Treatment of Epilepsy: A Review Of Antiepileptic Drugs

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Abstract

INTRODUCTION

Epilepsy is among the most common disorders encountered by neurologists in their day-to-day practice. It is characterized by the occurrence of at least two or more unprovoked seizures. Effective treatment of epilepsy begins with a correct characterization of the patient's seizure type. Modern treatment of seizures involves the use of an antiepileptic drug (AED) tailored to the patient's seizure type. In medically refractory epilepsy more radical treatment in the form of epilepsy surgery, vagal nerve stimulator (VNS), deep brain stimulator (DBS) and responsive nerve stimulator (RNS) may be offered. This article shall discuss the pharmacological management aspects of epilepsy.

TREATMENT OF EPILEPSY

Epilepsy as a disease has been recognized in the earliest medical writings of Hippocrates who refers to it as the Sacred Disease. The treatment of epilepsy has also evolved through the ages. In the ancient times when the mechanisms and pathogenesis of epilepsy was poorly understood treatment consisted of prayers and rituals to rid the patient of evil spirits. Over the years treatment of epilepsy has expanded to include various drug options.

Bromide: Modern treatment of epilepsy began in the 1850's when Sir Charles Locock, Queen Victoria's physician accoucheur, used potassium bromide for treating hysterical epilepsy. At that time epilepsy was thought to occur due to masturbation, and Locock believed that bromide controlled epilepsy by calming sexual excitement. Potassium bromide is used to treat epilepsy in dogs, either as first-line treatment or in addition to phenobarbital. In Germany it is approved as an AED in children and adoloscents for particular indications namely severe forms of generalized tonic-clonic seizures (GTCS) and severe myoclonic seizures of childhood. It has a very long half-life of about 6 weeks and a very narrow therapeutic window. High doses may cause bromism typically presenting with neurological, psychiatric and dermatological side-effects like somolence, encephalopathy, ataxia, tremor, seizures, impairment of memory, self-neglect, disinhibition and occasionally schizophrenic-like psychotic behavior or hallucinations. Bromoderma presenting as acne-like papular eruption of the face and hands or a macular rash with abnormal pigmentation in the sun-exposed areas has also been described. The mechanism by which bromide exerts its antiepileptic effects is still not fully elucidated but is thought to involve modulation of synaptic processes by its action on the transport systems or by substitution of chloride ions in actions of neurotransmitters. Recently there has been renewed interest in the drug especially in cases of refractory pediatric epilepsy. Korinthenberg et al. in their study investigated the efficacy and tolerability of potassium bromide in 113 patients (aged 1-20years) with severe epilepsy and GTCS. Potassium bromide was started at 45mg/kg and raised to 70mg/kg (median). After a median of 28 days steady-state blood levels were reached. Patients who had suffered GTCS during the last month dropped from 82 to 41, and the median frequency, dropped from 4.5 to 0 per month. Of the patients with GTCS during baseline, 49% showed none in the last 4 weeks of the study, and another 31% showed a reduction by more than 50%. They concluded that potassium bromide had a place as a drug of tertiary choice in the treatment of children with epilepsy. As they right stated more experience with the drug along with close clinical and pharmacological monitoring during use is needed to achieve the greatest benefit and avoid side effects.

Phenobarbital: is an inexpensive, widely used, and effective anti-epileptic drug that revolutionized the treatment of epilepsy. It is the oldest AED still in common use. In 1912 Bayer introduced it into the market under the brand name Luminal. Phenobarbital blocks sodium dependent action potentials and reduced neuronal calcium uptake. It is both a

sedative and hypnotic, altering the sensory, cerebellar and motor cortexes. Patients who had been institutionalized due to intractable seizures were able get reintegrated into society. The drug was quickly adopted as the first widely effective anticonvulsant. Phenobarbital is indicated in the treatment of all kinds of seizures with the exception of Absence seizures. It is metabolized via the liver CYP450 group of isoenzymes namely 2C9, 2C19, 2E1 and has a long half-life of 79 hours permitting once daily dosing. Usual effective dose for seizure disorder is 60 mg BID or TID and loading dose for status epilepticus is 18-20mg/kg of body weight given at a rate of 50-75mg/min. Dose adjustments are needed in patients with hepatic insufficiency (best to avoid in patients with hepatic encephalopathy) and renal impairment. For creatinine clearence < 10, it is better to administer every 12-16 hrly and in patients on hemodialysis the dose should be administered after the dialysis treatment. Phenobarbital use is contra-indicated in patients with history of porphyria and those with severe hepatic insufficiency. The possibility of drug-drug interactions altering serum drug levels should be kept in mind as it is metabolized by the CYP450 group of isoenzymes. Drugs which increase the effect of phenobarbital include CNS depressants like phenothiazines, antihistamines as well as valproic acid. Phenobarbital decreases the effect of oral anticoagulants, chloramphenicol, doxycycline and corticosteroids necessating dose adjustments.

Phenytoin has been and continues to be in some instances the standard of medical care for patients with epilepsy throughout the world primarily due to its low cost, facility of use, and efficiacy. It has recently fallen out of favor due to its unfavorable side-effect profile with physicians preferring to use the newer antiepileptic drugs. In the developing world it still maintains its position as the most prescribed drug for partial seizures and GTCS with limited value for clonic, myoclonic, atonic seizures and in Lennox-Gastaut syndrome. Phenytoin is metabolized by cytochrome P450 enzymes namely 2C19 and other forms from the 2C and 3A subfamilies primarily to 5-(p-hydroxyphenyl-), 5-phenylhydantoin (HPPH), which may be further metabolized to a catechol that spontaneously oxidizes to semiquinone and quinone species that covalently modify proteins. Phenytoin blocks and modulates neuronal voltage-dependent sodium and calcium channels. It has a half-life of about 22 hours permitting once daily dosing. The usual effective dose for seizure disorder is about 300-400mg q day (4-6mg/kg q day) and loading dose for status epilepticus is 18-20mg/kg of body weight given at a rate not to exceed 50mg/min. Therapeutic serum levels are between 10-20mcg/ml; free levels 1-2mcg/ml. Too rapid loading of intravenous phenytoin may cause an unsafe drop in blood pressure and can also precipitate a 2 nd or 3 rd degree AV block. Alteration of serum drug levels should be considered, as it too is metabolized by the CYP450 group of isoenzymes the possibility of drug-drug interactions. Rifampin and phenobarbital reduce serum phenytoin levels while amiodarone, chloramphenicol, cimetidine, disulfiram, fluconazole, fluoxetine, isoniazid, omeprazole and paroxetine increase levels. The most common side-effects of phenytoin are neurotoxic and include sedation, ataxia, nystagmus, dizziness, slurred speech and incoordination. These side effects usually settle down within a few days but may require a reduction in dose. Long term use of phenytoin may cause gingival hyperplasia, coarsening of facial features, hirusitism and acne (phenyotin facies). Cerebellar atrophy has been noted in long term users of phenytoin along with osteopenia and osteoporosis. Long term use of phenyotin causes multiple abnomalities in calcium and bone metabolism lowering serum 25 hydroxy vitamin D levels leading to a decrease in bone mineral density and increasing the risks of fractures. Souverein et al. conducted a case control study to assess the risk of fractures on patients on antiepileptic drugs. The risk of fractures increased with cumulative duration of exposure with the strongest association for greater than 12 years of use. They found no difference in the risk of fractures between users of antiepileptic drugs that induce and those that do not induce the hepatic cytochrome P-450 system, implying that liver-inducing potential per se is not responsible for all the increase in fracture risks. The risk estimates however, were higher in woman compared to men. Another study by Farhat et al., studied the effect of antiepileptic drugs on bone density in ambulatory patients generalized seizures. Findings indicated that the duration of epilepsy and polypharmacy with AEDs were significant determinants of bone mineral density especially in skeletal sites enriched in cortical bones. In their study Farhat et al. found that subjects on enzyme-inducing drugs such as phenytoin, phenobarbital, carbamazepine and primidone tended to have lower bone mineral density as compared to those on noninducers such as valproic acid, lamotrigine, clonazepam, gabapentin, topiramate and ethosuximide. Regular skeletal monitoring with bone DEXA scans and supplementation of calcium and vitamin D are indicated for all patients on chronic phenytoin therapy.

Fosphenytoin: is a water soluble phenytoin prodrug which

has become popular in the hospital settings for treatment of status epilepticus. Due to its solubility the drug does not cause extravasation injury and no cases of “purple glove syndrome” have been described with its intravenous use. Fosphenytoin doses are expressed as phenytoin equivalents (PE). Loading dose for status epilepticus is 18-20mg/kg of body weight. In comparison to phenytoin, fosphenytoin can be injected at a much faster rate of 150 mg/min and can also be given intramuscularly. Thus, it is preferred over phenytoin in the hospital settings for the rapid treatment of status epilepticus. The disadvantage of fosphenytoin is its higher cost compared to phenytoin and currently it is still not freely available in most hopital emergency departments. The mechanism of action, metabolism containdications and side-effect profile is otherwise similar to phenytoin.

Valproic acid: and its sodium salt sodium valproate is one of the front line antiepileptic drugs. Valproic acid is a broad spectrum anticonvulsant effective against both partial as well as generalized seizures. It is one of the frontline drugs used to control absence seizures, juvenile myoclonic epilepsy and the seizures associated with Lennox-Gastaut syndrome. Sodium valproate's exact mechanism of action is unknown but it is believed to act on the neurotransmitter GABA as a GABA transaminase inhibitor. It is also effective in myoclonus of cortical and subcortical origin such as in post hypoxic myoclonus. Parenteral preparations of valproate are used as second–line treatment of status epilepticus if intravenous loading of phenytoin fails to abort the status. Two studies have compared sodium valproate versus phenytoin for status epilepticus. In the study by Misra et al. sixty-eight patients with convulsive status epilepticus were randomly assigned to two groups to study the efficacy of sodium valproate versus phenytoin. Seizures were aborted in 66% in the valproate group and 42% in the phenytoin group. As a second choice in refractory patients, valproate was effective in 79% and phenytoin in 25% with no difference in side effects in the two groups. The authors concluded that sodium valproate may be preferable to phenytoin in convulsive status epilepticus because of its higher efficacy. Usual effective dose for seizure disorders is 10-15mg/kg/day divided qd-tid and for status epilepticus is 15-25mg/kg of body weight. Therapeutic drug levels for epilepsy range between 50-100 mcg/ml and the drug has a half-life of 9-16 hrs. Sodium valproate is metabolized in the liver via the CYP450 group of isoenzymes (2C9 weak inhibitor). It is associated with a 3-5% risk of fetal neural tube defects and an increased risk of other major congenital malformations (MCMs) affecting the heart, limbs and genitalia. There is also evidence from pregnancy registries that valproic acid may result in developmental delay and other neurobehavioral problems. These effects have been found to be dose dependent and the risk of MCMs increases with polypharmacy antiepileptic drugs. In a study dated from the North American Antiepileptic Drug Pregnancy Registry, the prevalence of congenital malformations among offspring of monotherapy VPA-exposed women was compared with that among infants of women exposed to all other antiepileptic drugs (internal comparison group) and with that among newborns in the Active Malformations Surveillance Program at Brigham and Women's Hospital (external comparison group). Sixteen affected cases were identified among 149 VPA-exposed women (proportion: 10.7%, 95%CI: 6.3 to 16.9%). The prevalence in the internal comparison group was 2.9% (95% CI: 2.0 to 4.1%; odds ratio: 4.0,95% CI: 2.1 to 7.4;$p<0.001$). Assuming a 1.62% prevalence in the external comparison group, the relative risk of having an affected offspring for VPA-exposed women was 7.3. The Australian Registry of Antiepileptic Drugs in Pregnancy, in which women with epilepsy enrolled voluntarily both prospectively and retrospectively, showed a MCM rate for valproate monotherapy of 17.1%. A dose effect was found for valproate; above 1100 mg per day was associated with a marked increased risk. Sodium valproate is best avoided in women with epilepsy of childbearing age.

Carbamazepine was first marketed in Europe for the treatment of trigeminal neuralgia. In the early 1970's, it was approved in U.S. as an anticonvulsant. It is one of the front-line antiepileptic drugs for the treatment of partial seizures as well as secondary generalized seizures. It acts on voltage gated sodium channels that are stabilized in their inactivated state. As a result, fewer channels are available thus reducing post-tetanic potentiation and seizure spread. Carbamazepine is metabolized in the liver by cytochrome (CYP) 450 group of isoenzymes: 3A4 substrate; 1A2, 2C9, 3A4 inducer. It induces its own metabolism with a half-life of 25-65 h on initial dosing and 12-17 h on repeated dosing. Usual effective dose for seizure disorder is 800-1200mg/day divided bid-tid while lower doses of 200-400mg/day suffice for trigeminal neuralgia. Common side effects include dizziness, nausea, vomiting, ataxia, nystagmus, hyponatremia and elevated liver transaminases not warranting drug discontinuation. Idiosyncratic drug reactions include Stevens-Johnson syndrome, toxic epidermal necrolysis, aplastic anemia, thrombocytopenia, pancytopenia, agranulocytosis, hepatic failure, leucopenia and pancreatitis. Carbamazepine interacts with other

medications altering their metabolism in the body. CYP 3A4 inhibitors like cimetidine, danazol, diltiazem, macrolides, erythromycin, fluoxetine, isoniazid, verapamil, protease inhibitors and valproate slow down carbamazepine metabolism thus increasing plasma carbamazepine levels while CYP 3A4 inducers like cisplatin, doxorubicin, rifampin, phenytoin, primidone, theophylline and felbamate decrease plasma levels of carbamazepine by increasing its rate of metabolism. Physicians should monitor carbamazepine levels closely and adjust dosage as needed to maintain optimal seizure control. A study with data from the Swedish Medical Birth Registry compared infants with congenital malformations and exposed to AED (infants exposed to AEDs, n=1398) with expected number estimated from all infants born (n=582656). 90% (1256) of the AED children were exposed to AEDs in monotherapy; carbamazepine (56%), valproate (21%). The odds ratio for having a malformation in the AED exposed group was 1.86 (95% CI, 1.42-2.44). Exposure to valproate monotherapy compared to carbamazepine in monotherapy gave an OR=2.51 (95% CI, 1.43-4.68) for a neonatal diagnosis of malformations. Carbamazepine compares more favorably than valproate when it comes to risk of MCMs in offspring's of women with epilepsy.

Ethosuximide: is a succinimide anticonvulsant and is the drug of choice for treating typical Absence seizures and lacks the hepatotoxic side-effects of the alternative drug for absence seizures namely valproic acid. Its mechanism of action is believed to involve blockage of voltage dependent T-type calcium channels. The typical dose needed to treat absence seizures is 250 mg BID (maximum dose 1.5g/day). Therapeutic drug levels are between 40-100mcg/m L, the drug is metabolized in the liver by cytochrome group of isoenzymes (CYP450: 3A4 substrate). Caution is advised when used in patients who have hepatic and renal insufficiency or those with a history of porphyria and mixed seizure disorder. Valproic acid may either decrease or increase the levels of ethosuximide however their combination is at times more effective in controlling absence seizures than either drug alone. In a study van Rijn et al. compared effects of the combination of valproate and ethosuximide on spike wave discharges in the EEG of rats. Isobolic analysis showed that a higher drug load of the combination was needed than the individual drugs to achieve a 50% reduction of spike wave discharges. The combination was found to be infra additive in their study.

Lamotrigine has FDA approval as monotherapy for partial seizures. It is also used for primary and secondary tonic-clonic seizures and for seizures associated with Lennox-Gastaut syndrome in the pediatric age groups. It also acts as a mood stabilizer and has FDA approval for maintenance treatment of bipolar I disorder and in patients who exhibit rapid cycling. It has a chemical structure of 6-(2,3-dichlorophenyl) 1,2,4-trizine-3,5-diamine, has relatively few side-effects and does not require monitoring of blood levels except in the special group of pregnant women with epilepsy. Though it is thought to be a Na^+ channel blocker, its exact mechanism of action has not been fully explained. It is metabolized in the liver (hepatic glucuronidation) by the CYP 450 group of isoenzymes. The drug's half-life is 25 hours which decreases to 14 hours with enzyme-inducing anticonvulsants. Valproate inhibits the clearance of lamotrigine by a mean of approximately 30% at a dose of 125mg/day and by a mean of 50% at doses of 250mg and higher thus increasing its half-life to 59 hours when used in combination. These data have practical implications: low dose (250mg/day) valproic acid can potentially be used exclusively as an inhibitor of lamotrigine clearance. This may allow better seizure control at doses where the risk of adverse effects due to valproate are low. Serious rash requiring hospitalization and discontinuing treatment has been associated with the use of lamotrigine. This includes Stevens-Johnson syndrome and rare cases of toxic epidermal necrolysis. Most life-threatening rashes occur in the first 2-8 weeks of treatment. This drug should be discontinued at the first sign of a rash, however discontinuing treatment is not a guarantee that the rash would not spread further and become life threatening. Use of valproic acid and lamotrigine simultaneously may increase the risk of rash, therefore lamotrigine should always be introduced at a low dose and slowly tapered up especially when it is been added as a component of a polytherapy regime which includes valproic acid. Therapy is initiated at 25 mg/day for 2 weeks when used as monotherapy and at 25mg every other day for 2 weeks when used as an adjunct to valproate. When used as an addition to valproate start at 25mg every other day for 2 weeks, then 25mg qd for another two weeks and then increase by 25-50mg/day every 1-2 weeks. Usually effective dose for seizures when used as monotherapy is 250mg BID. Lamotrigine has been found to be safer during pregnancy. The Glaxo Smith Kline (GSK) International Lamotrigine Pregnancy Registry reported a MCM rate of 2.7% (95% CI 1.8-4.2%) among 802 exposures. The distribution of dose did not differ between infants with and those without MCMs and a logistic regression analysis showed no difference in

the risk of MCMs as a continuous function of dose up to 400mg/day. A special mention is deserved for lamotrigine dosing during pregnancy. More frequent monitoring of levels may be required since serum levels have been shown to decrease by as much as 60-90% during pregnancy. This increased clearance of lamotrigine may occur within the first several weeks of pregnancy and usually returns to baseline within two weeks postpartum. Dose adjustments of lamotrigine are required early in pregnancy. Dramatic dose escalation may be required during pregnancy with a rapid downward escalation after delivery.

Topiramate is an anticonvulsant which is approved for treatment of partial and generalized tonic-clonic seizures in both adults and children as well as in the management of seizures associated with Lennox-Gastaut syndrome. The drug has rapidly gained popularity not just as an anticonvulsant but also for migraine prophylaxis. Off-label uses include treatment of bipolar disorder, obesity especially in the reduction of binge eating, to cut down the craving associated with alcoholism, treatment of bulimia nervosa, obsessive-compulsive disorder, pseudotumor cerebri, neuropathic pain and in smoking cessation. When used as monotherapy the usual effective dose for seizures is 200mg BID, start with 25mg PO BID for 1 week and then increase by 50mg/day q week until 100mg BID. It is metabolized via the liver minimally (CYP450: 2C19 inhibitor and 3A4 inducer) and the kidney (70% excreted unchanged) and has a half-life of 21 hours. Thus for CrCl 10-70, decrease dose by 50% and for CrCL less than 10, decrease dose by 75%. Topiramate has multiple mechanisms whereby it exerts its anticonvulsant effects. It enhances GABA-activated chloride channels and inhibits excitatory neurotransmission, through actions on kainate and AMPA receptors especially GluR5 kainate receptors. Topiramate is also an inhibitor of subtypes II and IV of carbonic anhydrase though this action is reportedly weak. Side effects reported with topiramate use include cognitive side-effects such as impairment in short term memory and especially word-finding difficulties. These may be avoided by starting the medication at low doses and gradual upward titration. Other side-effects reported include psychomotor slowing, dysgeusia (alteration in taste), paresthesias (pins and neddles sensation in the extremities), lethargy, kidney stones, rash, diplopia, dry mouth, dyspepsia, osteoporosis, anxiety, metabolic acidosis due to its inhibition of carbonic anhydrase and loss of weight. Acute myopia and angle closure glaucoma have been reported which in a small subset of patients may lead to permanent loss of vision. To avoid renal stones, patients should be encouraged to drink more water especially during the hot summer months.

Oxcarbazepine is a 10-keto analogue of carbazepine and appears to have a similar profile and degree of efficacy against partial and generalized tonic-clonic seizures. Off label uses include treatment of bipolar disorder and trigeminal neuralgia. Usual effective monotherapy dose for seizures is 600mg BID while lower doses may be effective for trigeminal neuralgia and bipolar disorder. Oxcarbazepine induces hepatic microsomal enzymes (CYP450: 2C19 inhibitor; 3A4/5 inducer), 95% is excreted in urine (<15 unchanged). Half life is about 9 hours for the metabolite. For CrCl <30 start at 150 mg BID. The exact mechanism of action is unclear but it is thought to block voltage-sensitive Na channels, stabilize neural membranes and decrease synaptic impulse propagation. The side-effects appear to be somewhat else as compared to carbazepine particulary with respect to leukopenia and depression of blood counts as well as the incidence of rash. Serous side-effects include hyponatremia, hypersensitivity reactions, leukopenia, thrombocytopenia, Stevens-Johnson syndrome, erhthema multiforme and toxic epidermal necrolysis. Other more common side-effects that have been reported include dizziness, ataxia, diplopia, fatigue, nystagmus and nausea. Hyponatremia may be severe and symptomatic necessating lower dosing or even discontinuation of the drug. This side effect is particularly problematic at dosages above 30mg/kg/day. A literature review by Montouris found that, compared with newborns in the general population, the newborns of women receiving oxcarbazepine monotherapy during pregnancy did not appear to show an increased risk for malformations. The Novartis safety database and pregnancy registries in six countries were identified. A total of 248 pregnancies involving maternal exposure to oxcarbazepine monotherapy and 61 involving adjunctive therapy were identified. There were six malformations among the monotherapy group, equating to a malformation rate of 2.4% (6/248). A malformation rate of 2-4% was reported in the general population. There were four malformations associated with oxcarbazepine adjunctive therapy, equating to a malformation rate of 6.6% (4/61).

Zonisamide is chemically related to a sulfonamide with the active ingredient zonisamide, 1,2-benzisoxazole-3-methanesulfonamide. It exerts its anticonvulsant activity through actions at sodium and calcium channels. It blocks sodium channels and reduces voltage-dependent, transient inward currents (T-type Ca 2+ currents), thus stabilizing

neuronal membranes and suppressing neuronal hypersynchronization. It does not appear to potentiate the synaptic activity of GABA and though it is a carbonic anhydrase inhibitor this does not appear to contribute to its anticonvulsant properties. In animal models it was found to be effective against tonic extension seizures induced by maximal electroshock but ineffective against clonic seizures induced by subcutaneous pentylenetetrazol. It is approved in the United States for adjunctive treatment of partial and generalized seizures. Off-label uses have included treatment of tremor in Parkinson's disease, for obesity, for migraine prevention and as a mood stabilizer. It is dispensed as 25mg, 50mg and 100mg tablets and dose for partial seizures ranges from 100-600mg/day in adults divided qd-bid. Treatment should be initiated at 100mg qd and titrated up q 2 weekly. It has a long half-life of 63 hours, 62% is excreted through the urine (35% unchanged). It should be titrated slowly in patients with hepatic and renal insufficiency especially for CrCl<50. Use should be avoided in patients with known hypersensitivity to sulfonamides, those with a history of nephrolithiasis and in pregnancy. Zonisamide was demonstrated to be teratogenic in rats and dogs. In a study by Kondo et al. twenty-six offspring exposed to zonisamide with or without other antiepileptic drugs (AEDs) were studied. Malformations were detected in 2 offspring (7.7%) exposed to zonisamide polypharmacy. Anencephaly was detected in one case at 16 weeks of gestation and atrial septal defect was detected in another case at 37 weeks of gestation. Thus it should be used in pregnancy only if the benefits outweigh the risk to the fetus.

CONCLUSION

For over eight decades, antiepileptic drugs have been successfully used for treatment of epilepsy. Effective use of antiepileptic drugs involves careful consideration of a patient's particular seizure type in conjunction with monitoring of drug levels and meticulous attention to side effects. Adequate seizure control can be achieved in the majority of patients with epilepsy. The future for patients with epilepsy looks promising as new drugs are developed and more experience is gained with newer modalities such as neurostimulation.

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