ORIGINAL ARTICLE

A quick review of carbamazepine pharmacokinetics in epilepsy from 1953 to 2012

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Background: Carbamazepine has been used as AEDs since 1965, and is most effective against partial seizures. Two basic mechanisms of action have been proposed: 1) enhancement of sodium channel inactivation by reducing high-frequency repetitive firing of action potentials, 2) and action on synaptic transmission. The aim of this study was to provide a review of carbamazepine pharmacokinetics and its management guidelines in Iranian epileptic population. **Materials and Methods:** Directory of Open Access Journals (DOAJ), Google Scholar, Pubmed (NLM), LISTA (EBSCO), Web of Science were searched; 1600, 722 and 167 research and review articles relevant to the topics; carbamazepine pharmacokinetics, carbamazepine pharmacokinetics in epilepsy and review on carbamazepine pharmacokinetics in epilepsy were found, respectively. **Results:** Carbamazepine is highly bound to plasma proteins. In patients the protein-bound fraction ranged from 75-80% of the total plasma concentration. Bioavailability ranges from 75-85%. The rate or extent of absorption was not be affected by food. It is completely metabolized and the main metabolite is carbamazepine-epoxide (CBZ-E). Carbamazepine induces its own metabolism, leading to increased clearance, shortened serum half-life, and progressive decrease in serum levels. Increases in daily dosage are necessary to maintain plasma concentration. Severe liver dysfunction may cause disordered pharmacokinetics. In cardiac failure, congestion of major vital organs, including kidneys, may result in abnormally slow absorption and metabolism. **Conclusion:** Carbamazepine shows variability due to its narrow therapeutic window. Therefore clinical management in a3n Iranian epileptic population should focus on results derived from therapeutic drug monitoring in order to reduce inter and intra- individual variability in plasma drug concentrations.

Key words: Carbamazepine, epilepsy, epoxide, pharmacokinetics, review

INTRODUCTION

Carbamazepine ($C_{15}H_{12}N_2O$) is a tricyclic compound that is most efficient against partial seizure with or without secondary generalization. The introduction of carbamazepine into the area of epilepsy specified a new phase to control epileptic attacks. Carbamazepine was discovered by chemist Walter Schindler in Switzerland (1953). It was first marketed as a drug to treat trigeminal in 1962 and has been used as an anticonvulsant and antiepileptic in the UK since 1965, and has been approved in the US since 1974[1-3] Epilepsy is a widespread continual neurological turmoil illustrated by seizures. Carbamazepine is an anticonvulsant and mood-stabilizing drug used mainly in the management of epilepsy, bipolar disorder (trigeminal neuralgia), attention-deficit hyperactivity disorder (ADHD), schizophrenia, phantom limb syndrome, complex regional pain syndrome, paroxysmal extreme pain disorder, neuromyotonia, disorder, borderline, and post-traumatic stress disorder (such as postcerbervascular accident thalamic pain). Carbamazepine might exacerbate juvenile myoclonic epilepsy, so it is important to uncover any history of jerking, particularly in the morning, prior to starting the drug. It may also worsen other types of generalized seizure disorders, particularly absence seizure.[4-9] Overload depolarization due to relentless sodium incurrent and also a disparity between inhibitory neurotransmitter and excitatory neurotransmitter are epileptogenic. In highly strung cells such as neurons sodium channels are accountable for the mounting part of exploit potentials. Sodium channels are vital covering proteins, which figure ion channels, caring out sodium during a cells plasma covering. In addition to diminution associated with high-occurrence rhythmic release of action potentials, carbamazepine also increases the inhibitory neurotransmitter GABA (gamma amino butyric acid) and decreases excitatory neurotransmitter glutamate (Glue). Generally, carbamazepine decreases neuronal excitability or enhances inhibition by altering sodium, potassium or calcium conductance or by affecting the δ-aminobutiric acid (GABA), glutamate or other neurotransmitters that may be concerned in seizure activity. Carbamazepine binds to the inactivated Na^+ channel and slows renewal inactivation. It also detains Ca^{++} entry into synaptic membranes. It depresses synaptic function and potentiation is reduced only in supratherapeutic levels. Carbamazepine obstructs catecholamine uptake at high concentrations. As it is

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chemically connected to the tricyclic antidepressants, it inhibits biogenic amine reuptake. Binding of carbamazepine to two subtypes of adenosine receptors, A_1 and A_2 would allow broad binding to occur at remedial meditations. Therefore carbamazepine acts throughout action at the A_1-receptor subtype as potent inhibitory manipulate adenosine on neuronal action and neurotransmitter discharge. Carbamazepine acts as an antagonist at these receptors and would be expected to increase neuronal excitability. Extended period related to prescription of drug results in an augmented amount of A_1 required location that could be linked with diminished sensitivity to systemically ordered drug.[10-14] Carbamazepine shows wide inter- and intra-individual variability that even in standard doses might cause convulsion, central nervous system toxicity or many other side-effects. As clinical management of this drug needs an individualized scheduled program, the aim of this study was to provide a review of the pharmacokinetics of carbamazepine and its management guidelines in an Iranian epileptic population.

MATERIALS AND METHODS

Data of this review were collected from our previous studies and experiences plus Directory of Open Access Journals (DOAJ), Google Scholar, Pubmed (NLM), Library, Information Science and Technology Abstracts (LISTA, EBSCO publishing) and Web of Science with key words relevant to "Carbamazepine, *Pharmacokinetics, Toxicity, and Seizure*".

RESULTS

1600 research and review articles relevant to the topic carbamazepine pharmacokinetics directly or indirectly have been found and the following features related to the kinetics of the drug in patients with epilepsy have been drawn out. Table 1 shows pharmacokinetic data. Carbamazepine is a highly lipid soluble which slowly dissolves in gastrointestinal fluid. There are no bioavailability data for neonates or infants, but physical chemical characteristics suggest deprived and inconsistent absorption in these groups.[15,16] The expected therapeutic range for carbamazepine in children as in adults is 4 to 12 ng/ml. In children receiving continuation treatment, the suspension is absorbed more quickly than are tablet formulations, resulting in a considerably earlier time to attain greatest serum concentration (T_{max}, C_{max}). The faster rate of absorption occasionally produces transient concentration-dependent central nervous system side-effects. Smaller doses given more frequently will usually correct this problem. Additional increases in maintenance doses may give rise to additional induction. In some children plasma concentrations continue unchanged or even decline despite doses as high as 40 to 50 mg/kg/day. Many deteriorating children require three or four daily doses to keep therapeutic plasma concentrations. Convulsion may be prohibited at comparatively inferior levels, and harmful effects may emerge at concentrations within the proposed remedial range, perhaps as a consequence of the high metabolite-to-parent drug concentration ratio in children. Concentration of CBZ-E and clearance of carbamazepine in children are higher than in adults for the respective parent-drug concentrations and these levels correlate to some degree with associated drugs, age, and sex.[17,18] It seems that carbamazepine tablets are significantly less well absorbed after prolonged exposure to high humidity.

Table 1: Carbamazepine pharmacokinetic data in epileptic patients[1-55]

Pharmacokinetic data[1-55]
Target trough Level (C_0): 4-12 mg/ml
Bioavailability (F): 75-85%
Volume of distribution (Vd): 0.8 to 1.2 l/kg
Time to reach steady state concentration: After beginning treatment, due to autoinduction 3-5 weeks
Time to reach maximum concentration (C_{max}): 4-8 h, in some patients 24-28 h

Metabolism=Hepatic through CYP450; Main metabolite: Carbamazepine-epoxide

DISCUSSION

Carbamazepine plasma protein binding reaches 70-80% and elimination depends almost entirely on hepatic biotransformation by expoxidation and hydroxylation. The elimination half-life is approximately 15 h. Because only 1% of carbamazepine is eliminated unchanged in urine, accumulation of parent drug or the epoxide metabolite is unlikely. Dose adjustment is not needed in either renal disease or dialysis. Close monitoring of serum levels of carbamazepine and the 10, 11 epoxide should be maintained, however, especially with long-term administration in patients with liver dysfunction. Carbamazepine is mainly eliminated by the cytochrome P-450 system and has an active metabolite. Its major metabolite, carbamazepine epoxide is an active anticonvulsant and is thought to have the same mechanism of action. Carbamazepine undergoes autoinduction in which clearance increases over time following exposure to the drug e.g., within 30 days after therapy begins, clearance increases by 300%. The half-life of carbamazepine ranges from 10 to 20 h but diminishes with autoinduction to 4 to 12 h.[19-24] The metabolite-to-parent-drug concentration ratio is markedly higher and adverse effects result when valproic acid is given concomitantly with carbamazepine. This increase in ratio could be due to either an enhanced carbamazepine clearance or an inhibition of CBZ-E clearance.[25] Carbamazepine is effective in the elderly for the control of both partial and generalized seizures. Metabolism of CBZ-E can also be induced by phenytoin or phenobarbital, resulting in a 100% increase in clearance.[26] Elderly patients may be more susceptible than younger patients to embarrassment or nervousness, atrioventricular heart block, and bradycardia. Hyponatremia is not occasionally connected with carbamazepine use in the elderly and is linked to variation in antidiuretic hormone regulation. Guided by plasma concentrations and clinical response in the elderly, carbamazepine could be initiated at 100 mg twice daily, instead of the usual recommended dose of 200 mg/day twice daily, and adjustments of doses to 100 mg/day each week rather than the standard recommendation of 200 mg/day. The dose is adjusted to the minimum effective maintenance dosage, usually 600 mg/day to 1.6 g/day.[15] Common adverse effects seen are drowsiness, headaches, migraines, motor coordination destruction and distress stomach. Less common side-effects may include cardiac arrhythmias, blurry or double vision, temporary loss of blood cells or platelets and in rare cases can cause aplastic anemia. With standard consume small reductions in white cell count and serum sodium is ordinary. In rare cases, the loss of platelets may become life-threatening. In this case frequent blood tests during the first few months of use could be followed by three to four tests per year for established patients. Additionally, carbamazepine may possibly exacerbate preexisting cases of hypothyroidism, so yearly thyroid function tests are advisable for persons taking the drug.[27-35] A 0.5% risk of spina bifida was described in children exposed to carbamazepine in polytherapy. The mechanism of carbamazepine teratogenicity is unknown. The highest rates of malformations among infants exposed to AEDs were in those exposed to carbamazepine, phenobarbital, and valproate simultaneously *in utero* and it was hypothesized that the increased metabolites were responsible.[36,37] Carbamazepine has capability for drug interactions. Cytochrome P450 enzymes are important for the metabolism of several drugs such as numerous AEDs.[38-46] Induction could affect enzymes involved in endogenous metabolic pathways, and can alter bone biochemistry, gonadal steroids, and lipid markers. Therefore, enzyme-inducing AEDs may contribute to the development of a number of comorbidities, including osteoporosis, sexual dysfunction, and vascular disease. Upon commencement of carbamazepine treatment, concentrations are predictable and follow individual pharmacokinetic parameters established for the specific patient. When the dosage of drug increasing, the CYP^3A^4 activity increasing. Subsequently clearance of drug speeding up and half-life become shortening which is called autoinduction. Autoinduction will continue with subsequent increases in dose but will usually reach a plateau within 5-7 days of a maintenance dose. Increases in dose at a rate of 200 mg every 1-2 weeks may be required to achieve a stable seizure threshold. Stable carbamazepine concentrations occur usually within 2-3 weeks after commencement of treatment. In combination of carbamazepine with valproic acid microsomal epoxide hydrolase; mEH (the enzyme in charge for the analysis of carbamazepine-10,11 epoxide into inert metabolites), could be restrain by valproic acid. By inhibiting mEH, valproic acid causes a buildup of the active metabolite, prolonging the effects of carbamazepine and delaying its excretion. The combination of valproate and carbamazepine results in increased concentrations of carbamazepine 10-11 epoxide. Lower levels of carbamazepine are seen when administrated with phenobarbital, phenytoin or half-life primidone. Drugs that are more rapidly metabolized with carbamazepine include warfarin, lamotrigin, phenytoin, theophylline, and half-life valproic acid. Drugs that decrease the metabolism of carbamazepine or increase its levels include erythromycin, cimetidine, propoxyphene, and calcium channel blockers. Carbamazepine also increases the metabolism of the hormones in birth control pills and can reduce their effectiveness, potentially leading to unexpected pregnancies. As a drug that induces cytochrome P450 enzymes, it accelerates elimination of many benzodiazepines and decreases their action. Grapefruit juice increases the bioavailability of carbamazepine by inhibiting CYP^3A^4 enzymes in the gut wall and in the liver.[47-51] Carbamazepine increases the risk of developing lupus,[52] auditory side-effect.[53-55] Carbamazepine has been linked to serious adverse cognitive anomalies and apoptosis of cultured cerebellar neurons. Patients with a particular human leukocyte antigen allele, HLA-B*1502 (HLA-A*3101 among Japanese) are significantly more common for Stevens–Johnson syndrome and toxic epidermal necrolysis.[30-55]

CONCLUSION

In conclusion many issues alter the comparative properties of carbamazepine concentration and its' relative enzyme affinity related to metabolic drug interactions. Substantial inter-patient inconsistency occurs with admiration to the enzymatic activity of the CYP450 isoenzymes. In spite of the recognized strategies for carbamazepine prescription and subsequently its management in epileptic patients, the question of monotherapy or polypharmacy, needs further investigation. Finally, carbamazepine should be prescribed in a rational basis based on therapeutic drug monitoring in Iranian epileptic population.

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