Antiepileptic Drugs – Current Use

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ABSTRACT: In the last few years a number of new antiepileptic drugs ahve been introduced for the treatment of epilepsy. In addition to the standard antiepileptic drugs, clobazam, vigabatrin, gabapentin, and lamotrigine have been introduced. The choice of the best antiepileptic drug for an individual patient has become more complex. In this review the clinical benefits of the standard and the new antiepileptic drugs are presented.

RÉSUMÉ: Les antiépileptiques - utilisation actuelle. Au cours des dernières années, plusieurs nouveaux antiépileptiques ont été introduits sur le marché. En plus des antiépileptiques standards, le clobazam, le vigabatrin, le gabapentin et la lamotrigine sont maintenant disponibles. Le choix de la meilleure médication antiépileptique pour un patient donné est devenu plus complexe. Nous présentons une revue des bénéfices cliniques de la médication standard et des nouveaux antiépileptiques.

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The number of major drugs useful for the treatment of epilepsy has doubled during the last 3 years. In addition to carbamazepine (CBZ), phenytoin (PHT), phenobarbital (PB) and valproate (VPA) (traditional drugs), we now have felbamate (FB), gabapentin (GP), lamotrigine (LT), vigabatrin (VG), and clobazam (CB) available in North America (VG and CB not available in the United States). In addition there are drugs presently marketed in other countries which will probably become available in the next few years (oxcarbazepine and zonisamide). Other drugs are into clinical testing (tiagabine, topiramate, LO-50; losigamone, ramacemide). The new drug application for fosphenytoin has been filed with the Federal Drug Administration in the United States. The choosing of the best drug for an individual patient will become more complex. Decisions will be made with consideration being given to efficacy, cost, adverse effects and pharmacokinetics. These will differ for individual patients.

In general the new drugs have been tested more rigorously against placebo than the traditional drugs (phenytoin, phenobarbital, carbamazepine, valproate) for partial and secondarily generalized seizure disorders. Other seizure types and epilepsy syndromes, with the exception of absence and Lennox-Gastaut, have not been so critically evaluated. Controlled clinical studies of efficacy in the partial epilepsies show small differences in efficacy. However, many of these drugs have different profiles in animal epilepsy models suggesting markedly different mechanisms of action, and differences in efficacy for other seizure types and syndromes are apparent. For example, VPA, FB and possibly LT are effective in Juvenile Myoclonic Epilepsy, juvenile myoclonus and typical absence. Some of the new drugs and VPA show efficacy in Lennox-Gastaut and West Syndromes. Phenytoin, CBZ, PB, and GP show little or no activity in the above syndromes. An accurate diagnosis of the patient's seizure type and epilepsy syndrome is very important in the correct choice of drugs.

Although the new drugs have had careful evaluations for safety in a limited number of persons, these evaluations have not been designed to detect rare (<1 in 2,000) adverse events. The traditional drugs have the advantage of years of experience. However, with the exception of felbamate, the new AED's appear to have a very favorable safety profile.

Major differences in cost exist between the new drugs and the traditional drugs. However, one needs to consider that the costs of a trip to the emergency room, lost days from work, feeling constantly sedated, and being less productive are probably more on an annual basis than the extra cost of an effective expensive drug. Only the treating physician is in the position to make this decision. But the treating physician must have a valid rational plan to justify use of expensive drugs.

Other differences between traditional and new drugs exist. There are major differences in the pharmacokinetics. Adverse effect and safety profiles are different. Initiation of therapy and use profiles for some require slow and careful initiation of treatment. Others can be loaded. Some can be administered in single daily doses and others require multiple daily doses. These differences are discussed in relationship to each drug.

In April, 1995 the traditional drugs accounted for over 90% of the antiepileptic drug (AED) market in the United States and Canada; phenytoin (PHT) 35%, carbamazepine (CBZ) 27%, phenobarbital (PB) 17% and valproate (VPA) 14%. All other drugs including the new drugs held only 7% of the AED market1. Significant changes in the use are occurring. The use of Gabapentin is expanding rapidly. Felbamate usage was rapidly expanding until reports of aplastic anemia and hepatic failure became prevalent in the summer of 1994. Lamotrigine, even with some disadvantages associated with initiation of therapy, is gaining an increasing share of the market. This new drug shows

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promise in some of the difficult to manage childhood epilepsies even though it is only approved in the United States for use as add-on therapy for partial seizures in adolescents and adults. Certainly, drug use patterns are changing and will continue to do so as physicians become more knowledgeable of the new drugs and as data from on-going clinical research is reported.

The following is a review of 3 of the traditional drugs (PHT, CBZ, VPA) and the newer drugs which are in current use (GP, FB, LT, VG, and CB) in Canada and the U.S. This survey will hopefully be helpful to the practicing physician and others who may have an interest in epilepsy and antiepileptic drugs.

Carbamazepine (Tegretol)

Carbamazepine was one of a group of carbamoyl compounds synthesized in the 1950s at J.R. Geigy Limited. This tricyclic compound proved very potent in animal experimental models. In addition to particular efficacy against maximal electroshock in animal models, single cell recordings have demonstrated CBZ, like PHT, acts to block sustained repetitive firing through action at the sodium channel.[2]

Carbamazepine has been extensively used for the past twenty-five years and is highly efficacious for treatment of partial and secondarily generalized tonic-clonic seizures in both adults and in children. Only PHT is comparably effective for both of these seizure types. Carbamazepine is also effective in treatment of generalized tonic-clonic seizures associated with primary or idiopathic epilepsy, as well as benign partial epilepsy, but is ineffective and occasionally exacerbates absence and myoclonic seizures. It also is the drug of choice for treatment of trigeminal neuralgia and is extensively used in the treatment of depression and aggressive psychoses.[3]

With long-term use, adverse effects are minimal, although during start-up and in early months, complaints of sedation, dizziness, and gastrointestinal upset can occur. The most common important adverse effect is the occurrence of hypersensitivity reaction with rash and occasionally systemic symptoms occurring in approximately 10% of patients.[4] Excessive dosage commonly produces dizziness, visual blurring or diplopia, and incoordination, as well as sedation. Chronic adverse effects are infrequent, but include weight gain, hyponatremia, and rare cardiac conduction problems. Some teratogenicity including mid line neural tube defects has been seen in animal models and in clinical use. Aplastic anemia, pancytopenia and pancreatitis have been reported.

Carbamazepine is available only for oral administration due to its very low solubility. Use of this AED at times is difficult due to complex pharmacokinetics. The drug is metabolized by the cytochrome P450 hepatic enzyme system to form an active metabolite, carbamazepine 10-11 epoxide which in turn is metabolized to the inactive diol by epoxide hydrolase. Carbamazepine induces its own metabolism, as well as that of other drugs and at times causes mild inhibition of PHT. The metabolism of CBZ may be markedly inhibited by concurrent use with propoxyphene and erythromycin and other non-AEDs. These complex drug interactions can make administration of the drug difficult at times especially when used with other drugs. Although carbamazepine is somewhat burdened with complex or unfavorable pharmaceutical and pharmacokinetic properties and occasional important adverse effects, it is nonetheless one of the most potent and effective antiepileptic drugs for the treatment of partial and generalized tonic-clonic seizures, and in most cases, is well tolerated. It remains one of the drugs of choice for treatment of partial epilepsy. Ten to 15 mg/kg/D is the usual dose on monotherapy. In Canada and Europe a sustained release preparation is available, however in the United States only a quick release preparation is available requiring three divided doses. Fifteen to 20 mg/kg/D is often required when CBZ is used with PHT or PB. Valproate and FB inhibit the metabolism of the epoxide metabolite and toxicity may occur.[5,6]

Valproate (Depakote, Epival, Depakene)

Valproic acid is a carboxylic acid that was synthesized in the 1800s and for 70 years primarily was used as a solvent. The serendipitous discovery of antiepileptic properties in the 1960s led to clinical trials and recognition that this was an effective, well tolerated antiepileptic compound. The mechanism of action has been less well defined than for some of the other antiepileptic drugs (AEDs), but it appears to have some ability to limit sustained repetitive firing similar to carbamazepine and phenytoin. It also has some effect in limiting metabolism of GABA resulting in an increase in concentration available at the receptor site. Valproate probably has some effect on calcium channel activity, and reduces gamma hydroxybutrate release similar to ethosuximide, thus accounting for its efficacy in absence seizures.[7]

The efficacy of VPA was first well established in control of absence and myoclonic seizures. Over the last two decades, VPA has been used in all seizure and epilepsy types and has proven to be a broad spectrum AED. It is as effective as ethosuximide for absence seizures and is the drug of choice in the treatment of myoclonic seizures. For idiopathic epilepsy with only tonic-clonic seizures, valproate is equally effective as other AEDs. Valproate is the drug of choice in the primary epilepsies. Although clinical trials are somewhat at variance, VPA appears to be comparable in efficacy to other antiepileptic drugs for treatment of secondarily generalized tonic-clonic seizures.[8] Some studies indicate it is not as effective as CBZ or PHT for simple and complex partial seizures.[9] Valproate is the drug of choice in the mixed seizures associated with mental retardation and after ACTH in infantile spasms. Valproate may also be used in treatment of migraine and bipolar affective disorders.

Valproate is generally well tolerated in long term use and has a favorable adverse effects profile. However, early adverse effects may occur. Hair loss can be alarming during the first few months of therapy. This can be ameliorated by administration of B complex vitamins and trace metals, especially zinc and selenium.[10] A well known dose related side effect is a familial like tremor. Other early side effects include gastrointestinal symptoms, but these are minimized by gradual dose increase and use of formulations that dissolve in the intestine. Idiosyncratic side effects include liver failure, primarily occurring in young children when co-administered with an enzyme inducing drug. Thrombocytopenia may also occur and be slowly progressive requiring discontinuation of the drug. Idiosyncratic hypersensitivity reaction with skin or multisystem involvement is rare. Rarely pancreatitis may occur even after long periods of therapy. Neurotoxic symptoms from high doses include not only sedation but sometimes encephalopathy. The most common long-term adverse effect is weight gain which occurs in a third to a half of patients. Valproate has been reported to be associated with a ten-fold increase in spina bifida in mothers receiving the drug during the first trimester of pregnancy.[11] Supplemental folate 0.8 to 1.2 mgm/D reduces this possibility.

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Valproate in the sodium salt form is highly water soluble and a parenteral formulation will soon be available. The pharmacokinetics of valproate are complex. The drug is rapidly and well absorbed, although the rate varies with the formulation. The drug is cleared by the liver through oxidation in the cytochrome P 450 enzyme system, as well as in the mitochondria where it is metabolized as a fat by beta oxidation. The microsomal clearance is inducible especially by PHT, the barbiturates, and CBZ, leading to shorter half life of VPA and requiring much higher doses to achieve blood levels compared to use as monotherapy. Valproate also inhibits the clearance of PB, CBZ epoxide, and to some degree PHT and ethosuximide. Valproate is highly protein bound (level dependent - less at higher levels) and may displace drugs such as PHT or CBZ, or be displaced by other drugs such as aspirin.[12]

Valproate is an effective broad spectrum antiepileptic drug that can be used for virtually all seizure types, but is specifically the drug of choice for idiopathic or primary epilepsy. Adverse effects may be serious but are rare. Its complex pharmacokinetics make it most suitable for use as monotherapy. Its nonenzyme inducing properties make it useful when an antiepileptic drug needs to be given with other medications such as oral contraceptives or immunosuppressants. The relative absence of cognitive and affective adverse effects also makes this drug potentially useful in the elderly.[13,14]

Gabapentin (Neurontin)

Gabapentin (GP) is a new antiepileptic drug that was synthesized an a GABA analog, and contains a cyclohexyl ring. Although initially expected to act as a GABA agonist, studies do not indicate interaction with GABA A or GABA B receptors, nor does it alter the reuptake of GABA, or the degradation by GABA transaminase. Evidence suggests increased GABA turnover and enhanced GABA release. In vitro GP interacts with branched chain amino acid transferase, glutamic acid decarboxylase, glutamine dehydrogenase and GABA transaminase but not with glutaminase or glutamine synthetase. It has been speculated that brain glutamic acid concentration may be reduced. Total brain GABA concentration is increased. Specific receptor binding is found in areas of the cerebral cortex.[15] Animal studies indicate effectiveness in the MES and pentylenetetrazol models, but not in the genetic absence seizure model of epilepsy.

Clinical trials have been of add-on design and reveal statistically significant improvement in seizure control of partial and secondarily generalized tonic-clonic seizures compared to placebo. Significant seizure reduction is found from 900 mg to doses of 1800 mg a day with an increased efficacy found at the higher doses. Clinical trials using doses up to 3600 mg have been used with evidence of increasing efficacy at higher doses. The maximal tolerated and effective dose has not been clearly defined.[16] Overdosage has not been reported to cause serious problems. The role of GP as monotherapy and use in the generalized epilepsies and seizure types is under study. Gabapentin has been recommended from a number of anecdotal reports and uncontrolled clinical trials for use as a monotherapeutic agent in elderly patients with epilepsy.[17] Gabapentin has been shown to not be involved in pharmacokinetic drug interactions and for this reason is particularly attractive in the elderly who often receive multiple medications for other indications. As with other AEDs uses other than the treatment of epileptic seizures have been reported. The use of GP in chronic pain states has received considerable attention. Good results of pain amelioration have been found in reflex sympathetic dystrophy, painful neuropathies, facial pain, syndromes and radiculopathies. Psychiatric use for mood elevation has received attention.

Adverse effects with use of gabapentin have been minimal. The use of GP has been associated with complaints of somnolence, dizziness, ataxia, and fatigue. These adverse effects are usually transient. Serious systemic idiosyncratic reactions involving allergic reactions, liver or other systemic dysfunction including the hematopoietic system have not been established. At the present time approximately 250,000 patients have chronically used the drug. In animal studies, gabapentin is not teratogenic, but insufficient information is available concerning the effect in human pregnancies.[18]

Gabapentin is available only in tablet form. The pharmacokinetics are distinctly different from other antiepileptic drugs. Gabapentin has saturable absorption due to an active L-amino acid transport mechanism; a decreasing percent of drug is absorbed as the dose is increased. Gabapentin is not metabolized by the liver. The drug is non-protein bound and widely distributed (VD1) throughout the body. Elimination is entirely renal. As a consequence, gabapentin is free of pharmacokinetic interactions with other drugs. Its elimination is affected only by changes in renal function. In cases of renal dysfunction, dosage can be calculated on the basis of creatinine clearance.[19] Patients on renal dialysis should be given 300 or 400 mgs after each dialysis. The drug half life is 5 to 7 hours. Three times a day dosing is recommended because of the saturable absorption and the short half-life.

Gabapentin is a new antiepileptic drug with a structure similar to GABA, but whose mechanism remains incompletely understood. It has documented efficacy in add on design studies for the treatment of partial and secondarily generalized tonic-clonic seizures, but its effectiveness as monotherapy, as well as its use in other seizure types remains to be defined. Gabapentin is an especially attractive new drug due to a low adverse effect profile and absence of drug interactions. This promises to make it a particularly useful drug for some populations of patients such as the elderly in whom polypharmacy is common, or in women taking birth control pills.[20]

Phenytoin (Dilantin)

Phenytoin (PHT) (Dilantin) was first used in the treatment of epilepsy in 1937. It is highly efficacious in the treatment of tonic clonic and partial seizures. It is not effective in absence, myoclonus, clonic or akinetic seizures. In North America it is the most commonly used antiepileptic drug (AED) accounting for 35% of the anticonvulsant market in 1995.

Phenytoin like CBZ blocks post tetanic potention and prevents the spread of seizure discharge. Many mechanisms of action have been attributed to PHT, the most important being a use dependent block of sodium (Na+) channels. PHT delays the recovery phase of the Na+ channel after depolarization thus preventing rapid neuronal firing which initiates the spread of epileptic seizure discharge from the epileptic focus.[21,22]

Phenytoin is slowly absorbed from the gastrointestinal tract and one time per day dosing can be recommended in adults. Oral loading with 10-15 mg/kg can be done without significant adverse effects (AEs).[23]

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The metabolism of PHT is rate limited and saturation kinetics occur resulting in a disproportionate increase in plasma levels as the dose is increased. Increasing the daily dose must be done with care in order to avoid large increases in plasma levels and toxicity. The T/2 of PHT ranges from 14 to 40 hrs. Phenytoin is metabolized by arene oxidase (one of the P450 mixed oxidase hepatic microsomal enzymes) to an epoxide which is immediately converted to inactive hydroxylated phenytoin and a hydrodiol. Patients with enzyme metabolizing defects are sensitive to PHT and serious adverse effects occur.[24,25] PHT is an enzyme inducer which increases the metabolism of many of the AEDs and other drugs metabolized by the microsomal P450 system. Drug interactions occur commonly when PHT is used in combination with other drugs.

Dose related adverse effects of ataxia, incoordination, cognitive impairment occur at toxic levels (usually over 30 μg/ml). Non-dose related adverse effects consist of gingival hyperplasia, occurring in 10% of patients, can usually be controlled with good oral hygiene. Hirsutism rarely occurs. Acute skin allergic reactions may occasionally occur. Systemic reactions, Stevens Johnson Syndrome, hepatic failure, lymphadenopathy, and blood dyscrasias occur with extreme rarity. Transient hypersensitivity with skin rash occurs in 5% of patients.

Birth defects have been reported with PHT therapy. Reports of mental retardation are unsubstantiated in control studies.[26,27,28] Neonatal coagulation defects can be prevented by the administration of Vitamin K to the mother prior to delivery and to the infant at delivery.

Phenytoin has been used prophylactically to prevent seizures after head trauma, stroke and supratentorial neurosurgery. No data exist to suggest efficacy in these situations except in the prevention of early seizures after substantial head injury.

Parenteral PHT is a drug of choice in the treatment of status epilepticus. It should be diluted in normal or 1/2 N saline and administered carefully in a large vein to avoid serious tissue reactions. Parenteral PHT is dissolved in a 50% propyleneglycol alcohol solution and adjusted to a pH of 12 with NaOH.[21] (Fosphenytoin is a prodrug for parenteral phenytoin. It was released for use in the United States in August of 1996. It is non tissue toxic and can be given by intramuscular or intravenous administration. It is rapidly converted to phenytoin by blood phosphatases and can be administered at a rate three times faster than parenteral phenytoin (150 mgs of phenytoin equivalent per minute) Wilder, BJ. The use of parenteral antiepileptic drugs and the role for fosphenytoin. Neurol 1996; 46; S1, 1-28.)

PHT is effective in partial and generalized tonic clonic seizures; however it is not effective in some of the childhood syndromes, West Syndrome, Lennox Gastaut, typical and juvenile absence and myoclonus. It is effective in primary generalized tonic clonic seizures but not in the other components of juvenile myoclonic epilepsy.

Felbamate (Felbatol)

Felbamate (FB) induces aplastic anemia and liver failure in a significant number of patients and should only be used with extreme caution in patients whose potential benefit may outweigh potential risk.[29]

Structurally related to meprobamate, this AED is not similar to other anticonvulsants. Unlike meprobamate, it is not sedating and may be mildly stimulating. In animal models it blocks maximal electroshock (MES) and chemically induced seizures. This activity predicts action against partial, generalized tonic clonic and other seizure types such as absence and myoclonus. It has been reported to be efficacious in Lennox Gastaut Syndrome. Felbamate also may block the glycine receptor in the NMDA receptor complex and have neuroprotective effects.[30]

Felbamate has been tested in double-blind, placebo-controlled monotherapy and add-on trials in refractory patients with simple and complex partial seizures with or without generalized tonic clonic seizures. In these trials, felbamate demonstrated statistically significant efficacy; however adverse effects frequently occurred.[31]

Felbamate shows promise in the management of some of the medically refractory syndromes. In a controlled clinical trial of patients with Lennox-Gastaut Syndrome, felbamate reduced the number of seizures and improved the ease of management rendered by parents and care givers.[32]

Felbamate is administered in a tablet formulation. Maximum serum concentrations are achieved after 2 - 4 hours. Protein binding is slight at 25 - 35 %. The volume of distribution is 0.8 L/kg. The half-life ranges from 18 to 24 hours in adults on monotherapy. The maximum daily dose of 3600 mg should be given in three or four divided doses because of gastrointestinal adverse effects associated with single large doses. Fifty percent of felbamate is metabolized to inactive metabolites and 50% is excreted unchanged in the urine.

Felbamate is an inhibitor of hepatic metabolism. Significant drug interactions occur when felbamate is coadministered with other AEDs. For instance, felbamate decreases carbamazepine plasma levels and increases carbamazepine epoxide levels. Felbamate increases the levels of phenytoin and valproic acid. Phenytoin, carbamazepine and phenobarbital decrease felbamate levels, and valproic acid increases felbamate levels. When felbamate is used as add-on therapy, levels of concomitantly administered AEDs should be carefully monitored.

Adverse effects have been reported by a number of investigators. Nausea, headache, anorexia, somnolence, insomnia, constipation, taste perversion, vomiting, dizziness, abdominal pain diarrhea and fatigue were reported by Sachdeo et al in 1992.[33] Tolerance developed to many of the above adverse effects; however, anorexia did not abate. Insomnia, taste perversion and fatigue continued in many of the patients reporting these adverse effects. In the author's experience abdominal distress, insomnia, and anorexia occurred chronically and weight loss persisted. Reported cases of aplastic anemia and hepatic failure occurred at a rate of approximately 1 in 2,000; however the rate may be much higher because of under reporting.

Lamotrigine (Lamictal)

Lamotrigine (LT) is a new AED chemically unrelated to drugs in current use. LT is a mild folate inhibitor. It shows anticonvulsant activity in maximal electroshock seizures and chemically induced seizures. It blocks sound-induced seizures in epilepsy-prone rats. It also blocks photically induced after discharge in experimental animals. In-vitro studies show that LT blocks the synaptic release of glutamate. It also blocks kainate neurotoxicity in vivo and is neuroprotective in a focal model of ischemia. Like PHT and CBZ it blocks repetitive firing of isolated neurons induced by a depolarizing current. This action is consistent with a use dependent block of voltage gated Na+ channels.[34]

Pharmacokinetic studies in humans show near complete absorption, with peak levels being achieved within 1-4 hours after dosing. Lamotrigine is approximately 50% bound to plasma proteins and is metabolized to an inactive glucoronamide. Lamotrigine has an elimination half-life of 24 hours in non-induced patients and 12 hours in patients on phenobarbital,

carbamazepine or phenytoin. Valproic acid inhibits lamotrigine metabolism and increased lamotrigine's elimination half-life to 50-60 hours in patients receiving both drugs. LT does not change the metabolism of other AEDs.[35] Lamotrigine is dosed 2 times daily.

Lamotrigine is effective in reducing and controlling seizures in a broad spectrum of seizure types. In double blinded placebo controlled add-on studies in refractory epileptic patients, LT reduces seizure frequency in partial and tonic clonic seizures.[36] Lamotrigine has been reported to be effective in a number of childhood seizure types which include typical and atypical absence, myoclonus and tonic clonic seizures. Preliminary reports of efficacy in Lennox-Gastaut and West Syndromes are encouraging.[37,38] Controlled clinical trials have shown a favorable side effect profile and monotherapy studies in newly diagnosed epilepsy comparing LT with CBZ and PHT showed a significant lowered incidence of side effects with LT. Also LT was associated with an increased quality of life measures with respect to placebo in a randomized controlled trial. Cognitive and behavioral improvement were independent of seizure control.[39]

Lamotrigine may become a favorable drug for elderly seizure patients. Lamotrigine received attention from psychiatrists in the treatment of the depressive phase of bipolar disorders.

It does not induce interactions in other drugs and has a low CNS adverse effect profile. Although LT produces a low incidence of central nervous system adverse effects, it has been shown to enhance adverse effects associated with concomitantly administered antiepileptic drugs. Lamotrigine also causes a high incidence of hypersensitivity skin rashes. These are significantly increased if the drug is not initiated at low doses and titrated upward slowly.[36] Stevens Johnson Syndrome has been reported. Fifty mg every other day is recommended as the initial dose if a patient is receiving PHT, PB or CBZ. This is followed by dose escalation to 500 to 700 mg/D over a period of 8 to 10 weeks in adults. If a patient is receiving VPA the dose of LT should begin at 25 mg every other day and escalated slowly over 8 to 10 weeks to 200 to 300 mg/D. The incidence of skin rash following initiation of treatment with LT is much higher in patients who are already receiving VPA. The occurrence of skin rash is further increased by as much as 5/fold if the initiating dose of LT is higher and titration faster than the recommended procedure.

Rare sporadic cases of Stevens Johnson Syndrome, epidermal necrolysis and toxic liver failure have been reported. Even with these reported idiosyncratic reaction LT appears to be safe if dosage and initiation of therapy guidelines are followed. Over 200,000 patients worldwide have received LT.[40,41]

Data from animal studies do not suggest teratogenesis, however, there are insufficient clinical data to recommend LT in pregnant patients.[41]

The arrival of LT in North America offers a drug which may be helpful not only in refractory patients with partial seizures but also in those patients with seizure syndromes which are refractory to other drugs. The low adverse effects profile may be of benefit to those patients who experience unpleasant adverse effects to VPA in the treatment of some of the primary epilepsies.

Vigabatrin (Sabril)

Vigabatrin (VG) is a novel new antiepileptic drug which was recently approved in Canada and is under consideration in the United States. Vigabatrin increases the brain concentration of GABA, the main inhibitory transmitted in the cerebral cortex. Two major classes of drugs act by influencing the action of GABA at inhibitory chloride receptors. Barbiturates prolong the effect of GABA and benzodiazepines facilitate the action of GABA. Vigabatrin is a GABA analog which irreversibly binds to GABA transaminase, the metabolizing enzyme for GABA. It has been aptly called a suicide enzyme inhibitor. Several hours after the administration of VG brain GABA levels increase several fold and remain so for many hours (> 24). Vigabatrin is most effective in blocking chemically induced seizures in animals. Its effect in preventing maximal electroshock seizures is controversial.[42]

Vigabatrin, in double blind placebo controlled studies, has been shown to be effective in partial and secondarily generalized seizures. It appears to be particularly effective in complex partial seizures, especially of temporal lobe origin. Vigabatrin, in clinical trials, is efficacious in children and infants with Lennox-Gastaut Syndrome and infantile spasms. Vigabatrin is not effective and may exacerbate absence and myoclonic seizures. It is not recommended in treatment of the primary epilepsies.[41]

Vigabatrin is readily absorbed from the gastrointestinal tract. It reaches peak blood levels in 1 to 2 hours and induces peak cerebrospinal fluid concentrations of GABA in less than 6 hours. It is not metabolized by the liver and 60 to 80% of a dose can be recovered unchanged in the urine. With the exception of a mild unexplained inhibition of PHT (< 20%) VG does not interact with other drugs. Drug half life is 5 to 7 hours, however the effect on GABA transaminase persist for 24 to 72 hours. The optimal daily dose in adults is 3 grams.[44]

The adverse effect profile of VG is generally favorable. Patients have reported fatigue, dizziness, blurred vision, tremor, agitation, rash, gastrointestinal upset, and weight gain. Psychiatric adverse effects, depression and psychosis have occurred in up to 5% of patients in some studies. Patients with a history of depression should be followed closely during therapy. Vigabatrin does not produce cognitive impairment or cosmetic changes.

Early reports of myelin vacuolization in animals has not occurred in humans.[45]

Vigabatrin represents an approach to the treatment of epilepsy based on a mechanism of drug action. Vigabatrin significantly elevates brain GABA levels and enhances inhibition. Considering the good tolerability and simple pharmacokinetics VG is a welcome addition to the treatment of complex partial seizures. It does not significantly increase adverse effects with polypharmacy or induce drug interactions.

Clobazam

Clobazam (CL) is a 1:5 benzodiazepine (BZD) which is similar in structure to diazepam. It was first used clinically as a non-sedative tranquilizer. Clinical testing began in 1977 and it was shown to be effective in a wide variety of seizure types, partial seizures, primary generalized seizures, Lennox-Gastaut and reflex epilepsy. Controlled clinical trials verified the initial studies.

The development of tolerance to the antiepileptic effects of the BZDs is well known. Such tolerance also develops to clobazam, however the anticonvulsant effect persists for a longer period in patients on clobazam than other BZDs. The adverse effect profile of CL is more favorable than other BZDs. Sedation is the most notable side effect. Rapid withdrawal of CL, similar to other BZDs, should be avoided because of the possibility of withdrawal convulsions.

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The daily dose of CL ranges from 10 to 50 mg. Clobazam is rapidly absorbed, lipophilic and has a very high volume of distribution. It is metabolized to active and inactive metabolites. Clobazam is effective in some patients for long term use; however it may best be used in acute situations or as intermittent therapy in selected patients.[46]

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