Gabapentin

J. Bruni

ABSTRACT: Gabapentin is a novel antiepileptic drug that has recently been introduced in Canada. Although its mechanism of action remains to be defined gabapentin is effective in a number of seizure models which predict its efficacy in partial and tonic-clonic seizures. Clinical studies support the clinical efficacy of gabapentin as adjunctive therapy in adults with epilepsy with partial and secondarily generalized tonic-clonic seizures. Gabapentin has a favorable pharmacokinetic profile and is generally well tolerated. More clinical data are required on the role of gabapentin in children and additional monotherapy experience is required before the role of gabapentin in the overall treatment of epilepsy can be better defined.

RÉSUMÉ: Le gabapentin. Le gabapentin est un nouvel agent antiépileptique qui a été introduit au Canada récemment. Bien que son mécanisme d'action ne soit pas encore défini, le gabapentin est efficace dans plusieurs modèles d'épilepsie, ce qui est en faveur d'une efficacité dans les crises partielles et les crises tonico-cloniques. Les études cliniques supportent l'efficacité clinique du gabapentin comme traitement d'appoint chez les adultes épileptiques qui ont des crises partielles et des crises tonico-cloniques avec généralisation secondaire. Le gabapentin a un profil pharmacocinétique favorable et il est généralement bien toléré. Il faudra recueillir plus de données cliniques sur le rôle du gabapentin chez les enfants et plus d'expérience en monothérapie pour mieux définir le rôle du gabapentin dans le traitement de l'épilepsie en général.

Chemical Properties

Gabapentin (1-[aminomethyl]-cyclohexaneacetic acid) is a new antiepileptic drug related in structure to GABA (Figure). It is fully water soluble, has a molecular weight of 171.34, and a pKa_1 of 3.68 and a pKa_2 of 10.70 at 25°C. Gabapentin freely crosses biologic membranes and can be detected by both gas chromatography and high performance liquid chromatography.[1,2]

Mechanisms of Action

Although gabapentin was developed as a GABA-mimetic compound subsequent studies have shown that it does not have a major effect on GABA receptors or other GABA mechanisms.

In animal models gabapentin is effective against chemically-induced seizures, maximal electroshock seizures and kindled seizures.[3] The spectrum of activity in animal models predicts its efficacy against partial and generalized tonic-clonic seizures.

Figure: Structure of gabapentin.

The time course of peak anticonvulsant activity in the maximal electroshock model indicates that maximal efficacy is observed when plasma and interstitial fluid concentrations are declining. This implies that gabapentin is causing some secondary biochemical change(s) that may be responsible for its anticonvulsant action.[4]

In vitro studies indicate a number of actions of gabapentin.[3] These include an increase in the rate of GABA synthesis in certain brain regions, a decrease in the release of monoamine neurotransmitters, inhibition of branched chain amino acid amino transferase and interaction with the L transport system. At present it is unclear as to its most important site of action and perhaps a novel receptor site will be identified. It is also uncertain as to whether the primary site of action is at the L system transporter itself, or whether there is some interaction at the intracellular level.

Pharmacokinetics

The absorption of gabapentin is dose dependent and saturable. It is transported by the L-amino acid transport system and food does not influence its absorption. After a 300 mg dose oral dose bioavailability is approximately 60 percent.[5] This decreases to approximately 35 percent with a dosage of 1600 mg three times daily.[6] Maximum plasma concentrations are reached in 2 to 3 hours.

From the Division of Neurology, The Wellesley Hospital, and the University of Toronto, Toronto
Reprint requests to: Dr. J. Bruni, Division of Neurology, The Wellesley Hospital, 160 Wellesley Street East, Toronto, Ontario, Canada M4Y 1J3
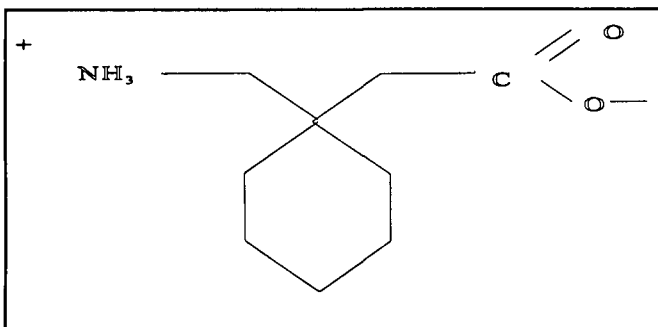
Gabapentin does not significantly bind to plasma proteins and protein binding interactions have not been reported. Gabapentin has a volume of distribution of approximately 58 litres.[6] The therapeutic range of serum concentration of gabapentin has not been established.

Gabapentin readily crosses the blood brain barrier and is carried across biologic membranes by an L-system amino acid transporter.

Gabapentin is eliminated unchanged in the urine and is not metabolized. It does not influence hepatic microsomal enzymes and its renal elimination is related to the glomerular filtration rate and creatinine clearance.[6,7] Gabapentin is removed by hemodialysis and dose adjustment is required in patients with impaired renal function. The plasma half life is 5 to 8 hours and generally gabapentin is administered as a TID dose.

Pharmacokinetic drug interactions with other antiepileptic drugs do not occur and this lack of interactions is a favorable feature in the use of gabapentin as adjunctive therapy. No significant interactions have been reported with other drugs but a small decrease (20 per cent) in the absorption of gabapentin may occur if administered with aluminum hydroxide and magnesium hydroxide antacid.[8] Gabapentin does not enhance the metabolism of oral contraceptives and thus does not increase the risk of oral contraceptive failure.

The Table summarizes the significant pharmacologic properties of gabapentin.

Efficacy

Since gabapentin was marketed over 120,000 patients have been exposed to the drug. Clinical trial data have been largely obtained from clinical trials using gabapentin as adjunctive therapy in medically refractory patients. It has demonstrated efficacy against partial seizures and secondarily generalized tonic-clonic seizures. It is ineffective against absence or myoclonic seizures. Monotherapy trials are currently ongoing and preliminary data indicate that some patients can achieve monotherapy.

The U.S. Gabapentin Study Group[9] assessed gabapentin in 306 patients. The gabapentin-treated patients 600 mg, 1200 mg, or 1800 mg daily doses) had a significantly greater reduction in seizure frequency as compared to placebo. Eight percent of placebo-treated patients versus 18 to 26 percent of gabapentin-treated patients had at least a 50 percent reduction in seizure frequency.

The International Gabapentin Study Group[10,11] reported a 21.8 percent decrease in seizure frequency in the 900 mg/day group, a 17.8 percent decrease in the 1200 mg/day group and a 0.3 percent decrease in the placebo group. The responder rate (percent of patients with ≥ 50% reduction) was 22.9 per cent in the 900 mg/day group and 10.1 per cent in the placebo group.

The U.K. Gabapentin Study Group reported a responder rate of 25 percent for patients receiving gabapentin compared with 9.8 percent for patients who received placebo.[12] The median percentage decrease in seizure frequency was 12.5 percent for placebo-treated patients versus a 29.2 percent decrease in patients treated with gabapentin 1200 mg/day.

The long term use of gabapentin has been reported in a number of open label trials.[13-18] These studies demonstrate that long-term control can be maintained and gabapentin has a good safety profile. In my own clinical experience doses up to 3200 - 4200 mg/day have been used with greater efficacy.

Few data are available in gabapentin monotherapy in the treatment of partial seizures but early data indicate that monotherapy can be achieved in some patients previously refractory to standard antiepileptic drug therapy.[19,20]

The role of gabapentin in the treatment of epilepsy in children needs to be further explored. Clinical trials are currently on-going in pediatric patients with partial seizure disorders including special syndromes such as benign rolandic seizures.

Adverse Effects

In virtually all clinical studies, gabapentin has been well tolerated and serious toxicity and allergic reactions are exceedingly rare.[9-18,21] In controlled clinical trials, dose ranges of 600 mg to 1800 mg/day have been assessed. In open trials doses up to 3600 mg/day have been used. The most frequently observed side effects included drowsiness, dizziness, fatique, and ataxia. In a review of the adverse effects reported in controlled clinical trials Ramsay[22] summarized the data. Somnolence was observed in 20 percent of gabapentin treated patients versus a 9 percent incidence in the placebo group; dizziness occurred in 18 percent versus 7 percent; ataxia was observed in 13 percent versus 6 percent; fatique was observed in 11 percent versus 5 percent. Overall, approximately 7 percent of patients treated with gabapentin withdrew compared to approximately 3 percent of placebo-treated patients. The most common reason for adverse-related discontinuation of therapy was the development of central nervous system side effects. These included drowsiness, dizziness, ataxia and fatigue. The incidence of rash has been reported as 0.54 per cent.

An overdose of 48.9 grams of gabapentin has been reported.[23] The patient developed lethargy and dizziness and fully recovered.

Gabapentin does not appear to have a negative effect on cognitive function.[24]

The teratogenic effects of gabapentin are not fully known. In rodents delayed skeletal ossification has been observed. Gabapentin is not mutagenic in vitro.[25] Ten pregnancies have been reported in women taking gabapentin. Six were electively terminated and four pregnancies resulted in normal births.

Gabapentin is a well tolerated and effective new antiepileptic drug in the treatment of partial and secondarily generalized tonic-clonic seizures. Its role in childhood epilepsies remains to be defined. It is well tolerated and has favorable pharmacokinetic parameters. No significant drug interactions occur. Gabapentin lacks adverse cognitive effects. From preliminary and on-going clinical studies some patients are able to achieve monotherapy.

Table: Gabapentin Pharmacokinetics.	
Bioavailability	60% (dose dependent)
Tmax	2-3 hours
Volume of Distribution	58L
Plasma Half-LIfe	5-8 hours
Protein Binding	0
Metabolism	0
Hepatic enzyme induction, inhibition	0
Elimination	Renal, 100% excreted unchanged
Drug Interactions	0 (Minor with antacids)
Serum Levels	Not related to efficacy

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