonvulsant effects in different animal models (5-7). Piracetam has also been reported to improve seizure protection in epileptic patients receiving carbamazepine (8).

Scientists at UCB reported the nootropic properties of UCB-L059, a close structural analog of piracetam, and it



J. Prous, N. Masly, J. Castañer, Prous Science Publishers, P.O. Box 840, Barcelona 08080, Spain.



was shown to be considerably more active than physostigmine in a scopolamine-induced amnesia model in mice (9). UCB-L059 also appeared to facilitate cholinergic function *in vitro* through a stereospecific mechanism (10). More recently, UCB-L059 was shown to exert potent anticonvulsant effects and was selected for further evaluation as an antiepileptic drug (11).

Pharmacological Actions

The anticonvulsant profile and neurotoxicity of UCB-L059 have been evaluated in a number of rodent models. In the audiogenic seizure assay in mice it was found to dose-dependently protect against both tonic and clonic convulsions with ED_{50} values of 7.0 and 9.7 mg/kg p.o., respectively, whereas higher doses were required to prevent wild running ($ED_{50} = 31.7$ mg/kg); it was also active against tonic seizures after i.p. administration ($ED_{50} = 8.8$ mg/kg). UCB-L059 induced dose-dependent protection against tonic convulsions induced by maximal electroshock in mice ($ED_{50} = 23.5$ mg/kg p.o.), with no effect against clonic convulsions. Tonic convulsions induced in mice by a maximal dose of pentylene-

trazol (100 mg/kg i.p.) were inhibited by 25–30% at doses of 5.4 mg/kg p.o. and higher, but no effect was observed on clonic convulsions. Using submaximal doses of pentylenetetrazol (80–90 mg/kg i.p.), UCB-L059 dose-dependently inhibited tonic convulsions ($ED_{50} = 26\text{--}65\text{ mg/kg p.o.}$). Bicuculline-induced tonic convulsions in mice were dose-dependently antagonized by title compound ($ED_{50} = 29.5\text{ mg/kg p.o.}$), and it also reduced clonic convulsions by 30–80% at doses of 17–170 mg/kg. UCB-L059 significantly reduced NMDA-induced tonic convulsions in mice at doses of 5.4–170 mg/kg i.p., clonic convulsions showing a significant reduction only at the highest dose. Pretreatment of mice with UCB-L059 (5.4–54.0 mg/kg i.p.) dose-dependently delayed the development of pentylenetetrazol-induced kindling, and in rats it reduced pentylenetetrazol-induced spike and wave discharge at doses of 5.4 and 17.0 mg/kg i.p. Tonic convulsions induced in rats by bicuculline were dose-dependently reduced ($ED_{50} = 7.7\text{ mg/kg p.o.}$, 5.1 mg/kg i.p.), but no effect was observed on clonic convulsions. UCB-L059 also dose-dependently (17 and 54 mg/kg p.o.) reduced picrotoxin-induced tonic convulsions in rats. The anticonvulsant activity was found to be stereospecific, the *R*-enantiomer, UCB-L060, showing low intrinsic activity in

these models. Title compound showed minimal neurotoxicity using the Irwin (mice and rats), rotarod (mice) and open-field (mice) tests, giving a neurotoxicity index (ED₅₀ for inhibition of tonic convulsions in audiogenic mice/ED₅₀ in the rotarod test) of > 243 (11).

The activity of UCB-L059 was also evaluated in rodent models of partial and generalized seizures. Although it was found to be inactive in the traditional maximal electroshock test in mice and rats and the s.c. pentylenetetrazol test in mice, it increased the thresholds for tonic electroshock seizures (TID₅₀ = 40 mg/kg i.p. in mice and 29 mg/kg i.p. in rats) and for myoclonic and clonic seizures induced by timed i.v. infusions of pentylenetetrazol (TID₅₀ = 40 mg/kg i.p.). In amygdala-kindled rats it suppressed secondarily generalized seizures (ED₅₀ = 40 mg/kg i.p.), and it significantly increased the focal seizure threshold and significantly decreased the afterdischarge duration and seizure severity at 54 mg/kg i.p. UCB-L059 significantly decreased body temperature in both mice and rats, but it showed no effect in the rotarod test, and minimal effects in the chimney and open-field tests in mice and rats (12).

In studies on the mechanism of action of UCB-L059 in rats, pretreatment with anticonvulsant doses of UCB-L059 prevented the increase in dopamine and DOPAC release induced by bicuculline in brain perfusates, whereas only partial blockade of the release of dopamine, DOPAC and homovanillic acid (HVA) induced by haloperidol was observed. These results indicate that the mechanism of action of title compound involves direct dopaminergic activation, as well as a possible effect on GABAergic function (13).

Clinical Studies

The safety of add-on therapy with UCB-L059 has been assessed in 18 patients treated with phenytoin, carbamazepine, valproate or carbamazepine + valproate. At doses of 500-2000 mg/day, UCB-L059 demonstrated no significant interactions with the classical antiepileptic drugs. Adverse effects of excessive sleep, nausea and decreased appetite were reported in five, two and two patients, respectively; the only significant laboratory abnormality was a tendency for a decrease in serum creatinine (14).

UCB-L059 is in phase II trials in Europe, where it is being developed for the treatment of both epilepsy and anxiety. It is being developed and copromoted by SIBIA as SIB-S1 in the USA and Canada for the treatment of epilepsy, and the FDA has granted approval for clinical trials (15, 16).

Manufacturer

UCB (Belgium); licensed to SIBIA, Inc. (USA).

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16. SIBIA receives FDA clearance to begin clinical trials of antiepileptic drug. SIBIA Press Release 1993, September 15.

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New antiepileptic drugs

ELAINE A. WILSON
MARTIN J. BRODIE

After a hiatus of nearly 20 years, no fewer than eight new antiepileptic drugs (AEDs) have received a licence in at least one country during the 1990s. Lamotrigine, vigabatrin, gabapentin and, to a more limited extent, oxcarbazepine are widely available, whereas felbamate, topiramate, zonisamide and tiagabine have as yet had more limited exposure. Some of these will, in the fullness of time, become first-line AEDs, whereas others already have problems with toxicity. Yet more new agents, including remacemide, levetiracetam and losigamone, are at an earlier stage of development with a few as yet 'numbered' compounds still undergoing phase one evaluation.

A feeling of optimism abounds regarding the pharmacological treatment of epilepsy. The major challenge will be to match individual AEDs with known mechanisms of action to specific epileptic seizures and syndromes. Monotherapy will continue to be the rule for most patients, although some will need more than one AED (Brodie and Dichter, 1996). The concept of 'rational polytherapy' is becoming part of the epilepsy specialist's vocabulary, although hard evidence in support of this enticing concept is still sparse. What is not in doubt, however, is that some of the newer AEDs are more 'user friendly' than many of their more established counterparts, allowing higher doses to be employed with the real potential of increased efficacy. In this review, we will detail what is known about the licensed new drugs, concentrating on their practical clinical use. Some of the more promising investigational compounds will also be previewed. Efficacy data, dosage schedules and side-effect profiles are summarized in Tables 1-4.

LAMOTRIGINE

Lamotrigine was developed in response to the erroneous hypothesis that a relationship existed between the antifolate effects of antiepileptic drugs and their therapeutic action. It has been licensed as add-on treatment in the management of refractory epilepsy in more than 70 countries. Its use in children and as monotherapy has been approved in some of these.

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Table 1. Efficacy of some new antiepileptic drugs against common seizure types and syndromes.

Drug	Partial	Secondarily generalized	Tonic-clonic	Absence	Myoclonic	Lennox- Gastaut	Infantile spasms
Lamotrigine	+	+	+	+	?+	+	?+
Vigabatrin	+	+	?	-	-	?+	+
Gabapentin	+	+	?	?	?	?	?
Oxcarbazepine	+	+	+	-	-	?	?
Felbamate	+	+	?	?+	?	+	?
Topiramate	+	+	?+	?	?	?	?
Tiagabine	+	+	?	?	?	?	?

Key to entries in table: + proven efficacy, ?+ probable efficacy, - worsens control, ? unknown.

Table 2. Dosage guidelines for some new antiepileptic drugs in adolescents and adults.

Drug	Starting dose	Commenced daily dose	Maintenance range	Dosage interval
Lamotrigine	12.5-50 mg*	200-400 mg†	100-800 mg	od-bd
Vigabatrin	0.5-1 g	3 g	2-4 g	od-bd
Gabapentin	300-400 mg	2400 mg	1200-4800 mg	ids
Oxcarbazepine	600-1200 mg	1800 mg	900-2700 mg	ids
Felbamate	1200 mg	2400 mg	1800-4800 mg	ids
Topiramate	25-50 mg	400 mg	100-1000 mg	bd
Tiagabine	5-10 mg	40 mg	20-60 mg	ids

* 12.5 mg with sodium valproate.

† 200 mg as monotherapy.

Table 3. Dosage guidelines for some new antiepileptic drugs in children.

Drug	Initial dose (mg/kg/day)	Maintenance dose (mg/kg/day)	Dosage interval
Lamotrigine	0.2-2*	1.5-15	od-bd
Vigabatrin	25	25-60	od-bd
Gabapentin	Not recommended for children under 12 years		
Oxcarbazepine	10	10-30	bd-ids
Felbamate	15	30-45	ids-qds
Topiramate	Not recommended for children under 12 years		
Tiagabine	Not recommended for children under 12 years		

* 0.2 mg/kg/day when administered with sodium valproate

Mechanism of action

Lamotrigine stabilizes presynaptic neuronal membranes by blocking voltage-dependent sodium channels, preventing the release of the excitatory glutamate and aspartate amino acid neurotransmitters (Leach et al, 1986). In mouse neuroblasts it inhibits high frequency sustained repetitive firing of sodium-dependent action potentials, suggesting a direct effect on voltage-activated currents (Cheung et al, 1992). More recent evidence supports a selective action on the slow inactivated state of the sodium channel (Xie et al, 1995). These studies do not explain lamotrigine's anti-absence and anti-myoclonic effects.

Pharmacokinetics

Lamotrigine is well absorbed after oral administration with a bioavailability approaching 100% (Brodie, 1992). Peak concentrations are achieved within 3 hours of dosing. Lamotrigine is 55% bound to plasma proteins and has a volume of distribution of 0.9–1.3 l/kg. It is extensively metabolized by the liver, largely to the inert glucuronide conjugate. Its kinetics are linear with an elimination half-life ranging from 24–41 hours. Peak concentrations are elevated by 27% in the elderly compared to younger people taking the same dose (Posner et al, 1991). Renal impairment does not affect lamotrigine's clearance.

Drug interactions

Lamotrigine does not influence the metabolism of other lipid soluble drugs, including other AEDs, warfarin and the oral contraceptive pill (McKee and Brodie, 1994). When given to patients already being treated with the enzyme-inducing agents, carbamazepine, phenytoin and phenobarbital, its rate of elimination is increased reducing the half-life to about 15 hours (Brodie, 1992). Sodium valproate inhibits lamotrigine metabolism prolonging its half-life to 60 hours (Yuen et al, 1992). Withdrawal of enzyme-inducing AEDs causes a rise in the circulating concentration of lamotrigine while that of sodium valproate produces a fall. A pharmacodynamic interaction resulting in symptoms of neurotoxicity (headache, dizziness, diplopia, ataxia) is a common consequence when lamotrigine is introduced in patients established on high dose carbamazepine (Wolf, 1992). It does not increase carbamazepine concentrations nor those of its active metabolite carbamazepine 10,11-epoxide (Stolarek et al, 1994). Patients taking carbamazepine should be warned of this possible interaction and advised to reduce their carbamazepine dose if they develop neurotoxic symptoms. A pharmacodynamic interaction has also been mooted as an explanation for the marked tremor seen in a few patients receiving sodium valproate and lamotrigine in combination (Reutens et al, 1993).

Clinical efficacy

Efficacy for lamotrigine against partial-onset seizures with or without secondary generalization has been demonstrated in all but one of 10 pivotal double-blind, placebo-controlled trials (Leach and Brodie, 1995a). Seizure severity was found to be improved in one study (Smith et al, 1992). Changes in 'happiness' and 'mastery' scores were interpreted as improving 'quality of life'. It has been suggested that lamotrigine's ability to reduce interictal spiking may explain the increased alertness reported by some patients (Besag, 1994). There is evidence of efficacy for lamotrigine against the primary generalized epilepsies, including atonic and tonic-clonic seizures, typical and atypical absences, and myoclonic jerks (Goa et al, 1993; Leach and Brodie, 1995a). In long-term studies, tolerance has not been observed to its anticonvulsant action (Goa et al, 1993).

A double-blind study comparing lamotrigine and carbamazepine in 260 newly diagnosed patients with partial-onset or generalized tonic-clonic seizures demonstrated similar efficacy for both drugs, although lamotrigine was better tolerated (Brodie et al, 1995a). An open, multicentre, comparative study against carbamazepine in 343 patients produced similar results (Reunanen et al, 1996), as did a double-blind comparison with phenytoin in previously untreated patients (Steiner et al, 1994). Studies involving children have demonstrated similar efficacy to adults across the complete range of seizure types (Goa et al, 1993; Besag et al, 1995; Leach and Brodie, 1995a). Lamotrigine appears to be of benefit in some children with infantile spasms (Veggioti et al, 1994), and also in the Lennox-Gastaut syndrome (Schlumberger et al, 1994).

Lamotrigine may have enhanced efficacy when combined with sodium valproate in patients with generalized absence and/or myoclonic seizures (Panayiotopoulos et al, 1993; Ferrie and Panayiotopoulos, 1994), and in those with partial and tonic-clonic seizures (Pisani et al, 1993; Brodie et al, *in press*). Good results have also been reported when lamotrigine was used in combination with vigabatrin in patients with partial seizures (Stolarek et al, 1994; Schapel et al, 1996).

Adverse events

The commonest side-effects with lamotrigine are headache, nausea and vomiting, diplopia, dizziness, ataxia and tremor (Brodie, 1992). Sedation rarely occurs. Rash complicates the initial management of 3–5% of patients. It is usually maculopapular in nature. In mild cases it may subside spontaneously without necessitating drug withdrawal. In some patients, however, there is an accompanying systemic illness with malaise, fever, arthralgia, myalgia, lymphadenopathy and eosinophilia. Rare cases of bullous erythema multiforme, Stevens-Johnson syndrome and Lyell's syndrome have been reported. There is some evidence that gradual introduction of lamotrigine lessens the incidence of rash (Brodie, 1996a), the risk of which is markedly higher in patients established on sodium valproate (Brodie et al, *in press*). To date, there is no evidence that lamotrigine produces teratogenesis. However there have only been a small number of pregnancies on lamotrigine monotherapy.

Dosage recommendations

Lamotrigine is produced in 25, 50, 100 and 200 mg tablets. A dispersible formulation is also available in doses of 5, 25 and 100 mg, which is useful in children and patients with difficulty in swallowing. Lamotrigine can be administered once daily as monotherapy or concomitantly with sodium valproate, or twice daily in patients being treated with enzyme-inducing drugs. A low dose, slow titration schedule should be employed to reduce the incidence of rash. The starting dose will depend on concomitant medication (Table 5). Some patients respond to and tolerate doses exceeding 600 mg

daily as monotherapy or above 800 mg daily in combination with enzyme-inducing AEDs. An equivalent high dose in valproate-treated patients would be 150–200 mg daily because of the extent of metabolic inhibition. Concentration monitoring is not required in clinical practice as no significant relationship has been established between lamotrigine levels and its anticonvulsant efficacy or the emergence of side-effects (Rambeck and Wolf, 1993; Kilpatrick et al, 1996).

Table 5. Lamotrigine dosage and titration schedules.

Add-on in treated adults and adolescents		
	Valproate	Others
Weeks 1–2	12.5 mg daily	50 mg daily
Weeks 3–4	25 mg daily	50 mg twice daily
Maintenance	50–100 mg twice daily	100–200 mg twice daily
Add-on in treated children		
	Valproate	Others
Weeks 1–2	0.2 mg/kg	2 mg/kg
Weeks 3–4	0.5 mg/kg	5 mg/kg
Maintenance	1.5 mg/kg	5–15 mg/kg
Monotherapy		
	Adults	Children
Weeks 1–2	25 mg daily	0.5 mg/kg
Weeks 3–4	25 mg twice daily	1 mg/kg
Maintenance	50–100 mg twice daily	2–8 mg/kg

Higher doses can be tried if seizures persist and the patient is tolerating the drug without complaint.

Therapeutic use

Although effective against partial seizures with or without secondary generalization, LTG seems to be particularly beneficial for the primary generalized epilepsies. Good results are being reported also in patients with learning disabilities who have a range of seizure types. In patients with partial seizures, it is often possible to withdraw concomitant phenytoin or carbamazepine with benefit. Controlled trials in children and in Lennox–Gastaut syndrome are in progress, as is a double-blind, comparative study against carbamazepine in the elderly. Lamotrigine's long elimination half-life, broad spectrum of activity and wide therapeutic ratio make it an attractive proposition as monotherapy in newly diagnosed epilepsy. Preliminary data hold out the possibility that it will not be teratogenic. Duotherapy with a regimen containing sodium valproate in refractory epilepsy is becoming a common therapeutic strategy.

VIGABATRIN

Vigabatrin was the first 'designer' AED to be introduced into clinical practice, as it was modelled on the structure of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).

United Kingdom and Ireland in 1989 as add-on therapy for partial seizures and is now available for this indication in many countries, although it has not yet been approved for use in the United States.

Mechanism of action

Vigabatrin is a water-soluble racemate with the *S*-enantiomer being the pharmacologically active moiety (Editorial, 1989a). Its antiepileptic effect is mediated by enzyme-activated suicidal inhibition of GABA transaminase, the enzyme responsible for the metabolic degradation of this important inhibitory neurotransmitter. This results in elevation of GABA levels in the plasma, CSF and brain (Ben-Menachem et al, 1989; Petroff et al, 1996). An inhibitory action on cellular GABA uptake has also been mooted (Leach et al, in press a).

Clinical pharmacokinetics

Vigabatrin is rapidly absorbed after oral administration with concentrations peaking 3 hours after dosing (Grant and Heel, 1991). It has an oral bioavailability of 60–80%, is not protein bound and has a volume of distribution of 0.8 l/kg. Vigabatrin is primarily excreted unchanged by the kidney, with a clearance similar to the glomerular filtration rate (Durham et al, 1993). Its renal clearance decreases significantly in old age and with renal impairment.

Drug interactions

Plasma concentrations of phenytoin are reduced by 20–30% by concomitant vigabatrin (Rimmer and Richens, 1989), although this rarely compromises seizure control (Browne et al, 1987). Vigabatrin does not induce or inhibit hepatic metabolic enzymes nor does it undergo any pharmacokinetic or pharmacodynamic interactions with AEDs other than phenytoin. To date, no reports have appeared suggesting that any other drug influences its pharmacokinetics.

Clinical efficacy

In six early double-blind, placebo-controlled, crossover studies in patients with therapy resistant partial-onset seizures given doses of vigabatrin ranging from 2 to 3 g daily as add-on therapy, the responder rate (50% or more seizure reduction) varied between 33 and 64% (Mumford and Dam, 1989). Vigabatrin's efficacy is against partial seizures with or without secondary generalization. It can worsen myoclonic jerks and generalized absences and may even precipitate status (Ferrie and Panayiotopoulos, 1995). Its anticonvulsant effect is maintained for at least 10 years, although some patients have experienced breakthrough seizures (Grant and Heel, 1991).

An early monotherapy study comparing vigabatrin and carbamazepine in newly diagnosed adult patients with partial-onset seizures suggested

similar or slightly inferior efficacy for the new drug, but with more patients on vigabatrin becoming seizure-free. Vigabatrin was also better tolerated than carbamazepine (Kalviainen et al, 1995). The pivotal double-blind comparative monotherapy studies against carbamazepine have just been completed and are about to be reported. Vigabatrin appears to be at least as effective as ACTH and corticosteroids in infantile spasms (Appleton, 1995). As it has a better side-effect profile than steroid therapy, some paediatricians already regard it as the treatment of choice for this indication (Ferrie and Robinson, 1995; Aicardi et al, 1996).

Adverse events

Sedation, dizziness and headache are the most frequently reported adverse events with vigabatrin, particularly when the dose is being increased. Other reported problems include fatigue and weight gain (Grant and Heel, 1991). Vigabatrin does not appear to produce cognitive impairment either acutely or in the long term (Gillham et al, 1993). However, phased introduction has been suggested to allow tolerance to early subjective sedation. Some patients taking vigabatrin report a change in mood; commonly agitation, ill-temper, disturbed behaviour or depression. Paranoid and psychotic symptoms can develop. Hyperkinesia and agitation can occur in children (Appleton, 1995). No idiosyncratic reactions have been reported with the drug. There is no evidence of a teratogenic effect of vigabatrin, although exposure to the drug as monotherapy is still limited.

Dosage recommendations

Vigabatrin is usually added to existing antiepileptic therapy, initially in a dose of 500 mg once or twice daily to allow tolerance to any subjective sedation. If the patient complains of agitation or a thought disorder, the drug should be summarily withdrawn. Further increments of 500 mg or 1 g daily will depend on the clinical status of the patient (French et al, 1996). Most patients respond maximally to 2–3 g vigabatrin daily. Few show a further useful improvement at higher doses (Penry et al, 1993). Indeed, there may be a ceiling to effective dosage in individual patients (McKee et al, 1993). Children should be commenced on 40 mg/kg daily, increased according to response up to 80–100 mg/kg daily. Infants with West's syndrome may require 100 mg/kg daily or more. Vigabatrin should be tapered off over 3–4 weeks, as abrupt cessation can produce a marked increase in seizures and may even precipitate psychosis. Lower doses should be considered in patients with a creatinine clearance less than 35 ml/min. Routine serum monitoring of vigabatrin concentrations is unnecessary as there is no proven concentration effect–toxicity relationship with the drug.

Therapeutic use

Vigabatrin has proven efficacy as adjuvant treatment of therapy-resistant

partial-onset seizures with or without secondary generalization. It may already be the drug of choice for infantile spasms (Appleton, 1995; Ferric and Robinson, 1995). Vigabatrin can aggravate myoclonic and absence epilepsy and should not be prescribed in patients with a history of behavioural disturbance or severe depression.

GABAPENTIN

Gabapentin is licensed in the UK, US and many European and other countries for use as add-on therapy in refractory seizures of partial onset. Similar to vigabatrin, it is a structural analogue of GABA.

Mechanism of action

Gabapentin is a water-soluble compound that crosses the blood-brain barrier via an L-amino acid transport system (Leach and Brodie, 1995b). Its mechanism of action is unclear. It does not appear to be GABA-ergic. Like many other AEDs, it inhibits voltage-dependent sodium currents (Wamil and McLean, 1994) and has recently been suggested to bind to a calcium channel in the brain (Gee et al, 1996).

Clinical pharmacokinetics

After oral administration, gabapentin is rapidly absorbed from the gastrointestinal tract via the same L-amino acid transport system that carries it into the brain. This process is thought to be saturable at doses above 1800 mg/day (McLean, 1994). At higher doses gabapentin continues to be absorbed, probably passively (Wilson et al, 1996). Peak gabapentin concentrations are achieved 2-3 hours after dosing. At low dosage, its bioavailability approximates 60%. This falls to around 35% above 2400 mg daily. Gabapentin is widely distributed throughout the tissues, with a volume of distribution of 50-60 l. It does not bind to plasma proteins. Brain and cerebrospinal fluid concentrations are approximately 80% and 5-35%, respectively, of plasma levels. Gabapentin is excreted unchanged by the kidney, its renal clearance being linearly related to that of creatinine (Comstock et al, 1990). Its elimination half-life in patients with normal renal function is 5-7 hours. Dosage reduction is advised in patients with severe renal impairment.

Drug Interactions

Gabapentin does not alter plasma concentrations of any other AED, nor does it influence the metabolism of lipid-soluble drugs in common use, including warfarin and the components of the oral contraceptive pill (McKee and Brodie, 1994). Its bioavailability is reduced by 20% when administered with antacids and its renal elimination slowed by 12% when given with cimetidine.

Clinical efficacy

In randomized, placebo-controlled trials in doses varying from 600 mg to 1800 mg daily, gabapentin has been shown to be an effective treatment for partial and secondary generalized tonic-clonic seizures (UK Gabapentin Study Group, 1990; US Gabapentin Study Group, 1993; Anhut et al, 1994; US Gabapentin Study Group, 1994). Tolerance to its antiepileptic effect has not been demonstrated (Ojemann et al, 1992). Monotherapy trials are currently being evaluated comparing gabapentin with standard treatment in patients with newly diagnosed epilepsy.

Adverse events

Gabapentin is a particularly well-tolerated drug whose administration has not been associated with idiosyncratic reactions. Side-effects include somnolence, dizziness, ataxia, fatigue, nystagmus, headache, tremor and, less commonly, diplopia, nausea and vomiting. Flatulence, diarrhoea and myoclonic jerking can occur at doses exceeding 3600 mg daily. These all resolve on dosage reduction. The drug is not likely to be teratogenic. Its use is not associated with cognitive impairment (Leach et al, 1996).

Dosage recommendations

Gabapentin is produced as 100, 300 and 400 mg capsules. The recommended dosage schedule in an adult is 300 mg on the first day of treatment, 300 mg twice daily on the second day, and 300 mg thrice daily on the third day with further titration of dose depending on clinical response. Most patients with refractory epilepsy required 2400–4800 mg daily, although those with a less severe seizure disorder may respond to lower doses. In some patients, especially those on polypharmacy, a slower titration period is advised, for example 300 or 400 mg daily initially increasing by 300 or 400 mg weekly until optimum improvement in seizure control is obtained or until side-effects are experienced. Dosing should be thrice daily in most patients due to the short half-life of the drug. There is some evidence that gabapentin continues to be effective in doses up to 6400 mg daily (Wilson et al, 1996). Routine concentration monitoring is unnecessary as the drug has a short elimination half-life and wide therapeutic ratio.

Therapeutic use

Gabapentin has an established place as add-on treatment for partial onset seizures with or without generalized tonic-clonic seizures. Its lack of drug interactions, including with the oral contraceptive pill, is a major advantage. Still to be defined is gabapentin's efficacy for other seizure types. It is the easiest drug to add on in clinical practice, and good tolerability makes it an attractive prospect as monotherapy in newly diagnosed epilepsy.

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OXCARBAZEPINE

Oxcarbazepine is the 10-keto analogue of carbamazepine. It is licensed for the treatment of partial and tonic-clonic seizures in more than 30 countries, but is still under evaluation in the UK and USA.

Mechanism of action

Oxcarbazepine is functionally a pro-drug which is rapidly and completely reduced in the liver to the active moiety, 10, 11-dihydro-10-hydroxy-carbamazepine (Editorial, 1989b). Like carbamazepine, its major effect is in preventing burst firing of neurons by blocking voltage-dependent sodium channels (Rogawski and Porter, 1990). However, recent studies suggest that it may also modulate calcium currents (Stefani et al, 1995).

Clinical pharmacokinetics

Oxcarbazepine is rapidly absorbed after oral administration with a bioavailability of 95–100%. It has a volume of distribution of around 1 l/kg and is 40% protein bound. It is rapidly and extensively converted to the 10-hydroxy metabolite (Theisohn and Heimann, 1982), most of which is eliminated in the urine as the glucuronide conjugate. The active moiety has a half-life of 8–10 hours (Larkin et al, 1991). A higher peak concentration, a greater area under the concentration–time curve and lower renal clearance of oxcarbazepine have been reported in the elderly (Van Heiningen et al, 1991).

Drug interactions

Substitution of oxcarbazepine for carbamazepine produces a rise in concentration of other AEDs averaging 25% because it is a more selective enzyme inducer (Houtkooper et al, 1987). Oxcarbazepine itself has no effect on the metabolism of other AEDs (McKee et al, 1994). It does not interfere with warfarin metabolism (Kramer et al, 1992) and also lacks the inhibitory interactions with erythromycin and dextropropoxyphene observed with carbamazepine. Oxcarbazepine does, however, appear to cause a reduction in the bioavailability of ethinyloestradiol and levonorgestrel, probably by inducing a single isoform (cyt 3A) of cytochrome p-450 (Klosterkov-Jensen et al, 1992), which may lead to breakthrough bleeding and loss of contraceptive efficacy in some patients.

Adverse events

Adverse events with oxcarbazepine most often involve the central nervous system and include drowsiness, dizziness, headache, diplopia, nausea and vomiting, and ataxia (Grant and Faulds, 1992). Skin rash occurs less frequently than with carbamazepine. Oxcarbazepine does not appear to produce blood dyscrasias or hepatotoxicity (Prijs et al, 1993). Hyponatraemia, probably secondary to an antidiuretic hormone-like

effect, is as common with oxcarbazepine as with carbamazepine (Amelsvoort et al, 1994). Most hyponatraemic patients are asymptomatic, although there have been rare cases of coma. There is no evidence that oxcarbazepine is a human teratogen, although high doses produce malformations in rodents.

Clinical efficacy

A number of clinical trials in which oxcarbazepine was substituted for carbamazepine has supported similar efficacy for the two drugs (Editorial, 1989b; Grant and Faulds, 1992). In a double-blind randomized comparative trial with carbamazepine in 235 newly diagnosed patients, no significant difference was found between the two agents in terms of seizure control (Darn et al, 1989). Oxcarbazepine has been compared recently in double-blind, randomized trials with sodium valproate (Christe et al, in press) and phenytoin (Bill and International Audit Oxcarbazepine/Phenytoin Trial Group, in press) in adults with newly diagnosed epilepsy and with phenytoin in children and adolescents (Guerreiro and International Paediatric Oxcarbazepine/Phenytoin Trial Group, in press). There were no differences in efficacy between the comparators, although oxcarbazepine was better tolerated. Similarly to carbamazepine, oxcarbazepine is not effective for generalized absences or myoclonic jerks. Good data in children are still needed, although open studies support similar efficacy to that reported in adults (Friis et al, 1993).

Dosage recommendations

The recommended starting dose of oxcarbazepine in adults is 600–1200 mg daily usually in three divided doses, although some patients can be well controlled on a twice daily regimen. The dosage can be titrated upwards as clinically indicated to 3000–4000 mg daily. A starting dose of 10 mg/kg in children over 3 years can initially be prescribed, increasing gradually to a maintenance of around 30 mg/kg (Patsalos and Duncan, 1994). If changing from carbamazepine to oxcarbazepine, replacement of every 200 mg carbamazepine with 300 mg oxcarbazepine is suggested. Plasma concentrations of the clinically active metabolite of oxcarbazepine increase linearly with dosage. No studies have attempted to relate these to the efficacy of the drug or to the likelihood of toxicity.

Therapeutic use

Oxcarbazepine is used for the treatment of partial-onset and tonic-clonic seizures. It is better tolerated than carbamazepine and patients report fewer neurotoxic side-effects and idiosyncratic reactions (Grant and Faulds, 1992). Like carbamazepine, however, it is not effective for absence and myoclonic seizures. It can be expected soon to be licensed widely as adjunctive therapy in refractory epilepsy and as monotherapy in drug-naïve

FELBAMATE

Felbamate was licensed in the USA for use as monotherapy and adjunctive therapy in refractory partial onset seizures in adults and for children with Lennox-Gastaut syndrome in July 1993. Following a high profile advertising campaign, over 100 000 patients received the drug within the first year after launching. Shortly after, cases of aplastic anaemia and hepatotoxicity emerged, which abruptly cut short its success story (Brodie and Pellock, 1995).

Mechanism of action

Felbamate is structurally similar to, but pharmacologically distinct from, the outmoded anxiolytic meprobamate. It limits the spread of seizure activity and increase the seizure threshold, perhaps via a dual mechanism involving inhibition of N-methyl-D-aspartate (NMDA) receptors and potentiation of GABA responses (Rho et al, 1994). It is effective in blocking sustained repetitive firing in mouse spinal cord neurons, suggesting that it also modulates sodium channel conductance (White et al, 1992). There is also evidence that it may act as a glycine antagonist (McCabe et al, 1993).

Clinical pharmacokinetics

After oral administration felbamate is rapidly absorbed from the gastrointestinal tract achieving its peak concentration within 2-6 hours. Bioavailability is around 95% in adults. Plasma protein-binding varies between 22 and 36%, and volume of distribution is 0.8 l/kg. The drug undergoes hepatic metabolism, mainly through hydroxylation and conjugation. Linear pharmacokinetics are observed at therapeutic dosage. Felbamate has a terminal elimination half-life of 15-23 hours.

Drug interactions

Concomitant administration with enzyme-inducing AEDs, particularly phenytoin and carbamazepine, reduces the half-life of felbamate to approximately 14 hours, and produces a 20% reduction in steady-state concentrations (Brodie, 1993). Felbamate increases the levels of phenytoin and sodium valproate, by around one third, and reduces those of carbamazepine by the same amount. There are no such interactions between felbamate and vigabatrin or oxcarbazepine. The drug may reduce the efficacy of the low dose contraceptive pill as breakthrough bleeding has been noted in some patients. It is not yet known whether felbamate affects the metabolism of warfarin, corticosteroids or cyclosporin.

Clinical efficacy

Six pivotal clinical trials involving a total of 370 patients were used to assess the efficacy of felbamate (Brodie, 1993). The first five studies

included 308 patients with therapy resistant partial seizures with or without secondary generalization. Two were conventional, placebo-controlled, crossover studies in adults with refractory epilepsy (Leppik et al, 1991; Theodors et al, 1991). A further two were monotherapy trials of felbamate versus low dose sodium valproate after medication withdrawal (Sachdev et al, 1992; Faught et al, 1993). A further study compared felbamate with placebo in patients about to undergo epilepsy surgery in whom existing AED therapy was withdrawn (Bourgeois et al, 1993). A major placebo-controlled trial in 73 children with Lennox-Gastaut syndrome completed the assessment (Felbamate Study Group, 1993). Felbamate reduced the frequency of atonic seizures and atypical absences.

Adverse events

Side-effects occur in around 50% of patients taking felbamate (Leppik and Wolff, 1995). Most common are gastrointestinal and neurological symptoms, including anorexia, nausea and vomiting, weight loss, headache, dizziness and diplopia. Some patients complain of insomnia on the drug and others of somnolence. Within a couple of years of being licensed, the FDA began to receive reports of aplastic anaemia and hepatotoxicity attributable to felbamate, some of which were fatal (Brodie and Pellock, 1995). The incidence of aplastic anaemia has been estimated at 1 in 2000-3000 (Leppik and Wolff, 1995) and that of fatal liver damage 1 in 24 000-34 000 patients (O'Neill et al, 1996).

Dosage recommendations

Felbamate is available as 400 and 600 mg tablets and as a suspension of 600 mg/5 ml. The usual daily dose is 3600 mg daily for adults and children above 14 years. This should be started at 1200 mg daily in three to four divided doses, with weekly or biweekly increments of 600 or 1200 mg as tolerated, and titrated upwards depending on clinical response. In children aged between 2 and 14 years, treatment should be initiated at 15 mg/kg in divided doses and titrated up to 30 mg/kg or even 45 mg/kg daily, depending on response. Doses of concomitant AEDs should be reduced by 20-33% on initiation of felbamate as this helps to reduce side-effects caused by the many pharmacokinetic interactions. Monitoring of felbamate concentrations may be useful as a guide to dosing in the occasional patient (Harden et al, 1996). In view of the reports of aplastic anaemia and hepatotoxicity, close monitoring of haematological parameters and hepatic function is mandatory. Full blood count and liver function tests should be checked prior to initiation of felbamate therapy. More importantly, patients should also be advised what symptoms to expect (Dichter and Brodie, 1996).

Therapeutic use

Felbamate remains available in the USA for the treatment of partial onset seizures and Lennox-Gastaut syndrome. The FDA, however, currently

recommends that it be given only to patients who have seizures refractory to all other medications and in whom risk-benefit considerations warrant its use (Dichter and Brodie, 1996). Eight European countries have licensed felbamate for various limited indications. Therapy with felbamate should only be initiated after other reasonable therapeutic options have been exhausted. In all patients, the risk of aplastic anaemia and hepatic toxicity should be explained and consent to treatment obtained. It is likely that, when the risk-benefit ratio is clarified, more patients will receive this effective drug.

TOPIRAMATE

Topiramate was licensed in 1995 in the UK for use as add-on therapy in partial-onset seizures with or without secondary generalization in patients not controlled on conventional AEDs. It is likely to be available for prescription world-wide within the next few years.

Mechanism of action

Topiramate is a sulphamate-substituted monosaccharide. It exhibits some inhibition of carbonic anhydrase, but its antiepileptic properties are independant of this effect (Shank et al, 1994). It is likely to have a triple action involving the blockade of sodium channels, attenuation of kainate-induced responses, and enhancement of GABA-mediated inhibition (Dichter and Brodie, 1996).

Clinical pharmacokinetics

Topiramate is rapidly absorbed from the gastrointestinal tract with a bioavailability exceeding 80%. Peak plasma concentrations occur 2-4 hours post-dosing (Leach and Brodie, 1995b). Plasma protein binding is minimal. Topiramate crosses the blood-brain barrier readily. Brain concentrations approximate 40% of those in plasma. It exhibits linear pharmacokinetics with an elimination half-life of about 21 hours. There are no age-related changes in its clearance, which is reduced in patients with severe renal or hepatic disease.

Drug interactions

Topiramate may reduce the plasma clearance of phenytoin in some patients. This is due to the inhibition of a specific isoenzyme of the cytochrome p-450 superfamily, namely cyt 2C19. It has no clinically relevant effect on the levels of any other AED. Phenytoin and carbamazepine induce its metabolism reducing topiramate concentrations by more than 40% (Dichter and Brodie, 1996). Topiramate itself produces a fall of 30% in serum ethinyloestradiol concentrations in women taking a combined oral contraceptive pill.

Clinical efficacy

Topiramate has proven efficacy as add-on in patients with partial-onset seizures, with or without secondary generalization, when used as adjunctive therapy (Ben-Menachem et al, 1996; Faught et al, 1996; Privitera et al, 1996). The combined results of five controlled trials have demonstrated a 50% or greater seizure reduction in 41% of treated patients (Ben-Menachem, 1995). There is no evidence of tolerance to its anti-convulsant effect. Studies are underway to evaluate its efficacy as add-on therapy for primary generalized seizures and as monotherapy in newly diagnosed epilepsy.

Adverse events

In common with all other antiepileptic drugs, topiramate can produce central nervous side-effects including ataxia, poor concentration, confusion, dizziness, fatigue, paraesthesia, somnolence and cognitive impairment (Leach and Brodie, 1995b). Less common problems are amnesia, anorexia and weight loss, diplopia, nausea and vomiting. Topiramate increases the risk of nephrolithiasis 10-fold (equivalent to the effect of acetazolamide) and, therefore, should be avoided in patients with a history of kidney stones and in those taking calcium supplements and high dose vitamin C. In pre-clinical studies involving mice, rats and rabbits, topiramate was teratogenic at high dosage. Its use is, therefore, not advised in pregnancy, unless the potential benefit of treatment is felt to outweigh the risk to the fetus.

Dosage recommendations

Patients can respond to topiramate in doses ranging from 100–1000 mg daily. It is usually administered in two divided doses, and should be introduced slowly. An initial 25–50 mg daily can be increased by 25–50 mg every 1–2 weeks until a maximum effective and/or tolerated dose is achieved. The optimum amount for most patients appears to be 200–400 mg daily (Faught et al, 1996; Privitera et al, 1996). During routine treatment, concentration monitoring of topiramate is not required. However, measurement of phenytoin levels may be necessary in patients who develop symptoms suggestive of toxicity.

Therapeutic use

Topiramate has demonstrated considerable efficacy within the clinical trials programme in patients with refractory partial seizures with or without secondary generalization. It does, however, also exhibit a wide range of side-effects. Women taking the oral contraceptive should use a formulation containing 50 µg ethinylestradiol. Particular interest is currently being directed in its potential use in the primary generalized epilepsies and in patients with learning disabilities who often have a range of seizure types.

TIAGABINE

Tiagabine is a new AED with a unique and specific mechanism of action that has recently been licensed in France and will soon be widely available.

Mechanism of action

Tiagabine hydrochloride is a nipecotic acid derivative linked by an aliphatic chain to a lipophilic anchor that enables it to cross the blood-brain barrier. It is a potent, selective and specific inhibitor of presynaptic GABA uptake in neurons and glia (Suzdak and Jansen, 1995). It binds to a single class of high-affinity binding sites, probably the GABA transporter GAT-1 (Borden *et al.*, 1994).

Clinical pharmacokinetics

Tiagabine is rapidly absorbed from the gut with peak concentration being achieved within 30–90 minutes of dosing. Food increases the rate of absorption but not the extent. Bioavailability approaches 100% after an oral dose. Protein binding is high at 96%. Tiagabine undergoes extensive hepatic metabolism mainly by isoform 3A of the cytochrome p-450 family. No active metabolites have been identified. Its absorption and clearance are linear at therapeutic dosage. The half-life is 5–9 hours (Gustavson and Mengel, 1995). Children eliminate tiagabine slightly more rapidly than adults, but its metabolism is substantially slower in patients with severe hepatic disease (Brodie, 1995). Clearance in the elderly and in patients with renal disease is similar to that seen in healthy volunteers.

Drug interactions

Tiagabine does not induce or inhibit hepatic enzymes (Gustavson and Mengel, 1995), and so does not alter the concentrations of lipid-soluble drugs including other AEDs (Richens *et al.*, 1995). The exception is an occasional small decline in valproate levels. Carbamazepine and phenytoin accelerate the metabolism of tiagabine and reduce its elimination half-life to 2–4 hours (So *et al.*, 1995). There are no clinically relevant pharmacokinetic interactions between tiagabine and cimetidine, digoxin, theophylline and warfarin; no pharmacodynamic interactions occur with the oral contraceptive pill, alcohol or triazolam (Brodie, 1995).

Efficacy

Five add-on, placebo controlled trials and six open-label, multicentre studies have been conducted and indicate that tiagabine has efficacy in patients with partial-onset seizures with or without secondary generalization (Ben-Menachem, 1995). At the highest doses (48–64 mg daily), a responder rate of 36% was achieved. A dose-response relationship has been demonstrated for complex partial seizures and all seizures combined

(Brodie, in press). Preliminary results in children have been promising. Initial studies also support a role for tiagabine as monotherapy (Schachter, 1995). Comparative monotherapy trials versus carbamazepine and sodium valproate are currently being undertaken in patients with newly diagnosed epilepsy.

Adverse events

Within the clinical trials, adverse events leading to discontinuation of tiagabine occurred in 13% of patients compared with 5% on placebo. Dizziness, asthenia, nervousness, tremor, diarrhoea and depression were reported significantly more often with tiagabine than with placebo. No idiosyncratic reactions have been associated with its use nor does it appear to impair cognitive function (Brodie, in press). Tiagabine is not teratogenic in animal models, although it is too early to say whether there will be a problem in human pregnancy.

Dosage recommendations

Tiagabine is available as 5, 10 and 15 mg tablets. Recommended dosage as add-on therapy is 30–50 mg/day, although some patients tolerate and respond to higher amounts. Some double-blind trials used tiagabine four times daily, while other studies have supported the suggestion that tiagabine can be prescribed twice (Ben-Menachem, 1995) or thrice daily (Brodie and Lassen, 1994). A reasonable schedule, therefore, would be to start with 5 mg twice daily and increase to thrice daily when the daily dose exceeds 30 mg. If the patient complains of dizziness, this may respond to spreading out the dose further over four daily increments. Tiagabine should be taken with food to avoid rapid rises in plasma concentration. Routine concentration monitoring is not helpful during treatment with this drug.

Therapeutic use

Tiagabine has proven efficacy as add-on therapy for patients with partial onset seizures, including secondarily generalized tonic-clonic seizures. Further studies in other seizure types are underway. It appears well-tolerated, and may have a useful role as monotherapy in patients with newly diagnosed epilepsy.

ZONISAMIDE

Zonisamide was developed in Japan in the 1970s where it is now licensed. The trial programme was initially halted in Europe and the USA due to a high incidence of renal calculi (Leppik et al, 1993). Zonisamide's mechanism of action is unknown, but it may block voltage-dependent sodium channels and T-type calcium channels (Dichter and Brodie, 1996). It is rapidly absorbed from the gut, achieving maximum concentration within

2-3 hours of dosing. It is less than 50% protein bound and undergoes partial metabolism by the liver involving acetylation and conjugation. Approximately 30% of an oral dose is excreted unchanged by the kidneys. Zonisamide has a long elimination half-life of nearly 60 hours. However, concomitant administration of carbamazepine and phenytoin can reduce this by about 50% (Ojemann et al, 1986). Zonisamide appears to have a broad spectrum of antiepileptic activity (Patsalos and Duncan, 1994). It is effective against partial and tonic-clonic seizures (Leppik et al, 1993; Schmidt et al, 1993) and may also be useful for the idiopathic epilepsies (Kumagai et al, 1991). Trials have now restarted world-wide.

REMACEMIDE

Remacemide hydrochloride is a novel water-soluble anticonvulsant, that has an active desglyciny metabolite (Clark et al, 1995). Both compounds are inhibitors of sodium channels and, in addition, the metabolite is a low affinity, non-competitive NMDA antagonist. Remacemide is rapidly absorbed after oral administration achieving peak plasma concentrations within 1-2 hours with a bioavailability of up to 90%. Remacemide and its active metabolite are 77% and 90% plasma protein bound, respectively. Its elimination half-life is short, being 3-4 hours. However, the desglyciny metabolite has a longer half-life of 12-15 hours (Clark et al, 1995). Both compounds are extensively metabolized in the liver and show linear kinetics at therapeutic dosage. Remacemide is a modest inhibitor of the cytochrome p-450 enzymes 3A4 and, to a lesser extent, 2C9. It increases carbamazepine and phenytoin levels by approximately 25% (Leach et al, in press b) and 20% (Leach et al, in press c) respectively. Enzyme inducers accelerate the metabolism of both remacemide and its active metabolite. Preliminary efficacy studies with remacemide have demonstrated statistically significant reductions in partial seizure frequency (Clark et al, 1995). The commonest side-effects were dizziness, fatigue, ataxia, diplopia and gastrointestinal upset, mainly dyspepsia and abdominal pain. Further clinical trials are underway to evaluate its efficacy over a range of doses in a range of seizure types.

LOSIGAMONE

Losigamone appears to stimulate chloride influx into the spinal cord by a GABA-sensitive mechanism at a site distant from the GABA channel (Dimpfel et al, 1995). After oral administration, peak concentrations are achieved in 2-3 hours. Losigamone undergoes extensive hepatic metabolism and has a short elimination half-life approximating 4 hours (Biber and Dienel, 1996). It does not appear to interact with carbamazepine or phenytoin. Preliminary studies support its efficacy in refractory partial seizures (Stein, 1995). The commonest side-effects were dizziness and headache. World-wide development is continuing.

LEVETIRACETAM

Levetiracetam possesses antiepileptic, anxiolytic and cognitive enhancing activities. It appears to have a unique mechanism of action involving a specific cellular binding site (Noyer et al, 1995). After oral administration, levetiracetam is rapidly absorbed with bioavailability approaching 100%. Maximum concentrations are achieved within 1 hour of dosing. The elimination half-life is 7-8 hours. It is metabolized by the liver but does not induce hepatic enzymes. Fifty to 60% of a dose is excreted unchanged in the urine. Levetiracetam may inhibit phenytoin metabolism (Sharief et al, 1996). Preliminary results indicate efficacy in patients with partial seizures with or without secondary generalization (Sharief et al, 1996). Side-effects included drowsiness, memory impairment, asthenia, dizziness, headache and mood changes. Double-blind trials evaluating its efficacy are under-way.

CONCLUSION

The recent influx of new AEDs is long overdue and provides a range of options for the epileptic patient and his or her doctor. As data accumulate, it is becoming apparent that at least some of these drugs represent welcome advances over the long established agents. In particular, they appear to be better tolerated, fuelling the hope that relatively higher doses will lead to improved efficacy. However, when a drug is launched, too little is known about it to guarantee an established place in the therapeutic armamentarium. No assumptions should be made regarding its efficacy and safety until 100 000 patients have been treated for at least a year (Brodie, 1996b). This milestone has been passed for three (or perhaps four) of the drugs (lamotrigine, vigabatrin, gabapentin and maybe oxcarbazepine) discussed in this review. Most of these are not yet licensed for children for whom they have particular promise. Only lamotrigine (and felbamate in USA) has been approved as monotherapy. Accordingly, much remains to learn about these new agents. There is the additional hope that a mechanistic approach will lead to a more rational choice of drugs for a range of seizures and syndromes. This strategy has particular attraction for patients with refractory epilepsy. There is no doubt that we are at the beginning of a revolution in the treatment of epilepsy that has the potential for greatly improving the quality of life of patients with this distressing disorder.

SUMMARY

No fewer than eight new antiepileptic drugs (AEDs) with diverse mechanisms of action have been introduced into clinical practice in the 1990s. Short monographs on lamotrigine, vigabatrin, gabapentin, oxcarbazepine, felbamate, topiramate and vigabatrin have been prepared for this review. Details are provided of mechanisms of action, clinical pharmacokinetics

and adverse drug interactions. Each section concentrates on the efficacy, tolerability and practical use of these drugs. The areas where they have potential for superiority over the established AEDs have been highlighted. Specific indications and dosage schedules have been provided. As many of these AEDs have, as yet, limited licences, an attempt has been made to identify ongoing studies and important omissions. Where possible, the eventual place of the new agent in the pharmacological management of epilepsy has been assessed. A more limited summary has been included of zonisamide which, although licensed in Japan, is still regarded as an investigational drug elsewhere. Short discussions of three of the most promising investigational compounds, namely remacemide, losigamone and levetiracetam, complete the picture.

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Behandlung der Epilepsien: Wo stehen wir heute?

Present Situation in the Treatment of Epilepsies

Zusammenfassung

Die moderne Behandlung der Epilepsien hat sich in allen drei Säulen wesentlich verbessert. Seit 1857 Sir Charles Locock die Bromide einführt und 1886 Sir Victor Horsley die moderne Ära der Epilepsiechirurgie eröffnete (18), sind aber auch mehr als 100 Jahre vergangen. Bei der medikamentösen Behandlung werden die «klassischen AED» (AED = antiepileptic drugs, Antiepileptika) der letzten Jahrzehnte, nämlich Phenobarbital (Hauptmann, 1912) und Phenytoin (Putnam und Merrit, 1938), weitgehend verdrängt durch Valproat (Mennier, 1963) und Carbamazepin (Lorge, 1963). Nur das Ethosuximid (Zimmermann, 1951) hat bei der 3b-Spike-wave-Absence-Epilepsie weiterhin seinen Platz behauptet, besonders in den USA (28, 29). Wegen der unangenehmen Eigenschaft, dass Ethosuximid zwar ein ausgezeichnetes Absenkmittel ist, aber Grand-mal-Anfälle fördern kann und daher mit einem sogenannten «Grand-mal-Schutz» (meist Phenobarbital) kombiniert werden sollte, ist Ethosuximid aber auch bei dieser Indikation in Europa durch Valproat auf Platz zwei verdrängt worden. Somit hat sich die Entscheidung, welches AED zu Beginn eingesetzt werden soll, wesentlich vereinfacht: Eigentlich liegt man mit dem – ein sehr breites Wirkungsspektrum aufweisenden – Valproat als Mittel der ersten Wahl bei fast allen Epilepsien richtig, vielleicht mit Ausnahme der fokalen Epilepsien (11). Insbesondere, wenn es sich um fokale Epilepsien mit temporalem Ursprung handelt, setzen wir das Carbamazepin als Mittel der ersten Wahl ein. In einigen Ländern (Dänemark) wird für diese Indikation wegen der geringeren Nebenwirkungen aber bereits Oxcarbazepin bevorzugt (Mogens Dam, persönliche Mitteilung).

Erhebliche Erfahrung und Wissen sind aber nach wie vor gefordert, wenn sich Therapieversitzer gegen eine lege artis durchgeführte klassische Monotherapie abzeichnet. Hier hat sich die Palette der Weiterbehandlung, auch durch die Verfügbarkeit der neuen AED, vervielfacht. Ein allgemein akzeptiertes Behandlungsschema für den Ersatz des einen Mittels durch ein anderes Mittel der ersten oder zweiten Wahl und vor allem für die «richtigen» Kombinationen mit Mitteln der dritten Wahl kann derzeit noch nicht aufgestellt werden. Hier ist der erfahrene Epileptologe gefragt, der Erfahrungen mit «theoretisch sinnvollen» Kombinationen hat und die dabei auftretenden Interaktionen überblickt. Für einige spezifische Epilepsiesyndrome hat der Königsteiner Arbeitskreis deutschsprachiger Epileptologen klare und verbindliche Empfehlungen für die AED-Therapie gegeben (so z. B. für die benigne juvenile Myoklonusepilepsie, Janz-Syndrom). Dieser Arbeitskreis hat zudem auch Empfehlungen für die erforderlichen klinischen und Laborkontrollen bei AED-Therapie mit potentiell schweren Nebenwirkungen (z. B. Valproat-Therapie bei Kindern mit erhöhtem Risiko) ausgearbeitet, die in den «Epilepsie-Blättern» der Deutschen Liga gegen Epilepsie publiziert und diskutiert wurden bzw. werden (4). Trotz allen Fortschritts der medikamentösen Behandlung hat sich aber statistisch die Zahl der medikamentös nicht befriedigend behandelbaren Epilepsien nicht dramatisch verringert, so dass die beiden anderen Säulen der Epilepsiebehandlung, nämlich die Epilepsiechirurgie und die verhaltenstherapeutischen Massnahmen, nach wie vor sehr wichtig sind.

Schlagwörter: Epilepsien – Therapie

Epilepsie ist eine häufige Erkrankung: Nach Schätzungen des National Institute of Health haben um die 10 % aller Amerikaner während ihres Lebens einen Anfall (8), und das lebenslange Risiko, an Epilepsie zu erkranken, liegt bei 3 % (6). 10 bis 20 % haben Anfälle, die durch die derzeit klinisch eingesetzten Antiepileptika («antiepileptic drugs», AED) nicht kontrolliert werden können.

Grundsätzlich kann man heute von drei Säulen der Epilepsiebehandlung sprechen: der medikamentösen, der chirurgischen und der Verhaltenstherapie. Vielleicht sollte man bei letzterer zutreffender von «verhaltenstherapeutischen Ansätzen» sprechen.

Für die medikamentöse Behandlung stehen eine Reihe bewährter («klassischer») AED zur Verfügung. Zu diesen gesellen sich in jüngster Zeit «neue AED» (22) (Tab. 1 bis 3). Felbamate, ein neues, ursprünglich sehr vielversprechendes AED, das in den USA bereits im Status eines «orphan drug» zugelassen war, zeigte leider schwere Nebenwirkungen, so dass sein klinischer Einsatz derzeit in Europa offenbar nicht weiterverfolgt wird.

Gegenwärtig ist es schwierig abzuschätzen, welche der über 20 neuen Substanzen mit experimentell guter antiepileptisch/antikonvulsiver Wirksamkeit in nächster Zeit zum klinischen Einsatz kommen werden. Tabelle 2 gibt eine unlängst von Löscher und Schmidt (7) publizierte Aufstellung neuer potentieller AED. Die

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Tab. 1. Medikamentöse Epilepsiebehandlung.

<i>klassische AED der ersten und zweiten Wahl</i>
Valproat
Carbamazepin
Ethosuximid
Phenytoin
Phenobarbital
Primidon
<i>klassische AED der dritten Wahl</i>
Diazepam, Clonazepam, Clobazam ¹
Mesuximid
Acetazolamid
Trimethadion
Sultiam
Brom ²
<i>neue AED der zweiten und dritten Wahl (in der Schweiz registriert (add-on))</i>
Vigabatrin (Sabril [®] , Marion Merrel Dow) ³
Lamotrigin (Lamictal [®] , Wellcome) ⁴
Gabapentin (Neurontin [®] , Parke Davis)
Oxcarbazepin (Trileptal [®] , Ciba-Geigy)
<i>Studienpräparate (in der Schweiz)</i>
Tigablin
Levetiracetam (uch L059)
Dextromethorphan ⁵

¹ siehe auch Wang et al., 1993 (20)
² siehe auch Steinhoff, 1988, Diener et al., 1994 (3, 17)
³ siehe auch Ruser et al., 1995 (12)
⁴ siehe auch Pfeifer et al., 1995 (26)
⁵ siehe auch Schmidt et al., 1994, Wieser und Beck, 1992 (15, 23)

Tab. 2. Neue potentielle Antiepileptika und deren Wirkmechanismen, soweit bekannt (modifiziert nach Löscher und Schmidt, 1994) (7).

Substanz	Mechanismus	Aktivität in experimentellen Modellen			klinische Effizienz
		MES-Test	PTZ-Test	Kindling	
Etenobarb	wie Phenobarbital?	+	+	NT	+(?)
Flupirtine	?	+	+	NT	+
D-20443	?	+	+	+	NT
Loreclezole	?	+	+	NT	+
Lorazepam	GABA(?)	+	+	NT	+(?)
Nafamidon	?	+	NE	+/-	+(?)
Denzimol	?	+	NE	NT	+(?)
COS 18416A	?	+	NE	NT	NT
Remacemide	Glutamat(?)	+	NE	NT	NT
Stiripentol	GABA(?)	+	+	NT	+(?)
Topiramant	GABA(?)	+	NE	NT	+
Trans-2-en-Valproat	wie Valproat?	+	+	+	NT
uch L059	?	+/-	NE	+	+(?)
Zonisamide	Na ⁺ (?)	+	NE	+	+
4-Chlorobenzenesulfamid	?	+	+	NT	NT
F-721	?	+	+/-	NT	NT
D-19274	?	+	?	NT	NT
AHR-12245	?	+/-	+	NE	NT
MDL 27,266	?	+	+	NT	NT
COP 33101	?	+	+/-	NT	NT

(bzw.) heisst, dass eine Neurotransmitter- oder Ionenkanalfunktion erhöht bzw. vermindert wird. ? deutet an, dass die Rolle des berichteten Effekts für die genaue Wirkung noch unklar ist. MES = maximaler Elektroshocktest, PTZ = Pentylenetetrazol-Test, kindling = elektrischer limbischer (Amygdala oder Hippokampus) Kindling-Modell-Test. Ineffizienz in den experimentellen Epilepsiemodellen MES oder PTZ schliesst nicht aus, dass eine Schwellenänderung in diesen Tests gefunden wurde. Die Beurteilung der klinischen Effizienz bezieht sich vorwiegend auf Studien bei Patienten mit Pharmakotherapie-resistenten partiellen Anfällen: + gezielte antikonvulsive/antiepileptische Wirkung, +/- schwache Wirkung, NE = nicht effektiv, ? = widersprüchliche oder unklare Ergebnisse bzw. keine einheitlichen Ergebnisse bei kontrollierten Studien, NT = nicht getestet.

Tab. 3. Antikonvulsiv/antiepileptisch wirksame Medikamente mit anderer Hauptindikation (Einsatz bei Therapie-resistenz auf «klassische AED» und bei bestimmten Epilepsiesyndromen). (5)

Allopurinol
Amanitin
Baclofen
Kalziumantagonisten
Plumazenil ¹
Progesteron ²
Immunoglobuline
Mexiletin
Vitamin E

¹ siehe auch Wieser et al., 1986 (25)
² siehe auch Scott-Lavigne, 1988 (13)
³ siehe auch Bäckström et al., 1994 (2)
⁴ siehe auch Rüdiger-Harman et al., 1994, Van Engelen et al., 1994, Pfeifer, 1994 (9, 10, 19)

enormen Kosten, die heute bis zur Registrierung eines neuen AED anfallen (und die sich in den «stolzen» Preisen der «neuen AED» widerspiegeln), lassen die diesbezüglichen Voraussagen angesichts der eher angespannten Situation im Gesundheitswesen als unsicher erscheinen. Die chirurgische Epilepsiebehandlung kann man – je nach Gesichtspunkt – in verschiedene Kategorien einteilen: Zum einen spricht man gerne von läsionsorientierter Epilepsiechirurgie und stellt sie der epilepsiechirurgisch orientierten Läsionektomie und der «funktionellen» Epilepsiechirurgie (ohne grobe strukturelle Läsion) gegenüber. Zum anderen spricht man gerne von einer «kurativen» bzw. «kausalen» Epilepsiechirurgie und stellt sie «palliativen» epilepsiechirurgischen Massnahmen gegenüber. Wo

bei «kurativ» impliziert, dass der Eingriff darauf abzielt, das anfallsgenerierende Hirnareal möglichst vollständig zu entfernen, womit postoperative Anfallsfreiheit angestrebt wird. Im Gegensatz dazu meint «palliativ», dass man a priori keine vollständige postoperative Anfallskontrolle, sondern «nur» eine Verbesserung der Schwere des Anfallsleidens anstrebt. Letztlich spricht man auch gerne von «standardisierten» Eingriffen und stellt diese individuell «massgeschneiderten» gegenüber. In Tabelle 4 sind die wichtigsten «standardisierten» epilepsiechirurgischen Eingriffe aufgezählt. Eine detailliertere Übersicht findet sich bei Wieser und Siegel (24). Verhaltenstherapeutische Ansätze umfassen «deconditionierendes Training», die Entwicklung und den be-

Tab. 4. Standardisierte epileptochirurgische Eingriffe.

- funktionale Hemisphärektomie (Rasmussen, Modifikation von Schramm)
- vordere En-bloc-Temporalappenresektion (Falconer)
- selektive Amygdala-Hippokampekтомie (AHE) (Trans-Sylvisch, Wieser, Yasargil)
- Spencersche Operation (TL-Polresektion und AHE)
- vordere Balkendurchtrennung
- multiple subpale Transsektion (Morell, Whilder)

wussten Einsatz «anfallsunterdrückender Strategien», aber auch die mehr allgemeine Anpassung der Lebensführung mit «Vermeidung von anfallsbegünstigenden Faktoren» und selten die gezielte Aufrechterhaltung einer bestimmten, für das Anfallsleiden günstigen Vigilanzlage. Letzteres wird oft durch unspezifische Gegenmassnahmen, manchmal durch EEG-Biofeedback, bewerkstelligt. Bei den eher seltenen «Reflexepilepsien» müssen die spezifischen anfallsauslösenden Faktoren vermieden werden. Eine Übersicht über die heutzutage am besten etablierten Möglichkeiten der Verhaltenstherapie findet sich bei Wolf (27).

Einige Grundsätze der medikamentösen Epilepsiebehandlung

1. Vor Aufnahme einer AED-Therapie müssen Anfälle nichtepileptischer Genese ausgeschlossen sein. Nur ausnahmsweise wird man sich bei unklarer Primärdiagnose zu einem «Exjuvantibus»-Behandlungsversuch mit AED entschliessen.

2. Beim ersten Anfall wird zu klären sein, ob es sich um einen sogenannten symptomatischen Anfall im Rahmen eines anderweitig behandelbaren Grundleidens handelt, um einen sogenannten «Gelegenheitsanfall», um einen provozierten oder unprovozierten Anfall. Die Behandlung eines ersten unprovozierten Anfalls bleibt Ermessenssache, und die Entscheidung wird im wesentlichen vom Patienten aufgrund seiner spezifischen Lebensumstände getroffen.

3. AED der ersten Wahl sind Valproat und Carbamazepin. Valproat hat nach

wie vor seinen Schwerpunkt bei Absenzen, Impulsiv-Petit-mal und bei Grand-mal-Anfällen ohne Herd im EEG. Bei fokalen Anfällen wird Carbamazepin als Mittel der ersten Wahl bevorzugt. Mittel der zweiten und dritten Wahl sind in Tabelle 5 aufgeführt.

4. Grundsätzlich wird der Monotherapie der Vorzug vor der Polytherapie gegeben. Kombinationen sind aber im Klinikalltag relativ häufig notwendig und auch durchaus sinnvoll, wenn die Interaktionen berücksichtigt werden. Theoretisch machen Kombinations-therapien dann Sinn, wenn die gegebenen Substanzen verschiedene Wirkmechanismen aufweisen und die Kombination einen «supraadditiven Effekt», das heisst einen verbesserten

therapeutischen Index (Effizienz versus Nebenwirkungen) hat (22).

Tabelle 6 gibt für einige Kombinationen die Interaktionen hinsichtlich antiepileptischer Wirksamkeit und Neurotoxizität. Aus der Berücksichtigung beider Spalten werden die sinnvollen Kombinationen ersichtlich. Nicht aufgeführt ist in dieser Tabelle die Kombination Valproat und Lamotrigin, die nach eigenen Untersuchungen (26) durchaus sinnvoll ist. Dabei ist aber zu beachten, dass die – in dieser Studie festgestellte – bessere antiepileptische Wirksamkeit der Kombination Valproat mit Lamotrigin gegenüber Kombinationen von Lamotrigin mit anderen AED, aber nicht Valproat, auch darauf zurückzuführen sein könnte, dass Lamotrigin in der Gruppe Valproat und

Tab. 5. AED-Standardtherapien epileptischer Anfälle im Jugendlichen- und Erwachsenenalter.

	Absenzen	Impulsiv-Petit-mal	fokale Anfälle	Grand-mal ohne Fokus
AED der ersten Wahl	Valproat	Valproat	Carbamazepin	Valproat
AED der zweiten Wahl	Ethosuximid	Phenobarbital Primidon	Phenytoin Valproat Phenobarbital Primidon Oxcarbazepin	Phenobarbital Primidon Carbamazepin Phenytoin Oxcarbazepin
AED der dritten Wahl	Clobazam Mesuximid Acetazolamid Trimethadion Lamotrigin	Ethosuximid Clobazam Acetazolamid Lamotrigin	Clobazam Vigabatrin Lamotrigin Gabapentin Seltiam Mesuximid Brom	Clobazam Lamotrigin Gabapentin Vigabatrin? Brom

Tab. 6. Pharmakodynamische Interaktionen zwischen AED (modifiziert nach Bourgeois, 1990) (1)

Interaktion		
Kombination	antiepileptisch	neurotoxisch
PHT + PB	additiv	infraadditiv
PHT + CBZ	additiv	additiv
CBZ + PB	additiv	additiv
VPA + ESM	additiv	infraadditiv
VPA + PB	additiv	additiv
VPA + CBZ	additiv	infraadditiv
PB + PRIM	supraadditiv	infraadditiv
PB + PEMA	supraadditiv	supraadditiv

PHT = Phenytoin, PB = Phenobarbital, CBZ = Carbamazepin, VPA = Valproat, ESM = Ethosuximid, PRIM = Primidon, PEMA = Phenyl-ethyl-malonamid. Sinnvolle Kombinationen sind durch Kursivdruck hervorgehoben.

Lamotrigin (trotz Halbierung der Lamotrigin-Dosis in Kombination mit Valproat) höhere Serumkonzentrationen aufwies als in der Gruppe ohne Valproat und dass sich in der Gruppe Valproat und Lamotrigin mehr generalisierte Epilepsien fanden.

Tabelle 7 zeigt auf, mit welchen pharmakokinetischen Interaktionen bei Zugabe eines zweiten AED zu einem bestehenden, ursprünglich eingesetzten AED der ersten Wahl.

Summary

The modern treatment of epilepsy has improved considerably in all three pillars. More than a century has passed, however, since Sir Charles Lucaris introduced the bromides in 1857 and Sir Victor Horsley pioneered epilepsy surgery in 1886 (18). In drug therapy, the 'classic AED' of the last decades, i.e. phenobarbital (Haugenmaur, 1912) and phenytoin (Putnam and Merrit, 1938) are being largely displaced by valproate (Meunier, 1963) and carbamazepine (Lange, 1963). Only ethosuximide (Zimmermann, 1951) has continued to maintain its position in 3x spike-wave-absence epilepsy, in particular in the USA (28, 29). Although it is an excellent drug against absences, it has the unpleasant property that it may induce GM seizures and should therefore be combined with a so-called 'GM protector' (mostly phenobarbital). For this reason ethosuximide has been relegated to second place in Europe by valproate. Thus, the decision as to which AED should be employed at the onset has been simplified considerably: actually, with valproate as the drug of first choice, which displays a very broad spectrum of action, we are on the right track for virtually all forms of epilepsy, perhaps with the exception of focal epilepsy (11). Especially in the event of focal epilepsy of temporal origin we employ carbamazepine as the preparation of first choice. In some countries (Denmark), because of the less severe side effects, oxcarbazepine is already preferred (Mogens Dam, personal communication).

Considerable experience and knowledge are still required, however, when resistance has developed to traditionally applied classic monotherapies. Here, the range of further treatment can also be greatly extended by the availability of the 'new AED'. A generally accepted protocol for the replacement of one preparation with another first- or second-choice drug and, above all, for the 'right' combination with third-choice preparations can as yet not be compiled. What we need

Tab. 7. Pharmakokinetische Interaktionen bei Zugabe eines zweiten AED zu einem bestehenden, ursprünglich eingesetzten AED der ersten Wahl.

ursprünglich eingesetztes AED	zugegebenes zweites AED (add-on)	Effekt des zweiten AED auf Serumkonzentration des ursprünglichen AED
Carbamazepin	Phenobarbital Phenytoin Primidon	
Phenobarbital	Carbamazepin Phenytoin Valproat Methsuximid	↓
Phenytoin	Carbamazepin Methsuximid Phenobarbital Primidon Valproat	↓ 0 0 0 ↓
Valproat	Carbamazepin Phenobarbital Phenytoin Primidon	↓
Primidon	Carbamazepin Phenytoin	↑ von Phenobarbital von Phenobarbital
Lamotrigin ¹	Valproat Carbamazepin Phenobarbital Phenytoin	

¹ Die Konzentrationen des «totalen» und «proteingebundenen» Phenytoins fallen, während die Konzentration des nichtproteingebundenen, «freien» Phenytoins vorübergehend ansteigen kann und dann wieder auf den Ursprungswert vor Zugabe des Valproats zurückkehrt.

² Lamotrigin (Lamictal[®]) ist vorderhand in der Schweiz nur als «add-on» zugelassen.

Tab. 9. Erfolgsaussichten der verschiedenen Möglichkeiten zur medikamentösen Weiterbehandlung erfolglos vorbehandelter Patienten mit fokalen Epilepsien mit einem Medikament der ersten Wahl und Tagesdosen im therapeutischen Bereich der Plasmakonzentration (aus 9).

	Anfallsfreiheit der Patienten (%)	zusätzlich mehr als 50%ige Abnahme der Anfälle der Patienten (%)
1. Erhöhen der Tagesdosis des Medikaments der ersten Wahl bis an die Grenze der klinischen Verträglichkeit	30	10
2. Austausch zwischen Medikamenten der ersten und zweiten Wahl, also alternative Monotherapie	10 bis 20	10
3. Zweiertherapie von zwei Medikamenten der ersten oder zweiten Wahl	10 bis 20	20
4. Zweiertherapie mit einem neuen Anti-epileptikum	10 bis 30	10

here is the expert epileptologist who has experience with 'theoretically useful' combinations and has an insight into the interactions occurring with such combinations. For

several specific epileptic syndromes the 'Königsteiner Working Group of German-Speaking Epileptologists' has given clear and binding recommendations for AED therapy

Tab. 8

Medikament	aktuelle Dosis bei Monotherapie (mg/Tag)	mg/kg	mittelschnelle Aufdosierung bei ambulanter Behandlung	Verteilung der Tagesdosis	sogenannte therapeutische Plasmakonzentration*		Proteinbindung (%)	Plasmaelimination (Halbwertszeit)
					µg/ml	Faktor µmol/l		
Carbamazepin	800 bis 1200	15 bis 20	alle 3 bis 7 Tage um 100 mg erhöhen	1 bis 4 ^b	8 bis 12 3 bis 7 (früher)	4,23 50	39 bis ~75	~19
Valproat ^c	1200 bis 2000	10 bis 20	alle 3 bis 5 Tage um 300 mg erhöhen	1 bis 3 ^d	50 bis 100	6,93 700	350 bis ~90	~17
Phenytoin ^e	300	5 bis 6	alle 3 bis 7 Tage um 100 mg erhöhen, ab 300 mg Tagesdosis nur mehr in 25-mg-Schritten erhöhen	1 bis 3	10 bis 20	3,96 80	40 bis ~90	24 ± 12
Phenobarbital ^f	150 bis 200	2 bis 3	alle 2 Wochen um 50 bis 100 mg erhöhen	1 bis 2	20 bis 35 (15 bis 40)	4,31 150	85 bis ~50	96 ± 12
Primidon	750 bis 1000	10 bis 20	alle 7 Tage um 62,5 mg erhöhen	3	Prima: 5 bis 12 PB: 35 ^g	4,58 55	23 bis ~19	~10 ^h
Ethosuximid	1000 bis 1250	15 bis 20	alle 2 Wochen um 250 mg erhöhen	1 bis 2	40 bis 100	7,08 700	285 bis <10	36 ± 6
Clobazam	20	0,2 bis 0,5	alle 4 bis 7 Tage um 10 mg erhöhen	1 bis 2				~20
Bromid	900 bis 1300	10 bis 20	alle 14 Tage um 600 mg erhöhen	2 bis 3	75 bis 125			
Eponid ⁱ					1 bis 4	3,97 ^j	4 bis 16	
Diazepam	5 bis 20				0,5 bis 0,7	3,51	1,7 bis ~98(7)	8 bis 10 ^k
Clonazepam	2 bis 4		vorwiegend abends		0,015 bis 0,07	3,16	0,047 bis 0,22	20 bis 60 ^l

* Die Werte geben den mittleren Wirkungsbereich an, in dem die Mehrzahl der Patienten problemlos und erfolgreich behandelt werden kann; oberhalb dieses Bereichs besteht ein zunehmendes Nebenwirkungsrisiko

^b Einmaldosis bei Retardpräparaten

^c Bei Valproat sind im Tagesverlauf starke Schwankungen möglich

^d Einmaldosis in Monotherapie bei niedriger oder mittlerer Dosis, wenn Slow-release-Form

^e nichtlineare Dosis-Spiegel-Beziehung

^f Phenobarbital direkt und als Metabolit des Primidons, Phenobarbital kann Absenzen verschlimmern

^g Zwei Metaboliten von Primidon sind bekannt mit unterschiedlicher antiepileptischer Wirksamkeit: PBMA (Phenobarbital-Metabolit A) mit einer t_{1/2} von ~36 Std. und Phenobarbital (etwa 15 bis 25% von Primidon) mit einer t_{1/2} von ~80 Std.

^h nicht sicher bekannt (siehe auch 20)

ⁱ Carbamazepin-10, 11-Eponid, ein Metabolit des Carbamazepins, kann in Gegenwart von Valproat erhöht sein, und Nebenwirkungen führen (siehe auch 16)

^j für parenterale Statustherapie: 0,1 mg pro Kilo Körpergewicht; in Abständen von 30 bis 60 s wiederholte Dosen von 0,05 mg pro Kilo Körpergewicht, auf Atemdepression achten

^k 3 Std. für «schnelle Phase» (= initiale Verteilungsphase), 48 Std. für «langsame Phase» (= terminale Eliminationsphase)

^l für terminale Phase

(e.g. for benign juvenile myoclonic epilepsy - Janz syndrome). This working group has also made recommendations for the necessary clinical and laboratory controls in AED therapy with potentially severe side effects (e.g. valproate therapy in high-risk children), which were published and/or are being published and discussed in the 'Epilepsie-Blätter' of the German League against Epilepsy (4). Despite all advances in drug therapy, the number of epilepsy patients not satisfactorily treatable with drug therapy has not been dramatically reduced statistically, so that the other two pillars of epilepsy therapy, i.e. epileptic surgery and behavioural therapy, continue to be very important.

Key words: epilepsy - therapy

Résumé

Le traitement moderne des épileptiques s'est sensiblement amélioré dans chacun de ses trois piliers. Plus de 100 ans se sont écoulés depuis que sir Charles Locock a introduit les

brumures en 1857, et que sir Victor Horsley a ouvert en 1886 l'ère moderne de la chirurgie de l'épilepsie (18). Dans le traitement médicamenteux, les «AED classiques» de ces dernières décennies, à savoir le phénobarbital (Hauptmann, 1913) et la phénytoïne (Putnam et Merris, 1938), ont largement été remplacés par le valproate (Meunier, 1963) et la carbamazépine (Lorge, 1963). Seul l'éthosuximide (Zimmermann, 1951) a confirmé sa place dans les absences pointées-ondes 3/sec., aux USA surtout (28, 29). Du fait de sa fâcheuse propriété de pouvoir déclencher des

croix (AM) et de devant donc être associée à une protection due -au- (AM) -phenobarbital en général. L'ethosuximide est certes un excellent médicament contre les absences, mais même dans cette indication, en Europe, il a été repoussé à la seconde place par le valproate. Le choix des AED à utiliser d'emblée est ainsi considérablement simplifié: nous tombons juste en choisissant comme médicament de première intention le valproate, à très large spectre dans pratiquement toutes les épilepsies. À l'exception peut-être des épilepsies focales (11). C'est surtout lorsque nous avons à faire à des épilepsies focales à localisation temporelle que nous utilisons la carbamazépine en première intention. Dans certains pays (Hannover), pour cette indication, l'oxcarbazépine est déjà préférée en raison de ses effets indésirables moins marqués (Meyerus Hann. communication personnelle.).

Mais il faut toujours une expérience et des connaissances approfondies lorsque se présente une résistance à une monothérapie conduite légitime. La polio du traitement s'est dans ce cas élargie, malgré le fait que nous disposons de «nouveaux AED». Il n'est actuellement pas possible de proposer un schéma thérapeutique généralement admis, pour remplacer un médicament de première ou de deuxième intention par un autre, et surtout pour les «humains» associations aux médicaments de troisième intention. Nous faisons appel à l'épileptologue expérimenté, celui qui dispose d'une certaine expérience avec les associations «théoriquement judicieuses», et qui en connaît les interactions potentielles. Le «Königsteiner Arbeitskreis deutschsprachiger Epileptologen» (Groupe de travail Königstein des épiléptologues de langue allemande) a émis des recommandations claires et obligatoires pour le traitement par AED de quelques syndromes épileptiques spécifiques (p. ex. pour l'épilepsie myoclonique infantile bénigne, le syndrome de Janz). Ce groupe de travail a en outre élaboré des recommandations pour les contrôles cliniques et de laboratoire, indispensables sous traitement par AED pouvant avoir des effets indésirables sérieux (p. ex. traitement par valproate d'enfants à haut risque), publiés et discutés dans les «Epilepsie-Mitteilungen der Deutschen Liga gegen Epilepsie» (4). Malgré tous les progrès du traitement médicamenteux, le nombre des épilepsies traitées de manière non satisfaisante n'a pas baissé de manière significative, statistiquement parlant, ce qui fait que les deux autres piliers du traitement antiépileptique, à savoir la chirurgie et la thérapie comportementale, gardent toute leur importance.

Mots clés: épilepsies - thérapie

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Brigard & Castro
SANTA FE DE BOGOTA - COLOMBIA

PODER

POWER OF ATTORNEY

Yo (nosotros)

I (We) UCB, S.A.

Domiciliado(s) en

domiciled in BRUSELAS, BELGIUM

allée de la Recherche 60, B-1070 Bruxelles, Belgium

Nombre (amos) a: RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA de Santafé de Bogotá Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar (de las oficinas y autoridades colombianas administrativas judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y ensenanzas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones o solicitudes de patentes, diseños industriales, modelos de utilidad en el ejercicio en ajorrecito de medidas cautelares y en otras acciones o medidas similares.

Hereby appoint RAMIRO CASTRO DUQUE and/or HECTOR GOMEZ MEJIA, of Santafé de Bogotá, Colombia, my (our) true and lawful attorneys with special ample and sufficient power to obtain from the Colombian administrative, judicial and police of offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial design and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measure and in other actions or similar proceedings.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations nullities, appeals and claims; to pay taxes, quotas an assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to that effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir comprometer y la de sustituirlo en todo o en parte y revocar sustituciones Asimismo nombro(amos) a: RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) verdaderos y legales apoderados judiciales y extrajudiciales con el presente poder para recibir notificaciones y designar apoderados judiciales y extrajudiciales.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, as to substitute this power in whole or in part and I revoke substitutions. At the same time I (We) hereby appoint RAMIRO CASTRO DUQUE and/or HECTOR GOMEZ MEJIA, domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorneys in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Otorgado y firmado en

Granted and signed in

Firma

Nombre
Cargo

Name
Title

Brussels, on November 8, 2000

UCB, SA

Henriette VAN CAENEGEM
Proxy and Legal Representative

31 MAY 2005

OSCAR ALARCON NUÑEZ
NOTARIO CUARENTA Y SEIS

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de personalmente compareció ante mi

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él es

de

Sociedad legalmente constituida para un periodo de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

estado de con fecha

y que quien confiere el presente poder es su representante

Notario Público (sello)

CERTIFICADO NOTARIAL PERSONA NATURAL

Hoy de de compareció(n) ante mi

a quien (as) conozco y me consta que en(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) otorgan el mismo para los fines y propósitos que en el mismo se expresan

Notario Público (sello)

LEGALIZACION ANTE CONSUL COLOMBIANO REQUERIDA.

NOTARIAL CERTIFICATE (CORPORATE)

On this 13th day of November 2000 of personally appeared before me Henriette Van Caenegem to me known and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the proxy and legal representative

of

UCB, S.A. of Allée de la Recherche 60 B-1070 Bruxelles, Belgium

Which is legally constituted for a term not yet expire that deponent is authorized by said Company to confer this Power of Attorney that the seal affixed herewith by the deponent in the name said on behalf of said Corporation is the corporate seal thereof, and that purpose for which this instrument is granted is included within the corporate purpose of the company

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

Belgium
state of under date of

and that he (she) who grants the present power attorney is its Representative.

T. VAN HALTEREN
NOTAIRE
Rue de l'Association 30
1000 BRUXELLES

NOTARIAL CERTIFICATE NATURAL PERSON

On this day of personally appeared before me

who is (are) known to me and who I attest executed foregoing instrument (they) declared he (she) grant(s) the document for the purposes herein expressed,

Notary Public (Seal)

LEGALIZATION BEFORE COLOMBIAN CONSUL IS REQUIRED

31 MAY 2005

OSCAR ALARCÓN LÓPEZ
NOTARIO CUARENTA Y SEIS

143

26



Vu pour légalisation de la signature de

M. *van Halbeek*

sur le présent document

Bruxelles, le 16-11-2000

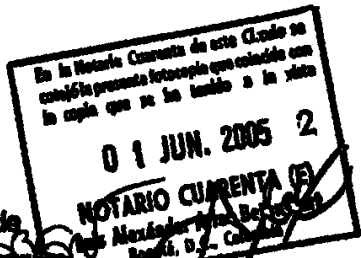
Pour le Ministre des Affaires Etrangères
Le Fonctionnaire délégué



N°

Melard

C. MELARD





CONSULADO GENERAL DE COLOMBIA
BRUSELAS

No.924

Bruselas, 16 DE Noviembre DE 2000

El suscrito Cónsul de Colombia en Bélgica, vistos los documentos presentados por los interesados,

CERTIFICA:

Que el señor C. MELARD, quien constató que la autenticación de la firma del signatario del poder precedente fue efectuada de conformidad con la ley Belga, ejercía a la fecha como Funcionario del Servicio de Legalizaciones del Ministerio de Relaciones Exteriores del Reino de Bélgica, y que su firma corresponde a la registrada en este Consulado;

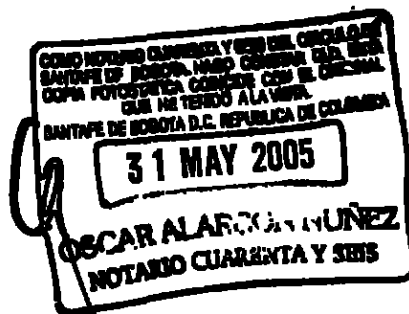
Que la UCB S.A. es una entidad constituida de acuerdo con las leyes del Reino de Bélgica y que cumple con su objeto conforme a las mismas;

Que la señora HENRIETTE VAN CAENEGEM es su representante legal en este país.

El Cónsul no asume responsabilidad alguna por el contenido de este documento.


MAURICIO GONZÁLEZ LOPEZ
Cónsul General de Colombia

Derechos Pagados:
Fondo Rotatorio USD: 15
Impuesto de Timbre USD: 7
Total: USD 22



22 145 149

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2003 FEB 20 A 9 44

EDAS
OFICE DE LEGALIZACIONES
ESTADO DE OREGON D.C.

MINISTERIO DE RELACIONES
EXTERIORES

4 14 98

Alvaro Gonzalez
CUYAFIL
DUCUM
LAS FUER

En la Notaría Certifico de esta G.c. que se
copia la presente fotocopia que coincide con
la copia que se ha leído a la vista
01 JUN. 2005 2
NOTARIO GARET
Luis Alvarado Arce
Bogotá, D.C. Colombia

34 146 150

TRADUCCIÓN OFICIAL DEL INGLÉS AL ESPAÑOL de las legalizaciones que se encuentran a continuación de un **PODER** otorgado por **UCB S.A.** sociedad domiciliada en **Alée de la Recherche, 60, B-1070 Bruselas, Bélgica** al doctor **RAMIRO CASTRO DUQUE** y/o **HECTOR GOMEZ MEJIA**, de **Santafé de Bogotá, Colombia**, y firmado el **9 de Noviembre de 2000** por **Henriette Van Caenegem**, **Apoderado y Representante Legal** de dicha compañía. Las cuales para su identificación se sellan con el **Sello del Traductor** al mismo tiempo que la presenta.

El texto del poder no se traduce ya que se encuentra en Español.

Un **CERTIFICADO NOTARIAL (SOCIEDAD)** fechado **13 de Noviembre de 2000**, autenticando la firma de **HENRIETTE VAN CAENEGEM**, **Apoderado y Representante Legal**, de la Empresa **UCB S.A.** y certificando también la existencia de la misma. El certificado se encuentra debidamente firmado y sellado por **T. VAN HALTEREN**, **Notario Público de Bruselas**.

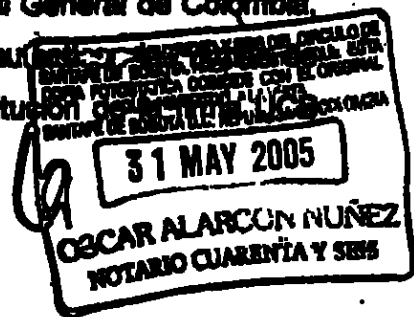
El texto del certificado no se traduce ya que se encuentra en Español.

El documento está debidamente sellado y firmado al respaldo así:

EN FRANCÉS: Un sello de caucho en tinta roja, que dice: **Presentado para la legalización de la firma de T VAN HALTEREN** quien certifica este documento. **Bruselas, 16-11-2000. Por el Ministro de Relaciones Exteriores.- El Funcionario Delegado.** Esta certificación se encuentra debidamente sellada y firmada por **El Funcionario Delegado del Ministerio de Comercio y Relaciones Exteriores, Sr. C. MELARD.**

SELLO REDONDO EN RELIEVE

EN ESPAÑOL: Pegado al documento se aprecia un certificado del Consulado de Colombia en Bélgica identificado con el No. 924 y fechado 16 de Noviembre de 2000, debidamente firmado y sellado por el **Cónsul General de Colombia, MAURICIO GONZALEZ LOPEZ**, mediante el cual se autentica la firma de **C. MELARD** y **Henriette VAN CAENEGEM** y la constitución de **UCB S.A.**



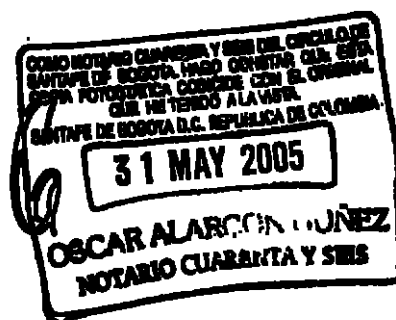
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32
Al respaldo de este documento se aprecian dos sellos de caucho en tinta azul:
Uno del Ministerio de Relaciones Exteriores con el número 414981 y el
segundo del Jefe de Legalizaciones fechado: 2003 FEB. 20.

TRADUCTORA : MARIA EUGENIA MEDINA DE SÁNCHEZ

FECHA: 28 de febrero de 2003

FIRMA Y SELLO DEL TRADUCTOR


MARIA EUGENIA DE SANCHEZ
TRADUCTORA OFICIAL
COLECCION No. 1000 DE
TRADUCTORES DE JOYERIA





ORGANIZACION ELECTORAL
REGISTRADURIA NACIONAL DEL ESTADO CIVIL

REGISTRO CIVIL DE DEFUNCION

Indicativo
Serial

5562241

Datos de la oficina de registro							
Clase de oficina:	Registraduría	Notaría	☒	Consulado	Corregimiento	Insp. de Policía	Código
País - Departamento - Municipio - Corregimiento o Inspección de Policía							
COLOMBIA CUNDINAMARCA BOGOTA D.C.						NOTARIA 32.	

Datos del inscrito	
Apellidos y nombres completos	
CASTRO DUQUE RAMIRO	
Documento de identificación (Clase y número)	Sexo (en Letras)
C.C. No. 170322 DE BOGOTA	MASCULINO

Datos de la defunción			
Lugar de la Defunción: País - Departamento - Municipio - Corregimiento o Inspección de Policía			
COLOMBIA CUNDINAMARCA BOGOTA D.C.			
Fecha de la defunción		Hora	Número de certificado de defunción
Año	2 0 0 4	04:10 PM	A- 2094375.
Mes	1 0		
Día	3 0		
Presunción de muerte			
Lugar que profiere la sentencia		Fecha de la sentencia	
Documento presentado		Nombre y cargo del funcionario	
Autorización judicial ☐ Certificado Médico ☒		ANDRES DIAZ CAMPOS.- R. M. No. 79982662	

Datos del denunciante	
Apellidos y nombres completos	
EDGAR DAVID REGINO II.	
Documento de identificación (Clase y número)	Firma
C.C. No. 15.030.154 DE LORICA/ CORDOBA	

Primer testigo	
Apellidos y nombres completos	
Documento de identificación (Clase y número)	Firma

Segundo testigo	
Apellidos y nombres completos	
Documento de identificación (Clase y número)	Firma

Fecha de inscripción		Nombre y firma del funcionario que autoriza	
Año	2 0 0 4	BLANCA REYES RESTREPO	
Mes	1	NOTARIA	
Día	0 2		

PADRES: ALFONSO CASTRO		ESPACIO PARA NOTAS	
MERCEDES DUQUE			

NOTARIA 32

DEL CIRCULO DE SANTA FE DE BOGOTA, D.C.

Germán Eleázar Moreno L.
Notario

COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL
CIRCULO DE BOGOTA

CERTIFICO QUE:

La presente acta es fiel copia del original tomada del registro
civil de defunciones serial indicativa número: 56224
que expido en la ciudad de Bogotá D.C. hoy: 05 NOV. 2004

SECRETARIO DELEGADO

NOTARIA 32 DEL CIRCULO DE BOGOTA D.C.
NELSON FLORES C.
SECRETARIO DELEGADO PARA COPIAS
DECRETO 1334 DE 1998

③ **DEMANDE DE BREVET EUROPEEN**

④ Numéro de dépôt: 85870088.3
Date de dépôt: 14.05.85

⑤ Int. Cl.⁴: C 07 D 207/27, A 61 K 31/40

Priorité: 15.05.84 GB 8412357

Date de publication de la demande: 21.11.85
Bulletin 85/47

Etats contractants désignés: AT BE CH DE FR GB IT LI
LU NL SE

⑦ Demandeur: U.C.B. S.A., 326, Avenue Louise,
B-1050 Bruxelles (BE)

⑧ Inventeur: Gobert, Jean, 120, rue du Cornet,
B-1040 Bruxelles (BE)
Inventeur: Geerts, Jean-Pierre, 12, Heberu,
B-6737 Leglise (BE)
Inventeur: Bodson, Guy, 248, rue de la Chevrotte,
B-6736 Belfontaine (Tintigny) (BE)

⑨ Mandataire: Duseeldorp, Raymond et al, U.C.B. S.A.
Département D.T.B. 33, rue d'Anderlecht,
B-1020 Drogenbos (BE)

⑩ (S)-alpha-éthyl-2-oxo-1-pyrrolidinesoétamide.

Le (S)-alpha-éthyl-2-oxo-1-pyrrolidinesoétamide, sa préparation et compositions thérapeutiques renfermant ledit composé. Il est préparé soit par réaction de l'acide (S)-alpha-éthyl-2-oxo-1-pyrrolidinesoétique successivement avec un halogénoformate d'alkyle et de l'ammoniac, soit par cyclisation d'un (S)-2-aminobutanamide de formule $X-CH_2CH_2-Y-NHCH-(C_2H_5)CONH_2$ dans laquelle lorsque $X = ZOOC-$, $Y = -CH_2-$, et lorsque $X = HalCH_2-$, $Y = -CO-$; Z = alkyle et Hal = halogène.

Le composé est utilisable notamment pour le traitement des agressions de type hypodque et lachémique.

162 036 A1
EP

(S)-alpha-éthyl-2-oxo-1-pyrrolidineacétamide.

La présente invention se rapporte à un composé nouveau, le (S)-alpha-éthyl-2-oxo-1-pyrrolidineacétamide ainsi qu'à des procédés pour le préparer. Elle concerne également les compositions thérapeutiques
5 renfermant ledit composé.

Dans le brevet britannique n° 1.309.692 au nom de la demanderesse, on décrit l'alpha-éthyl-2-oxo-1-pyrrolidineacétamide (point de fusion 122°C) et on indique que les substances de ce type sont utilisables dans le domaine thérapeutique, par exemple pour le traitement du mal de
10 mouvement, des hyperkinésies, des hypertonies et de l'épilepsie.

D'autre part, on y mentionne aussi que ces composés peuvent trouver une application dans le domaine des troubles de la mémoire dans des conditions normales ou pathologiques.

En outre, il est connu également que l'alpha-éthyl-2-oxo-1-pyrrolidine-acétamide possède une activité de protection envers les agressions du système nerveux central causées par des hypoxies, de l'ischémie cérébrale, etc. (Pharmazie, 37/11, (1982), 753-765).
15

Poursuivant ses travaux de recherche dans ce domaine, la demanderesse a préparé et isolé l'énantiomère lévogyre de l'alpha-éthyl-2-oxo-1-pyrrolidineacétamide et elle a trouvé que ce composé se distingue de manière tout à fait imprévue de la forme racémique connue
20 (1) par une activité de protection envers l'hypoxie (anti-hypoxie) 10 fois plus élevée et
(2) par une activité de protection envers l'ischémie cérébrale (anti-ischémie) 4 fois supérieure.
25

De cet ensemble imprévisible de propriétés, il résulte que l'énantiomère lévogyre de l'alpha-éthyl-2-oxo-1-pyrrolidineacétamide convient mieux pour le traitement et la prévention des agressions du type hypoxique et ischémique du système nerveux central. La contribution importante du phénomène hypoxique dans certaines pathologies du système nerveux
30 central laisse pressager un effet thérapeutique de ce produit dans le traitement des suites d'accidents vasculaires cérébraux et de traumatismes crâniens, des séquelles du processus de vieillissement ou des

insuffisances circulatoires du système nerveux central résultant d'accidents cérébroischémiques ou d'hypoxie survenant p.ex. lors de la naissance. Par extension, il est permis d'envisager l'utilisation de ce produit dans les affections du type hypoxique d'autres organes ou tissus:

5 coeur et reins.

C'est pourquoi la présente invention a pour objet l'énantiomère lévogyre de l' α -éthyl-2-oxo-1-pyrrolidineacétamide qui possède la configuration absolue S, ledit composé étant substantiellement exempt de l'énantiomère dextrogyre ayant la configuration absolue R.

10 Le (S)- α -éthyl-2-oxo-1-pyrrolidineacétamide conforme à la présente invention ne peut pas être obtenu directement à partir de la forme racémique par séparation des deux énantiomères. Il peut être préparé par l'un ou l'autre des procédés suivants:

(a) on fait réagir l'acide (S)- α -éthyl-2-oxo-1-pyrrolidineacétique

15 successivement avec (1) un halogénoformiate d'alkyle de formule HalCOOZ dans laquelle Hal représente un atome d'halogène et Z un radical alkyle ayant 1 à 4 atomes de carbone et (2) de l'ammoniac. L'halogénoformiate d'alkyle est de préférence du chloroformiate d'éthyle.

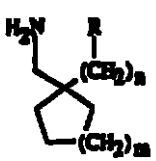
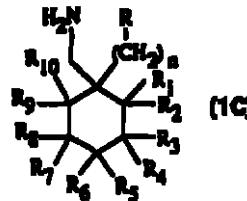
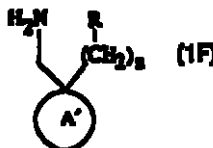
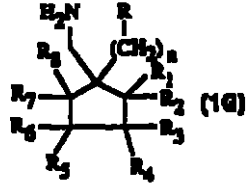
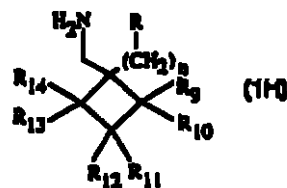
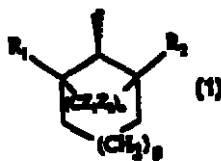
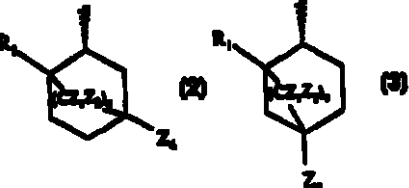
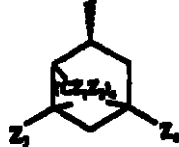
20 Cette réaction est généralement effectuée dans le dichlorométhane, à une température comprise entre -10 et -60°C . L'acide (S)- α -éthyl-2-oxo-1-pyrrolidineacétique, utilisé dans cette réaction, peut être obtenu à partir de l'acide ($\pm$)- α -éthyl-2-oxo-1-pyrrolidineacétique racémique, par résolution chimique selon

25 des méthodes connues en soi, par exemple en formant un sel de cet acide avec une base optiquement active et en isolant le sel formé avec l'acide (S)- α -éthyl-2-oxo-1-pyrrolidineacétique, par cristallisations successives dans un solvant approprié (p.ex. le benzène).

30 A titre d'exemples de bases optiquement actives pouvant être utilisées pour cette résolution, on peut citer des alcaloïdes comme la brucine, la quinine, la strychnine, la quinidine, la cinchonidine et des amines comme l' α -méthyl-benzylamine et la déhydroabiétylamine (cfr. S.H. WILKIN et al., Tetrahedron, 33, (1977), 2725-2736). Des

35 résultats particulièrement favorables sont obtenus en utilisant l' α -méthyl-benzylamine et la déhydroabiétylamine.

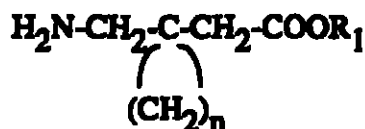
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 257/04, A61K 31/41, C07D 271/06, C07F 9/38, A61K 31/66, C07D 291/04, C07C 311/10, A61K 31/18, C07C 311/07, 239/14, A61K 31/16, C07C 309/25, A61K 31/255	A1	(11) International Publication Number: WO 99/31075 (43) International Publication Date: 24 June 1999 (24.06.99)
(21) International Application Number: PCT/US98/23918 (22) International Filing Date: 10 November 1998 (10.11.98) (30) Priority Data: 60/069,773 16 December 1997 (16.12.97) US 60/105,005 20 October 1998 (20.10.98) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (73) Inventors/Applicants (for US only): BRYANS, Justin, Stephen [GB/GB]; Dean Cottage, 3 W. Wickham Road, Balham CB1 6DZ (GB). CAPRIS, Thomas [US/US]; 14816 Green- briar Court, Plymouth, MI 48170 (US). HORWELL, David, Christopher [GB/GB]; 8 West Hill, Foxton, Cambridge CB2 6SZ (GB). KNEEN, Clara, Octavia [GB/GB]; Slade Cottage, Peters LN, Little Walden, Essex CB10 1XH (GB). WUS- TROW, David, Juergen [US/US]; 5101 John Holmes Road, Ann Arbor, MI 48103 (US).		(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al. (51) Designated States: AL, AU, BA, BE, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.
(54) Title: 1-SUBSTITUTED-1-AMINOMETHYL-CYCLOALKANE DERIVATIVES (GABAPENTIN ANALOGUES), THEIR PREPARATION AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISORDERS (57) Abstract Novel amines of formulas (1), (1C), (1F), (1G) and (1H) or a pharmaceutical acceptable salt thereof wherein n is an integer of from 0 to 2; m is an integer of from 0 to 3; R is sulfonamide, amide, phosphonic acid, heterocycle, sulfonic acid, or hydroxamic acid; A' is a bridged ring selected from (1), (2), (3), (4), (5) wherein is the point of attachment; Z₁ to Z₄ are each independently selected from hydrogen and methyl; o is an integer of from 1 to 4; and p is an integer of from 0 to 2. In formula (1) above R cannot be sulfonic acid when m is 2 and n is 1 are disclosed and are useful as agents in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, inflammatory diseases, and gastrointestinal disorders, especially irritable bowel syndrome.  (1)  (1C)  (1F)  (1G)  (1H)  (2)  (3)  (4)  (5)		

1-SUBSTITUTED-1-AMINOMETHYL-CYCLOALKANE DERIVATIVES (=GABAPENTIN ANALOGUES), THEIR PREPARATION AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISORDERS

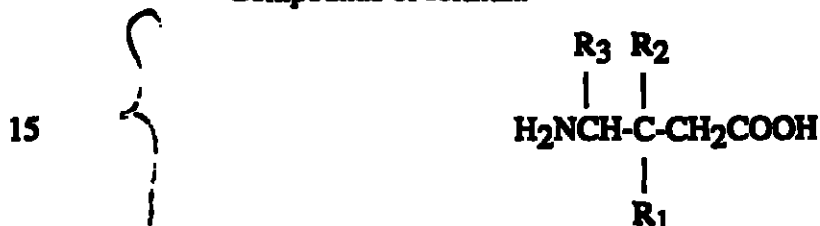
BACKGROUND OF THE INVENTION

Compounds of formula



5 wherein R₁ is hydrogen or a lower alkyl radical and n is 4, 5, or 6 are known in United States Patent Number 4,024,175 and its divisional United States Patent Number 4,087,544. The uses disclosed are: protective effect against cramp induced by thiosemicarbazide; protective action against cardiazole cramp; the cerebral diseases, epilepsy, faintness attacks, hypokinesia, and cranial traumas; 10 and improvement in cerebral functions. The compounds are useful in geriatric patients. The patents are hereby incorporated by reference.

Compounds of formula



wherein R₁ is a straight or branched alkyl group having from 1 to 6 carbon atoms, phenyl, or cycloalkyl having from 3 to 6 carbon atoms; R₂ is hydrogen or methyl; and R₃ is hydrogen, methyl, or carboxyl are known in United States Patent Number 5,563,175 and various divisionals. These patents are hereby incorporated by reference.

SUMMARY OF THE INVENTION

25 The compounds of the instant invention are novel amines and their pharmaceutically acceptable salts useful in a variety of disorders. The disorders include: epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological

disorders, inflammatory diseases, and gastrointestinal disorders, especially irritable bowel syndrome.

The compounds of the invention are those of formulas 1, 1C, 1F, 1G, and 1H below.

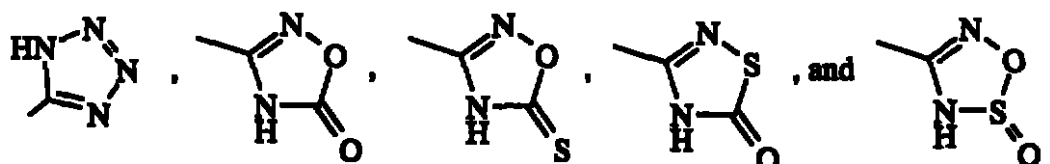
5 Preferred compounds are those wherein R is a sulfonamide selected from $\text{-NH}\text{SO}_2\text{R}^{15}$ or $\text{-SO}_2\text{NHR}^{15}$ wherein R^{15} is straight or branched alkyl or trifluoromethyl.

Especially preferred is N-[2-(1-aminomethyl-cyclohexyl)-ethyl]-methanesulfonamide.

10 Other preferred compounds are those wherein R is a phosphonic acid, $\text{-PO}_3\text{H}_2$.

Especially preferred are (1-aminomethyl-cyclohexylmethyl)-phosphonic acid and (2-aminomethyl-4-methyl-pentyl)-phosphonic acid.

15 Other preferred compounds are those wherein R is a heterocycle selected from:



Especially preferred are C-[1-(1H-tetrazol-5-ylmethyl)cyclohexyl]-methylamine and 4-methyl-2-(1H-tetrazol-5-ylmethyl)-pentylamine.

DETAILED DESCRIPTION OF THE INVENTION

20 The amines of the instant invention are compounds of formulas 1, 1C, 1F, 1G, and 1H and the pharmaceutically acceptable salts thereof.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: A61K 31/35, 31/70	A1	(11) International Publication Number: WO 97/13510 (43) International Publication Date: 17 April 1997 (17.04.97)
(21) International Application Number: PCT/US96/16385 (22) International Filing Date: 11 October 1996 (11.10.96) (30) Priority Date: 08/542,950 13 October 1995 (13.10.95) US (71) Applicant: NEW ENGLAND MEDICAL CENTER HOSPITALS, INC. [US/US]; 750 Washington Street, Boston, MA 02111 (US). (72) Inventors: EHRENBERG, Bruce, L.; 56 Melrose Street #2, Boston, MA 02116 (US). WAGNER, Anita, K.; 67 Newport Street, Arlington, MA 02174 (US). (74) Agent: CLARK, Paul, T.; Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110-2804 (US).		(51) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: TREATMENT OF MIGRAINE (I) (57) Abstract A method for treating migraine in non-epileptic subjects which involves administering to subjects an effective amount of a pharmaceutical composition comprising a sulfamate of formula (I).		

TREATMENT OF MIGRAINEBACKGROUND OF THE INVENTION

5 This invention relates to treatment of migraine syndrome.

Description of Related Art

A working definition of migraine is a benign recurring headache and/or neurologic dysfunction, more common in women than men.

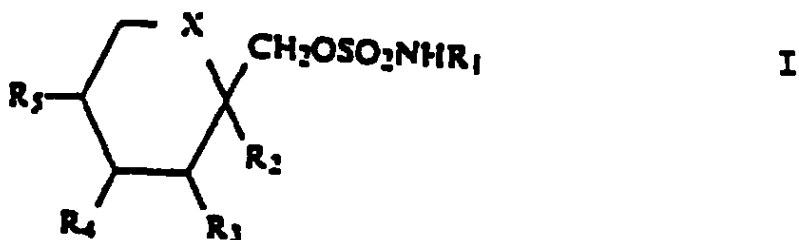
10 Classic migraine (migraine with aura) refers to the syndrome of a severe, throbbing headache which often is preceded by sensory, motor or visual symptoms, referred to as an "aura." Common migraine (migraine without aura) denotes a headache without the aura.
15 Common migraine is the most frequent headache type reported by patients.

Many drugs are now available for prophylactic treatment of migraine. They must be taken daily. The major drugs for prophylaxis are propranolol,
20 amitriptyline, valproate, verapamil, phenelzine, and methysergide. Use of methysergide carries with it the danger of retroperitoneal fibrosis. Aspirin-like drugs, including aspirin, naproxen, ibuprofen, mefenamic acid, flufenamic acid, and tolfenamic acid are in use as
25 prophylactic agents. The high dosage of these compounds required for effectiveness is a drawback. It has been estimated that the probability of success with any one of the available prophylactic antimigraine drugs is about 60 to 75% (*Harrison's Principles of Internal Medicine*, eds.
30 Isselbacher et al., McGraw-Hill, Inc., New York, 1994, p. 69). Accordingly, development or identification of drugs for prophylactic treatment of migraine is an area of continuing medical need.

- 2 -

SUMMARY OF THE INVENTION

The invention features administering sulfamates of the following formula (I):



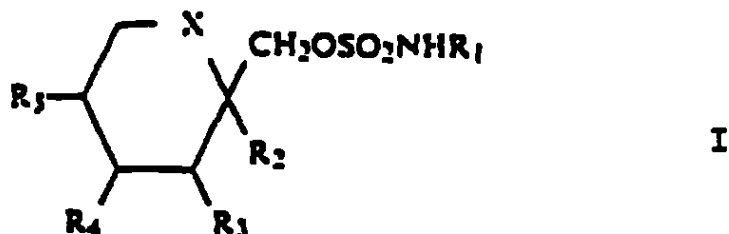
5 wherein X is O or CH₂ and R₁, R₂, R₃, R₄, and R₅ are as hereinafter defined, to prophylactically control migraines in non-epileptic subjects. The most preferred compound is topiramate, described below. Topiramate has been used to treat epileptics, including epileptics who
 10 suffer from migraine, to prevent seizures.

The above discussed and other features and attendant advantages of the present invention will become better understood by reference to the following detailed description of the invention, and from the claims.

15 **DETAILED DESCRIPTION**

By treating migraine patients with the sulfamate compound of formula (I) or a pharmaceutically acceptable salt or derivative thereof, a substantial decrease in frequency of migrainous episodes can be achieved.

20 The administered compound is a sulfamate of the following formula:



**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020

Bogotá, D.C., 14 de julio de 2006

Doctor

JUAN PABLO CADENA SARMIENTO

(Apoderado)

ASUNTO

Radicación 00091771

Trámite 002

Evento 001

Actuación 430

Oficio 7803

Folios 016

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados:

Los textos estudiados fueron la descripción (Folios: 4 a 60) y las reivindicaciones 1 a 20 (Folios: 61 a 65).

La presente solicitud reivindica prioridad europea N° EP99124269.4 de 01 de diciembre de 1999 y cumple con lo establecido en los artículos 9, 10 y 11 de la Decisión 486 de la Comisión de la Comunidad Andina.

Objeto de Invención:

La presente solicitud se titula: "Un derivado de pirrolidinacetamida solo o en combinación para el tratamiento de trastornos del sistema nervioso central (CNS)".

El objeto de la presente solicitud se refiere a el uso de (S)-(-)alfa-etil-2-oxo-1-pirrolidinacetamida para la preparación de fármacos para el tratamiento curativo y/o profiláctico de desórdenes bipolares, migraña, dolor crónico o neuropático y con composiciones farmacéuticas que comprenden (S)-(-)alfa-etil-2-oxo-1-pirrolidinacetamida y por lo menos un compuesto que induce la inhibición neural mediada por receptores GABAa.

Según la descripción, es también conocida la (S)-(-)alfa-etil-2-oxo-1-pirrolidinacetamida (levetiracetam: nombre internacional no patentado). El uso de levetiracetam, como agente protector para el tratamiento y prevención de agresiones de tipo hipóxico e isquémico del sistema nervioso central se describe en la patente europea EP-B-0162036. El compuesto puede emplearse además en el tratamiento de epilepsia, una indicación terapéutica para la cual se ha demostrado que su enantiómero dextrorrotatorio, (R)-(+)-alfa-etil-2-oxo-1-pirrolidinacetamida, es totalmente inactivo. Este último compuesto se ha descrito igualmente en la patente europea EP-B-0645139, para el tratamiento de la ansiedad.

De acuerdo con la presente solicitud, ahora, sorpresivamente se ha descubierto que el levetiracetam posee propiedades terapéuticas que lo hacen particularmente útil en

el tratamiento y profilaxis de trastornos bipolares, manía, migraña y dolor crónico o neuropático. Estas actividades no se observan en el enantiómero dextrorrotatorio, (R)-(+)-alfa-etil-2-oxo-1-pirrolidin-acetamida. De este modo, la presente solicitud concierne al uso del levetiracetam para la preparación de fármacos para el tratamiento de trastornos bipolares, manía, migraña y dolor crónico o neuropático. Igualmente la presente solicitud tiene que ver con un método para tratar migraña, trastornos bipolares, manía y dolor crónico o neuropático, que comprende administrar una dosis terapéutica de levetiracetam a un paciente con necesidad de dicho tratamiento.

Lo que se reivindica como novedoso es lo siguiente: uso de levetiracetam para la manufactura de un medicamento para el tratamiento de trastornos bipolares, manía, migraña y dolor crónico o neuropático.

Una composición farmacéutica para el tratamiento de trastornos bipolares, manía, migraña y dolor crónico o neuropático que incluye una cantidad terapéuticamente efectiva de levetiracetam y un vehículo farmacéuticamente aceptable.

Un método para tratar a un paciente al que se le administra una cantidad de por lo menos un compuesto, que induce inhibición neural mediada por receptores GABA_A, la que, si se administrara sola, no sería terapéuticamente efectiva, que incluye administrarle a dicho mamífero una cantidad terapéuticamente efectiva de levetiracetam para el tratamiento de una enfermedad seleccionada entre epilepsia, abstinencia de alcohol, trastorno bipolar, manía, trastorno compulsivo obsesivo, trastorno pánico, ansiedad y trastorno de ansiedad, depresión, migraña, cefalalgia, trastornos de dolor, isquemia y trauma de la cabeza.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/40, C07D 207/00.

Respecto de los artículos 28 y 30:

El artículo 28 de la Decisión 486 de la Comisión de la Comunidad Andina establece "La descripción deberá divulgar la invención de manera suficientemente clara y completa para su comprensión y para que una persona capacitada en la materia técnica correspondiente pueda ejecutarla."

De acuerdo con lo anterior, el título de la solicitud no es acorde con lo reivindicado.

El artículo 30 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: "Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción."

Las reivindicaciones podrán ser independientes o dependientes. Una reivindicación será independiente cuando defina la materia que se desea proteger sin referencia a otra reivindicación anterior. Una reivindicación será dependiente cuando defina la materia que se desea proteger refiriéndose a una reivindicación anterior. Una reivindicación que se refiera a dos o más reivindicaciones anteriores se considerará una reivindicación dependiente múltiple."

De acuerdo con lo anterior, aparecen términos que no son concisos y conllevan a ambigüedad, como por ejemplo: "por lo menos".

Evaluación de la Unidad de Invención:

El artículo 25 de la Decisión 486 de la Comisión de la Comunidad Andina establece: "La solicitud de patente sólo podrá comprender una invención o un grupo de invenciones relacionadas entre sí, de manera que conformen un único concepto inventivo."

Según lo anterior la (s) reivindicación (es) 3 a 8 y 20 (folios: 61 y 62, 65), que se refiere(n) a una composición farmacéutica que incluye levetiracetam y, por lo menos, un compuesto que induce inhibición neural mediada por los receptores GABA_A, no guarda(n) unidad de invención con la reivindicación 2, que se relacionan con una composición farmacéutica... que incluye una cantidad terapéuticamente efectiva de levetiracetam y un vehículo farmacéuticamente aceptable.

Excepciones de Patentabilidad:

El artículo 20 de la Decisión 486 se establece: "No serán patentables: a) las invenciones cuya explotación comercial en el territorio del País Miembro respectivo deba impedirse necesariamente para proteger el orden público o la moral. A estos efectos la explotación comercial de una invención no se considerará contraria al orden público o a la moral solo debido a la existencia de una disposición legal o administrativa que prohíba o que regule dicha explotación; b) las invenciones cuya explotación comercial en el País Miembro respectivo deba impedirse necesariamente para proteger la salud o la vida de las personas o de los animales, o para preservar los vegetales o el medio ambiente. A estos efectos la explotación comercial de una invención no se considerará contraria a la salud o la vida de las personas, de los animales, o para la preservación de los vegetales o del medio ambiente sólo por razón de existir una disposición legal o administrativa que prohíba o que regule dicha explotación; c) las plantas, los animales y los procedimientos esencialmente biológicos para la producción de plantas o animales que no sean procedimientos no biológicos o microbiológicos; d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales."

De acuerdo con lo anterior, la(s) reivindicación(es): 15 a 19 (Folios: 63 a 65), que se refiere(n) a un método para tratar a una paciente al que se le administra una cantidad de por lo menos un compuesto, que induce inhibición neural mediada por receptores GABA_A, no es (son) patentable(s).

Reivindicaciones de uso:

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece: "Los Países Miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial".

De acuerdo con lo anterior, la(s) reivindicación (es) 1, 9 a 14 (Folios: 61 a 63), que se refiere(n) a uso de levetiracetam para la manufactura de un medicamento para el tratamiento de trastornos bipolares, manía, migraña y dolor crónico o neuropático, no se encuentra(n) dentro del campo de la patentabilidad nombrado en el artículo 14.

Reivindicaciones de segundo uso:

El artículo 21 de la Decisión 486 de la Comisión de la Comunidad Andina establece: "Los productos o procedimientos ya patentados, comprendidos en el estado de la técnica, de conformidad con el artículo 16 de la presente Decisión, no serán objeto de nueva patente, por el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial".

De acuerdo con lo anterior, la(s) reivindicación (es) 1, 9 a 14 (folios: 61 a 63) que se refiere(n) a uso de levetiracetam para la manufactura de un medicamento para el tratamiento de trastornos bipolares, manía, migraña y dolor crónico o neuropático, no cumplen con el artículo 21 de la Decisión, por tratarse de un segundo uso de levetiracetam.

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de

Patente o, en su caso, de la prioridad reconocida.

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40°.

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 01/12/1999, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se hizo la búsqueda de documentos relevantes en el estado de la técnica, entendiendo como estado de la técnica la definición provista en el artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina y las excepciones fijadas en el artículo 17 de la misma.

Se encontró como anterioridades (documentos cuya fecha de publicación es anterior a la fecha de presentación de la primera solicitud de patente sobre la cual se reivindica prioridad o de la fecha de presentación de esta solicitud) que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
1	EP 0162036	(S)-alpha-éthyl-2-oxo-1-pyrrolidineacétamíde	21 de noviembre de 1985
2	WO 99/31075	1-substituted-1-aminomethyl-cycloalkane derivatives (gabapentin analogues), their preparation and their use in the treatment of neurological disorders	24 de junio de 1999
3	WO 97/13510	Treatment of migraine	17 de abril de 1997
4	Artículo 1 ¹	Levetiracetam	1994
5	Artículo 2 ²	New antiepileptic drugs	1996
6	Artículo 3 ³	Behandlung der epilepsien: Wo Stehen wir heute?	1996

Evaluación de los requisitos de Patentabilidad:

El Artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina el cual establece: "Los Países Miembros otorgarán Patentes para las invenciones, sean de producto o de procedimiento en todos los campos de la tecnología siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial".

Se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

1 PROUS. "Levetiracetam". Drugs of the future. Barcelona (España). 1994. 19(2) pp. 111-113

2 WILSON E. A. ET AL. «New antiepileptic drugs ». Baillière's Clinical Neurology. Londres (GB). 1996. 5(4) pp. 723-747

3 WIESSER H G. "Behandlung der epilepsien: Wo Stehen wir heute?". Schweizerische Rundschau für Medizin/Praxis. 1996. 85(4) pp. 74-79

Evaluación de Novedad:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Una invención se considerará nueva cuando no está comprendida en el estado de la técnica". "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".

Esta se evaluó por comparación entre lo solicitado y los documentos encontrados en el estado de la técnica y que se relacionan con el objeto reivindicado y de acuerdo con la definición de novedad del Artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina.

Comparando elemento por elemento el objeto de esta solicitud con lo mencionado en las anterioridades, tenemos que:

La presente Solicitud de Patente Colombiana No. 00091771, se refiere a:

Una composición farmacéutica... que incluye una cantidad terapéuticamente efectiva de levetiracetam y un vehículo farmacéuticamente aceptable.

La anterioridad: EP0162036 (folios: 153 a 155), se relaciona con: 1'alfa-etil-2-oxo-1-pirrolidinacetamida (levetiracetam) empleado en terapia de hiperquinesis, hipertonías, epilepsia.

El artículo 1 (folios: 123 a 125) menciona el levetiracetam que se administra a los pacientes para el tratamiento de la epilepsia.

El artículo 2 (folios: 126 a 138) se relaciona con fármacos antiepilépticos, entre los cuales está el levetiracetam, cuya administración vía oral es rápidamente absorbida con una biodisponibilidad del 100% (ver folio: 135, vuelto).

El artículo 3 (folios: 139 a 144) menciona el medicamento de levetiracetam para el tratamiento de la epilepsia (ver folio: 140).

Estos documentos revelan el compuesto levetiracetam administrado para el tratamiento de la epilepsia; por un lado, si es administrado es porque obviamente dicho fármaco está en una forma de administración, es decir, está con un vehículo, de otro lado, aun cuando se emplea para otro tipo de enfermedad, de todas maneras la molécula y preparaciones de levetiracetam ya se encontraban en el estado de la técnica.

Como se observa, el objeto de esta solicitud puede ser idéntico a lo comprendido en el estado de la técnica, con lo cual se considera que podría no cumplir con el requisito de Novedad.

Evaluación de Nivel Inventivo:

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica".

El Nivel Inventivo se evaluó por comparación entre lo solicitado y encontrado en el estado de la técnica y que se relaciona con el objeto reivindicado y de acuerdo con la definición de nivel inventivo del Artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina.

La anterioridad: WO 99/31075 (folios: 156 a 158), trata sobre: derivados de 1-sustituido-1-aminometil-cicloalcano (análogos de gabapentina); dichos compuestos son empleados para el tratamiento de la epilepsia, hipoquinesia, desórdenes craneales, desórdenes neurodegenerativos, depresión, ansiedad, dolor, enfermedades inflamatorias, etc. También menciona composiciones de estos compuestos.

La anterioridad WO 97/13510 (folios: 159 a 161) menciona compuestos de sulfamato empleados para el tratamiento de la migraña y composiciones de los mismos.

El documento EP 0162036 menciona el levetiracetam que tiene actividad sobre el sistema nervioso central.

Como puede observarse en las anterioridades WO 99/31075 y WO 97/13510, los compuestos que se citan allí son semejantes al levetiracetam que se menciona en EP 0162036, por lo cual puede decirse que el documento WO 99/31075 junto con EP 0162036 ó WO 97/13510 junto con EP 0162036, le sugieren a una persona medianamente versada en la materia una composición farmacéutica de levetiracetam.

La respuesta al problema técnico que se pretendía resolver, resulta obvia partiendo de dichas anterioridades.

Como se observa, el objeto de esta solicitud podría resultar obvio para una persona del oficio normalmente versada en la materia y derivarse de manera evidente del estado de la técnica.

Evaluación de la Aplicación Industrial:

El artículo 19 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Se considerará que una invención es susceptible de aplicación industrial, cuando su objeto pueda ser producido o utilizado en cualquier tipo de industria, entendiéndose por industria la referida a cualquier actividad productiva, incluidos los servicios".

El objeto de la presente solicitud cumple con el requisito de Aplicación Industrial.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	EP 0162036	2 a 8, 20	Novedad y Nivel Inventivo
2	WO 99/31075	2 a 8, 20	Nivel Inventivo
3	WO 97/13510	2 a 8, 20	Nivel Inventivo
4	Artículo 1 ^º	2 a 8, 20	Novedad
5	Artículo 2 ^º	2 a 8, 20	Novedad
6	Artículo 3 ^º	2 a 8, 20	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
 Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 29 JUL 2006

CONCEPTO TÉCNICO Nº: 1120	EXAMINADOR TÉCNICO Código N°: 202005	EXAMINADOR JURÍDICO Código N°:
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