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REVIEW

Recent Advances in Anti-Epileptic Drugs

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Epilepsies are a group of disorders of the CNS characterized by paroxysmal cerebral dysrhythmia, manifesting as brief episodes (seizures) of loss or disturbance of consciousness, with or without characteristic body movements (convulsions), sensory or psychiatric phenomena. Epilepsy has a focal origin in the brain, manifestations depend on the site of the focus, regions into which the discharges spread. Some newer anti-epileptic drughs have recently been developed. They have some advantages over the older drugs. These newer drugs may control seizures more effectively. They are effective in complex partial and secondary generalized seizures. These are felbamate, vigabatrin, gabapetin, clobazam, lamotrigine, oxcarbazepine, tiagabine, topiramate, fosphenytoin and zonisamide.

Key Words: Epilepsy, Sezures, Lennox-Gastaut syndrome.

INTRODUCTION

Seizure is a paroxysmal event due to abnormal excessive hypersynchronous discharge from an aggregate of CNS neurons. Seizures are associated with loss or disturbance of consciousness and usually accompanied with convulsions or other body movements. The seizures are usually accompanied by both change in the rate or force of the electric pulsation of the cerebral cortex. About 3 % of the population is expected to have epilepsy at the same time during their life[1]. The prevalence rate of epilepsy is 1.3-8.0/1000 around the world and 5.5/1000 in India[2].

Mechanism of epilepsy

Neuronal excitability is the intrinsic property of the neurons, which occurs due to the changes, in conductance of ion channels. It depends on the response characteristics of membrane receptors and cytoplasmic buffering.

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Seizure initiation and propogation are dynamic process occurring in the neurons. An ideal anti-epileptic drug should have following characteristics: (**i**) effective for a number of seizure types, (**ii**) enhanced therapeutic index, (**iii**) minimal serious or chronic adverse effects, (**iv**) mild acute toxic or idiosyncratic effects, (**v**) longer half life, (**vi**) should not interact with other drugs, (**vii**) lack of teratogenic potential, (**viii**) should not target haemopoietic system and (**ix**) cost effective. Some newer anti-epileptic drugs have recently been developed. They have some advantages over the older drugs. There are:

Felbamate

Felbamate was introduced in 1993 and is approved for adjunctive or monotherapy in adults with partial seizures or without secondary generations. It is also approved for use in children with lennox-gastaut syndrome, a childhood disorder with multiple seizure types, slow spike-wave electroencephalograms, mental retardation and resistance to standard therapy with anti-epileptic drugs.

Felbamate acts as inhibitory on NMDA and facilitatory on GABA receptors. It also reduces Na^+ currents. Presently, it is used in pateints having seizures refractory to all other medications. It is indicated as third/fourth line drug. Recommended dose is 1.5 mg/kg/day 3-4 doses up to 45 mg/kg/day (400 mg 2-3 times, increase 400 mg every two weeks upto 4800 mg per day).

Felbamate is absorbed well orally with bioavailability greater than 90%. Absorption is not affected by food[3]. Half life of this drug is 1.5-2.3 h. Metabolism occurs by hepatic cytochrome P_{450} system, but 40-50 % of the drug is excreted unchanged in the urine. It is metabolized in the liver and excreated by the kidneys.

Felbamate affects the steady-state concentrations of other anti-epileptic drugs that depend on hepatic metabolism. The addition of felbamate increases the level of phenytoin and valporic acid and decreases the levels of carbamazepine while concurrently increasing its epoxide concentration. The addition of phenytoin or carbamazepine reduces felbamate levels by 40%. Because felbamate is only 25 % protein bound, minimal binding effect occur with protein bound drugs[4].

Felbamate is also considered as category C medication during pregnanacy. Because it is found in breast milk, breast feeding is not recommended for the patients taking felbamate. Pedriatic use is approved only for adjunctive therapy in children with lennox-gastaut syndrome.

The most common side effects include anorexia, vomiting, insomnia, nausea, headache, dizziness and somnolence[5]. Clinical effects of over dose include epigastric distress and tachycardia.

After initial marketing of the drug, two very serious toxic effects appeared : aplastic anemia and hepatic failure. The risk of aplastic anemia in patients taking felbamate is 100 times greater than it is in the general population. One in every 3600-5000 patients taking felbamate will have aplastic anemia. The fatality rate of this complication approaches 30 %. Aplastic anemia may not manifest itself until several months after initiation of treatment and patients may remain at risk for an undetermined amount of time after treatment is discontinued. The syndrome may begin with warning and may not be reliably detected by routine testing. Patients taking felbamate should remain alert for signs of infection, bleeding and easy brusing or symptoms of anemia such as fatigue or weakness[6,7].

Hepatotoxicity leading to hepatic failure is estimated to occur in one in every 24000 to 34000 patientstaking felbamate. Felbamate should not be used in patients with a history of hepatic dysfunction[3,8].

The need for monitoring drug levels has not been established. However baseline laboratory testing should include a completer blood count, platelet count and reticulocyte count, as well as determination of liver enzyme levels. Haematologic evaluations should be performed frequently during treatment and after discontinuation of treatment. Liver enzyme level should be determined after every 1 to 2 weeks and felbamate therapy should be discontinued if the asparate amino transferase, alanine amino transferase or bilirubin levels increase above baseline.

Because of serious side effects, felbamate is not recommended as first line therapyin the treatment of seizures. The manufacturer recommends its use only in patients who do not adequately respond to alternate therapy and whose epilepsy is so serious that the substantial risk of aplastic anemia and hepatic failure are deemed acceptable[3]. Its use requires that the physician should be thoroughly familiar with the drug. The manufacturer recommends the written consent be obtained before initiation of therapy.

Monotherapy in adults should begin with 1200 mg of felbamate daily given in divided doses every 6 to 8 h. Daily dosage should increase by 600 mg every 2 weeks to a total daily dosage of 2400 to 3600 mg. As adjunctive therapy, treatment should begin at 1200 mg daily, given in divided doses every 6 to 8 h. If the patient is taking phenytoin, valporic acid or carbamazipine, a 20-35 % reduction in the dosage of these drugs is recommended during felbamate therapy. Levels of anti-epileptic drugs should be followed as the dosage of felbamate therapy. Levels of anti-epileptic drugs should be followed as the dosage of felbamate is increased to 2400-3600 mg daily.

The beginning dosage of felbamate in children aged 2-14 years with lennox-gastaut syndrome is 15 mg per kg, given in 3 to 4 divided doses. Dosage of other anti-epiliptic drugs should be reduced by 20 % with

further reduction based upon side effects or drug levels. The daily dosage of felbamate should increase by 15 mg per kg weekly, to a maximum of 45 mg per kg.

Felbamate is available commercially in 400 and 600 mg tablets and as a suspension of 600 mg per 5 mL.

Vigabatrin ($C_6H_{11}NO_2$)

It is structurally similar to GABA except for vinyl group. It acts as irreversible inhibitor of GABA transferase by covalent binding to active sight of the enzyme. This causes accumulation of GABA at the synapse and cause neuronal inhibition. Recovery of enzyme activity takes several weeks. Presently, it is used in partial epilepsy. In newly diagnosed patients with partial epilepsy, vigabatrin and carbamazepine have same efficacy but vigabatrin has fewer side effects. In west's syndrome and infantile spasm, 2/3rd patients notice reduction of about 50 % the number of spasms; 40 % become seizure free. Best response is seen in the patients having infantile spasms in tuberculosis sclerosis[3]. Dose in children is 10-20 mg per day up to 40-100 mg per day and in adults it is better to start with 500 mg per day. Dose can be increased once in 2-4 weeks. Maximum dosage should not exceed 2-4 g per day. Half life of the drug is 5-7 h. It is excreated unchanged in urine.

Side effects: Fatigue, irritability, dizziness, diplopia, weight gain, hyperactivity, depression and psychosis. Symptomatic visual field constriction and neurotoxicity have been reported. Microvaculation of cerebral white matter has been seen in rodents and dogs, but not in humans. Drug interactions include reduction of phenytoin levels[9,10] by 2.5 %.

Gabapetin ($C_9H_{17}NO_2$)

Gabapetin has been approved as adjunctive therapy in adults with parital seizures with or without secondary generalization. It is a structural analogue of GABA. Though the mechanism of action is not clearly known, it enhances the release of GABA and inhibits voltage dependent Na^+ channels at times of excessive neuronal firing. Presently, it is medicated in intractable partial and secondary generalized seizures as a second line drug. It has an effect on absence or primary generalized tonic clonic seizures. It is also useful in patients with painful neuropathy. This drug has no serious toxicity and is well tolerated. It appears safe in the elderly patients due to the low incidence of neurotropic side effects.

Gabapetin is well absorbed orally, circulates mostly unbound in the plasma and is excreated unchanged in the kidneys without appreciable metabolism in the body. Oral bioavailability is *ca.* 60 % and is not affected by food. The half life is 5-7 h and is related to the creatnine clearance. Therefore, excretion is decreased in patients with renal impairment and

decreased cardiac function and in elderly patients. Gabapetin can be removed from the system through haemodialysis.

In clinical studies[8] gabapetin was found to be effective in adults with refractory parital seizures and was also effective in preventing the progression of partial seizures to generalized tonic-clonic seizures.

Because gabapetin has no known pharmacokinetic interactions with any other anti-epileptic drugs, it is useful in patients taking other anti-epileptic medications.

The only known contraindication to gabapetin is hypersensitivity to the drug. As with any other anti-epileptic drug, withdrawl should be gradual, performed over a minimum of one week, to minimize the risk of withdrawal seizures and status epilepticus. Side effects include somnolence, fatigue, ataxia, dizziness, gastrointestinal upset dyspnea and a sense of well being[11].

Gabapetin has shown no effects on phenytoin, carbamazipine, valporic acid and phenobarbital levelts. No clinically important interaction has been demonstrated with oral contraceptives. However, when taken concurrently with antacids, the bioavailability of gabapetin is reduced by 20 %. Gabapetin may also cause a urine dipstick test to show a false positive result for protein.

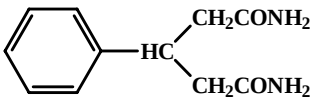
High doses of gabapetin have cuased pancreatic acinar cell carcinoma in laboratory rats; however in humans pancreatic carcinoma is usually ductal in origin[9]. Increased rates of pancreatic tumour occurance have not been reported in patients using gabapetin although data to data are limited.

Overdose of 15 times the usual daily dose have resulted in diplopia, slurred speech, drowsiness, lethargy and diarrhoea. In all reports of overdose, the patients recovered with supportive care. If necessary, overdose can be treated with haemodialysis.

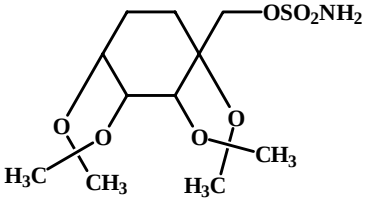
Gabapetin has been shown to be toxic to the fetus in laboratory rats and is thus considered a category C medication during pregnanacy. It should be used during pregnancy only if the potential benefit justifies the potential risks. It is not known weather gabapetin is excreated into breast milk.

Gabapetin has been found to be useful in the treatment of neuropathic pain. It is effective in decreasing intractable pain at anti-epileptic dosages with minimal side effects and minimal drug interactions[12], although it currently is not officially indicated for this use.

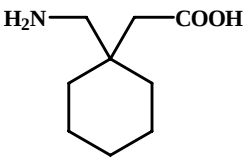
The usual dosage is 900 to 1800 mg daily, divided into three doses, Dosing should begin with 300 mg daily and increased by an additional 300 mg every one to three days[6]. Dosage up to 3600 mg have been given.The dosage should be adjusted according to creatinine clearance. Gabapetin is available in 100, 300 and 400 mg capsule[11].



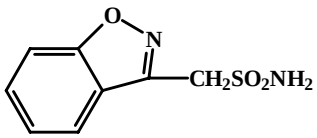
Felbamate



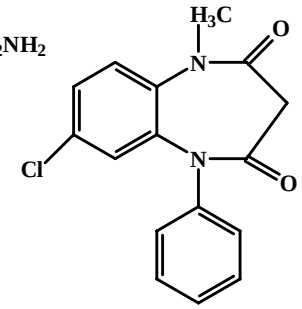
Topiramate



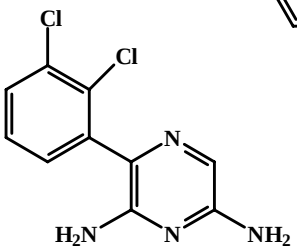
Gabapetin



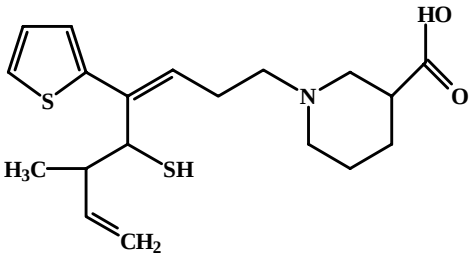
Zonisamide



Clobazam



Lamotrigine



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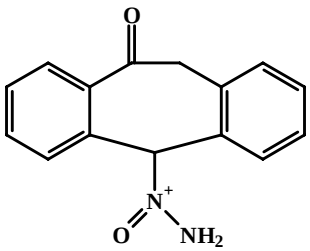
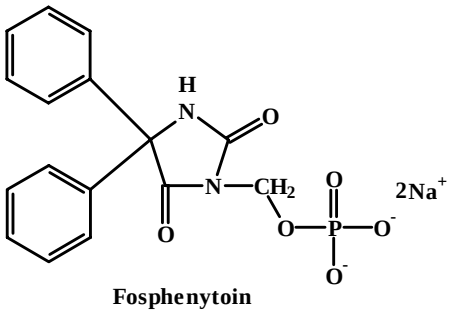
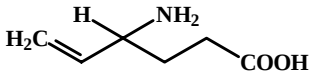


Oxcarbazepine



Fosphenytoin



Vigabatrin

Gabapetin may be used as adjunctive therapy in adults with poorely controlled parital seizures. In the future, gabapetin may become first line therapy in patients with newly diagnosed epilepsy. Gabapetin is easy to

use and has relatively mild side effects. Lack of drug-drug interaction makes it an attractive therapy.

Clobazam ($C_{16}H_{13}N_2Cl$)

It is 1,5-benzodiazepine, a compound related to the benzodiazepine group and having similar activity. Presently, it is useful as adjunctive therapy in refractory epilepsy. It can be used in all ages safely. It has a broad spectrum and is useful in a number of situations like complex partial seizures, simple partial seizures, simple partial seizures, secondary generalized seizures, benign myoclonic epilepsy and lennox-gastaut syndrome. It can also be used for short term prophylaxis in catamenial epilepsy. Febrile convulsions and seizure free period for a particular event like weeding. The Canadian study group remmends it as first time monotherapy for all partial and secondary generalized childhood epilepsies. Dose is 10 mg at bed time up to 30 mg/day. If no response is seen at 3 months then withdraw it gradually. Half life is 18 h.

Side effects: Excessive sedation, depression, galactorrhoea, nausea, diarrhoea, ataxia, irritability and disturb sleep wake cycle. 9-17 % of patients using this drug may develop tolerance by third method[3,13].

Lamotrigine

Lamotrigine is included in the phenyltriazine class. It is used as adjunctive therapy or monotherapy in adults with partial seizures with or without secondary generalization. The mechanism of action is unknown. Lamotrigine has been shown to act at voltage sensitive sodium channels, stabilizing neural membranes and inhibiting the release of excitatory neural transmitters[11].

Lamotrigine is well absorbed orally, with up to 98 % bioavailability. Absorption is not affected by food. About 55 % of the drug is protein bound; therefore, clinical interaction with other protein bound drugs is unlikely. 90 % of the drug undergoes glucuronic acid conjugation in the liver, with the conjugate and the remaining 10 % of unmetabolised drug excreted in urine[14]. Clearance is markedly increased by the co-administration of other antiepileptic drugs that induce hepatic enzymes. These include carbamazepine, phenobarbital, phenytoin and primidone. The half life of lamotrigine may be reduced by about 50 % with concomitant use of one or more of these medications. However, when combined with valproic acid, its elimination is decreased and its half life may be more than doubled.

Lamotrigine does not impair cognition and has a relatively broad spectrum of activity against multiple types of seizures. Three multi-center clinical studies have demonstrated its efficacy as adjunctive therapy in adults with refractory partial seizures[12].

The only contraindication to lamotrigine is hypersensitivity to the drug. The need for monitoring drug levels has not been established. The most frequently encountered adverse reactions include dizziness, ataxia, somnolence, headache, blurred vision, nausea, vomiting and rash. Up to 10% of patients discontinue lamotrigine therapy because of side effects. One case of acute hepatic failure has been reported. Because lamotrigine depresses the central nervous system, patients who are taking the drug should be cautioned about driving or operating complex machinery.

A macular, popular or erythematous rash may develop in *ca.* 10 % of patients during the first 4-6 weeks of treatment with lamotrigine. Although the rash often ressolves with continuous use, it may sometimes be indcative of serious systemic involvement. The occurence of a rash or systemic symptoms such as fever or lymphadenopathy necessitates prompt discontinuation of the drug and medical evaluation one in every 1000 adults treated with lamotrigine develops severe, life-threatning rashes such as Stevens-Johnson syndrome, toxic epidermal necrolysis and angioedema with fever, facial swelling and lymphadenopathy. The risk is increased more than three fold with co-administration of valporic acid.

In children, the risk of developing a life threatening rash is 1 in 50. Hence use of lamotrigine is not indicated in children under 16 years of age[14]. The risk of rash may increase if lamotrigine is given more than the recommended dosages or if initial dosing is accelerated over recommendations provided by the manufacturer[11].

Because of the potential of severe life threatening skin reactions, the FDA required that the manufacturer of lamotrigine publish a special warning on the label of this product.

There is a risk of withdrawal seizures if therapy is discontinued abruptly; thus gradual tapering of the medication over a 2 week period is recommended. Caution is advised in patients with conditions that could affect elimination such as renal or hepatic impairment or the co-administration of valporic acid. Dosage reduction is mandated in patients with significant renal impairment.

Lamotrigine binds to melanin containing tissues such as the iris of the eyes, but the long term effects of this binding and accumulation are unknown. Use in pregnant women is recommended only if the benefit outweighs the potential risk. Lamotrigine is classified as a category C medication during pregnancy. A registry of pregnant women using lamotrigine is maintained by the manufacturer. The drug is found in breast milk; thus nursing is not recommended during the treatment. Lamotrigine is contraindicated for use in patients under the age of 16 because of the increased risk of developing a life threatening rash.

Over does of up to 10 times the usual daily dosage have been reported. Recovery occurred with supportive care. There is no specific antidote.

The starting dosage in the patients not taking valporic acid should be 50 mg daily for 2 weeks, increasing to 50 mg twice daily for an additional 2 weeks and then increasing by 100 mg per day weekly to a maintenance level of 150-200 mg twice daily[8].

In patients who are taking valporic acid plus other anti-convulsant drugs that induce hepatic enzymes, the initial starting dosage should be reduced to 25 mg every other day for 2 weeks, then increased to 25 mg daily for 2 weeks. The dosage may be increased by 25 to 50 mg daily every 1 to 2 weeks up to a maximum of 75 mg twice daily.

It is generally recommended that lamotrigine not be combined with valporic acid in a 2-drug regimen. Lamotrigine is available in 25, 100, 150 and 200 mg tablets.

Oxcarbazipine

It is a 10,11-dihydro-10-oxo derivative of carbamazepine. It is a prodrug and in the liver it is converted to 10-hydroxy and dihydroxy carbamazepine. It is to be used as monotherapy in the treatment of partial seizures, but the side effects and drug interactions are few. This drug is better tolerated. Due to its longer half life (10-15 h) it can be given in twice daily doses. It does not cause induction of hepatic enzymes. For initiation of monotherapy in adults as well as in children, dose of 8-10 mg/kg up to a maximum of 600 mg per day in two divided doses is used. Dose is 1200-2400 mg/day which may be increased by 600 mg/week. Theraputically 300 mg oxcarbazepine is equivalent to 200 mg carbamazipine. The most common side effects observed are headache, dizziness, somnolence nausea, vomiting and ataxia. Skin-rash, multiorgan hypersensitivity reaction (rash, lymphadenopathy, abnormal liver functions, eosinophillia and arthralgia), SLE and Steven-Jhonson's syndrome has been reported. This drug increases the concentrations of phenytoin and phenobarbitone and reduces plasma concentrations of oral contraceptives and felodipine. It has no interaction with warfarin, cimetidine and erythromycin. Renal impairment and severe hepatic dysfunction affects the pharmacokinetic of this drug. Its safety in pregnancy and lactation is not yet established[3,15].

Tiagabine

It is a GABA uptake inhibitor. It increases synaptic GABA and influx of Cl^- ions increasing repolarization of neuronal cell membrane. It is indicated as adjuvant therapy in simple partial seizures and secondarily generalized seizures in patients that are not controlled on by first line drugs. This drug is associated by a high incidence of side effects like dizziness, somnolence, asthma, nervousness, tremor, depressed mood and confusion. It also has an incovenient dosing schedule. It is metabolized by hepatic cytochrome P_{450} and by glucouronidation. The half life is 7-9 h but is

reduced in patients with reduced hepatic enzyme inducing drugs like phenytoin and phenobarbitone. Initial dose is 4 mg once daily which may be increased by 4-8 mg at weekly interval until clinical response is seen. The maximum dose should not exeed 32 mg per day in adolescents and 50 mg per day in adults in divided form. Tiagabine has no interaction with warferin, digoxin and contraceptives, antipyrine and climetrdine. The dose needs to be reduced in the patients with hepatic impairment. No alteration is required in patients with renal failure. Its safety in pregnant and lactating mother is yet to be established[12,15].

Topiramate

Topiramate has been approved for adjunctive treatment in adults with partial seizures. It has a novel chemical strucutre derived from D-fructose that blocks voltage sensitive sodium channels, enhances the activity of GABA, an inhibitory neurotransmitter and blocks the action of glutamate, an excitatory neurotransmitter. It is also a weak carbonic anhydrase inhibitor[16].

Topiramate is well absorbed orally with a bioavailability of 80 %. It is less than 20 % protein bound. When used alone, 20 % of the drug is metabolized. With concurrent use of other anti-epileptic drugs, 50 % of the drug is metabolized. Excretion is primarily renal, with 50-80 % of each dose excreated unchanged. The half life is 20-30 h.

A 30 and 48 % median reduction in seizure frequency occurs at the dosages of 200 and 400 mg/day, respectively. No improvement in seizure reduction occurs at dosage above 400 mg[13]. The only known contraindication is hypersensitivity to the drug. Side effects include dizziness and somnolenceataxia, impaired concentration, confusion, fatigue, paresthesias, speech difficulties, diplopia and nausea[17]. There is an increased risk of nephrolithiasis, which may be due to carbonic anhydrase inhibition. Concomitant use of topiramate with other carbonic anhydrase inhibitors such as dichlorphenamide, oracetazolamide should be avoided.

Topiramate increases phenytoin concentration by 25 % and decreases valporic acid concentration by 11 %. Topiramate does not change the concentration of carbamazepine, phenobarbital and primidone when co-administered. Concentrations of topiramate decreases upto 48 % when phenytoin is co-administered upto 40 % with co-administration of carbamazepine and up to 14 % with valporic acid.

Topiramate is classified as category C medication during pregnancy. It is not known if it is excreted in the breast milk.

Over doses have been managed to date with prompt induction of emesis or lavage. topiramate is effectively removed by haemodialysis.

The starting dosage is 50 mg per day given in the evening, increasing by 50 mg per week until a dosage of 200 mg given twice daily is reached.

It is not necessary to monitor drug levels. Dosing beyond 400 mg per day does not increase efficacy.

Topiramate can be taken with food if desired. The patients with renal function impairment should use 1/2 of the recommended dosage. Topiramate is available in 25, 100 and 200 mg coated tablets.

Fosphenytoin

Fosphenytoin is a phenytoin precursor that is rapidly converted after paranteral administration. It is indicated for short term parenteral when the oral form is not available or less advantageous[16]. In addition to its use as a short term substitute for oral phenytoin, it can be used to control status epilepticus and to prevent and control seizures during neurosurgery.

The use of parentral phenytoin is complicated by poor solubility, high alkalinity, hypotension, cardiac arrhythmias and the potential for soft tissue injury with extravasation. However fosphenytoin can be administered intravenously or intramuscularly with a low risk of tissue irritation. No significant electro-cardiographic changes have been noted with either intravenous or intramuscular administration. Mild decrease in mean systolic blood pressure have been reported with intravenous administration.

Theraputic serum levels of phenytoin are attained within 10 min of infusion of intravenous fosphenytoin[18]. Peak serum phenytoin levels are attained 1.5 h after intramuscular administration. Fosphenytoin administered intravenously or intramuscularly is 100 % bioavailable and 90 to 95 % protein bound. A 1.5 mg dose of fosphenytoin is equivalent to 1 mg of phenytoin.

Fosphenytoin is contraindicated in patients with hypersensitivity to phenytoin or other hydantoins and in patients with sinoatrial block, second and third degree atrioventricular block and Strokes-Adams syndrome[17].

Common adverse effects include pruritis, nystagmus, dizziness, somnolence, ataxia, nausea, tinnitus and hypotension. Up to 64 % of patients experience gross discomfort on intravenous administration, which usually dissipates within 1 h.

Concominent use with carbamazepine or diazepam has shown no effect on fosphenytoin binding. fosphenytoin binding did decrease in patients with excessive concentrations of phenobarbital or valporic acid.

For patients with status epilepticus, 22.5-30 mg/kg of fosphenytoin should be administered intravenously at a rate of 100 mg/min. For nonemergent therapy or to prevent seizures, 15-30 mg/kg can be administered intravenously or intramuscularly in the loading dose, followed by a daily maintenance dosage of 6-12 mg/kg. Patients who are already at therapeutic levels of oral phenytoin can be given fosphenytoin at 1.5 times the daily phenytoin dose.

Zonisamide

The exact mechanism of action is not known, but it is postulated that it may block Na^+ and Ca^{2+} channels. The proposed indication is as adjuvant therapy in partial seizures in patients that are not controlled by first line drugs. This drug has no effect on the concentrations of other anti-epileptic agents and can be given twice daily. About 35 % of the drug is excreted unchanged while the rest is metabolized by hepatic cytochrome P_{450} and by glucouronidation. The half life is 60 h if taken alone and 27-46 h when taken with enzyme inducing drugs. Its metabolites are not biologically active. The initial dose is 100 mg per day, which may be increased by 100 mg weekly or biweekly basis and maximum up to 400 mg/day. The most common side effects are dizziness, diplopia, anorexia, tiredness, headache, nausea, ataxia, confusion, mental slowing, memory loss, irritability, depression, insomnia, tremors and emotional lability. The side effects develops in first week and decline over time. Weight gain has been reported. Renal stones are also reported and this drug is also contraindicated in patients with a history of allergy to sulfonamides. In adults the hepatic enzyme inducing drugs reduce the half life of the drug. Its excreation reduces in patients with renal failure, so the dose has to be reduced. It has been reported to be teratogenic and caused reproductive toxicity in animals[3,15].

Conclusion

25-40 % of the patients with epilepsy continue to have seizures despite optimal treatment with traditional anti-epileptic drugs. Treatment with standard anti-convulsants such as phenytoin, carbamazepine, valproic acid and phenobarbital is often complicated by side effects and by failure to adequate control seizures. Up to 61 % of patients with seizures report having side effects with anti-epileptic drugs.

Newer anti-epileptic drugs may control seizures more effectively but their significant potential for serious side effects requires a through knowledge of the drug and careful consideration of the risks and benefits.

All the newer drugs, which are defined here are effective in complex partial and generalized seizures. Vigabatrin is a drug of choice in infantile spasms. Lamotrigine can be used in resistant absence and primary generalized tonic clonic seizures. Lamotrigine or topiramate can be tried in Lennox-Gastaut syndrome. Valporate and vigabatrin are to be avoided in obsese patients as they affect appetite. Vigabatrin, clonazepam and zoniasamide are to be avoided in depression. Gabapetin, lamotrigine and topiramate are approved for use in adults with partial seizures with or without generalization. Felbamate is approved for the above indication and also for use in children with Lennox-Gastaut syndrome, a rare childhood seizure

disorder. Felbamate and lamotrigine have the potential of significant side effects and should be prescribed by physicians experienced in managing patients with complicated epilepsy. Fosphenytoin is a parentral prodrug of phenytoin that is more tolerable then parentral phenytoin.

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