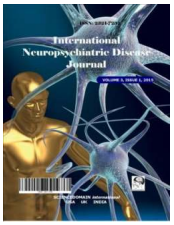

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Therapeutic Serum Concentration Measurement of Oxcarbazepine in Epilepsy Patient

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Authors' contributions

This work was carried out in collaboration between all authors. Authors Rakshya Koirala and Ramesh Khadka designed the study. Author Rakshya Koirala undertook all experimental procedure, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author Ramesh Khadka managed the analyses of the study and the literature searches. Author Wangmengmeng managed the case collection. Author WJ reviewed the study and draft of manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To study measurement of the therapeutic serum concentration of Oxcarbazepine (OXC) in children diagnosed with epilepsy and to analyze the relationship among the serum drug concentration of OXC based on drug dose/weight. To observe therapeutic range of OXC to provide them a reference basis for the effective treatment plan (dose of drug, effectiveness of ongoing drug, adverse reactions). This will help us to make an early decision on the plan of treatment and management to ensure the quality rehabilitation and good prognosis.
Place and Duration of Study: The study was performed in Jiamusi Central hospital, China from Jan. 2016 to May. 2016.
Objective: To measure the therapeutic serum concentration of Oxcarbazepine (OXC) in 33 Chinese children diagnosed with epilepsy. To investigate and study the association of serum drug

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concentration of OXC based on drug dose/weight and clinical effects. The aim of our research is to understand the basis of therapeutic range of OXC and possibility of their practical significance as a reference basis for effective treatment plan, thus, helping us to make an effective decision on the plan of treatment and management to ensure quality rehabilitation and good prognosis.
Methodology: Thirty-three cases (18 girls,15 boys: age range 3-12 years) were considered based on strict eligibility criteria for Epilepsy along with clinical examination and EEG. From all patients, 100 µl venous blood sample was drawn and sent for API 3200 SERIES HPLC (High performance liquid chromatography): MHD standard for further analysis. Data analysis was performed from obtained measured serum OXC valued using SPSS20.0 Statistical software.
Results: From blood samples of thirty-three epileptic patients, our result showed the mean plasma level of MHD was 11.9 mg/l (mean range 3.44 mg/l to 17.045 mg/l), with mean OXC dose 20.32 mg/kg/day (mean range 5.5 mg/kg/day to 32.14 mg/kg/day) prescribed for 3 weeks to 6 months. Even at lowest serum OXC concentration 3.44 mg/l, seizure was well controlled with no adverse toxicity. Complete seizure control attained among eleven patients. OXC exhibits a linear relationship between drug dose/weight and serum OXC concentration ($r=0.0728$, $p< 0.01$); independent to sex and age. 2 cases out of 33 was found to be drug resistant epilepsy.
Conclusion: Our study provided us a time window determination for the effective treatment choice, complete control of epileptic seizures drug resistant epilepsy and no serious side effects were documented. Based on our findings, routine practice of measuring OXC concentration in epilepsy can be a clinical significance. However, further research is required to validate our hypothesis.

Keywords: Oxcarbazepine (OXC); Epilepsy; Anti- epileptics; HPLC; MDH; therapeutic drug concentration.

ABBREVIATION

TDM : Therapeutic drug monitoring
AED : Anti Epileptic Drug
OXC : Oxcarbazepine
EEG : Electroencephalography
HPLC : High performance liquid chromatography

1. INTRODUCTION

1.1 Epilepsy

Epilepsy is a group of neurological disorders characterized by an enduring predisposition to generate epileptic seizures that vary from brief duration to long duration caused by excessive, abnormal or synchronous activities of neurons in the brain leading to neurological, cognitive, psychological and social consequences of this condition. A seizure is defined as a transient occurrence of signs and symptoms resulting from abnormal excessive neuronal brain activity. Seizure disorder includes several disorders, including epilepsy, febrile seizures, secondary seizures, etc. Epileptic syndrome manifests specific seizure types on specific age of onset or other etiologies and specific prognosis.

Diagnosis of Epilepsy is based on: [1-3]

1. Occurrence of at least two unprovoked epileptic seizure or reflex occurring more than 24 hours apart.
2. One unprovoked seizure or reflex with probability of similar seizures after two unprovoked seizures over next 10 years with positive EEG findings and clinical information that demonstrate the predisposition that can develop recurrences in the future.
3. Diagnosis of an epilepsy syndrome.
   A person is considered to be resolved for those individuals who had an age dependent epilepsy syndrome, but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicine for the last 5 years. Diagnosis of epilepsy is made by brain imaging, blood tests, electroencephalogram [4, 5].

The clinical manifestation of epilepsy varies depending on type of epilepsy: hemifacial sensorimotor seizures, oropharyngolaryngeal ictal manifestations, arrest of speech in a form of anarthria, Hyper salivation, Syncope-like epileptic seizures may occur, as a symptom of Panayiotopoulos syndrome, Consciousness and recollection, progressing to hemi convulsions or generalized tonic–clonic seizures. Status epilepticus are often associated with continuous spikes and waves on an EEG during NREM sleep. Atypical manifestations such early age at presentation with developmental delay, atypical abnormalities in the EEG.

The underlying etiology of Epilepsy are: perinatal brain injury due to maternal infection, illness or injury during childbirth, postnatal falls, accidents, brain tumor, stroke, substance abuse, electrolyte imbalance. Following brain insults a normal brain changes to epileptic, this process of epileptogenesis is described as a prolonged high rate of nonlinear dynamic regimens of intermittent type following a potential epileptogenic insult resulting enhanced Matrix Metalloproteinase-9(MMP-9), regulated by removal from MMP-gene, DNA methylation and Poly comb repressive complex 2 (PCR2), heteromeric receptor operated cation channels, transient receptor di-hydroxy-phenyl-glycine (DHPG) generation producing epileptic discharge in hippocampus with initial phase of short discharge followed by prolonged discharge leading to excitotoxic neuronal cell death [6,7]. Seizure related neuronal injuries due to apoptosis and necrosis of neurons presents with impaired blood brain barrier as a hallmark of brain injury. Status epilepticus is common neurological emergency due to excitotoxicity, ischemia and inflammation of hippocampus. Epileptic state of increased excitability mediated by NMDA receptors via voltage gated calcium channels activating calcium calmodulin dependent protein kinase (ca MKII) and calcineurin, phosphate eventually leading to mossy fiber sprouting or intrinsic burst firing [8,9]. Abundantly released Zinc in neurological insults from hippo campus mossy fibers of synaptic vesicles inhibits metabotropic& ionotropic GABAA receptors (responsible for pre-synaptic inhibition causing depolarization or post-synaptic inhibition causing hyperpolarization) affecting dopaminergic neurons via pre-synaptic N-methyl-D-aspartate(NMDA)receptors. There exist 9% to 12% chance of epilepsy if parents have idiopathic epilepsy; higher risk of epilepsy in siblings and identical twins if one child have epilepsy; family h/0 suggests genetic determination of epileptic syndromes. However, some gene remains unidentified and some genetic conditions arise spontaneously through mutations. Single gene mutation involves Autosomal dominant partial epilepsy with variable focus, AD nocturnal frontal lobe epilepsy, Benign familial neonatal convulsions, Familial temporal lobe epilepsy, Generalized epilepsy with febrile seizure plus and progressive myoclonic epilepsies. Complex disorders involve myoclonic -astatic epilepsy, benign epilepsy of childhood with centrotemporal spikes, benign myoclonic epilepsy of infancy juvenile myoclonic epilepsy and absence epilepsy (childhood and juvenile). Other genetic disorders are Mitochondrial disorders; Chromosomal disorders (Down syndrome, Wolf-Hirsh horn syndrome, Angel man syndrome). However, the exact cause of epilepsy remains idiopathic (75%) or unknown. The occurrence of seizure remains variant according to age, intensity, frequency and remission.

1.2 International Classification Of Epilepsy {Fisher, 2017 #88}

A recent International Classification of Epilepsy 2017 have classified epilepsy under following categories: focal onset, generalized onset, unknown onset and unclassified.

i. Focal onset:

-Focal aware seizure (Simple partial)
-Focal Impaired awareness (Complex partial)

Motor onset focal seizure	Non-motor onset focal seizure
1. Automatisms 2. Clonic: focal rhythmic jerking 3. Atonic: focal loss of tone 4. Epileptic spasms: focal flexion or extension of arms and flexion of trunk 5. Hyperkinetic: thrashing and pedaling 6. Myoclonic: brief irregular focal jerk 7. Tonic	1. Autonomic: g.i.t sensations; sense of heat and cold; flushing; respiratory change; sexual arousals; goosebumps; palpitations 2. Behavior arrest: unresponsiveness; cessation of movement 3. Cognitive: Déjà vu; jamais vu; illusions; hallucinations 4. Emotional: Fear; Anxiety; Anger; Agitation; Joy; Paranoia; Ecstasy; Pleasure; Gelastic; Dacrystic 5. Sensory

ii. Generalized onset:

Motor	Non-Motor
1. Tonic -clonic	*1.* Typical
2. Clonic	*2.* Atypical
3. Tonic	*3.* Myoclonic
4. Myoclonic	*4.* Eyelid myoclonia
5. Myoclonic-tonic-clonic	
6. Myoclonic-atonic	
7. Atonic	
8. Epileptic spasms	

iii. Unknown onset:

Motor	Non-Motor
1. Tonic-clonic	Behavior arrest
2. Epileptic spasms	

iv. Unclassified:

It refers to seizures of unknown onset or associated additional motor, non-motor, epileptic spasms, tonic-clonic features.

1.3 International Classification or Epilepsy and Epilepsy Syndrome

a. Localization-related (focal, local, partial) epilepsies and syndromes (see Table 1)
b. Generalized epilepsies and syndromes (see Table 2)
c. Epilepsies and syndromes undetermined as to whether they are focal or generalized (see Table 3)
d. Special syndromes
-Situation-related seizures: Febrile convulsions; Isolated, apparently unprovoked epileptic events; Seizures related to other identifiable situations such as stress, hormonal changes, drugs, alcohol, or sleep deprivation

1.4 Antiepileptic Drugs

Category 1	Category 2	Category 3
Phenytoin	Valproic acid	Levetiracetam
Fosphenytoin	(Sodium	Lacosamide
Carbamazepine	valproate);	Tigabine
Phenobarbitone	Divalproex	Gabapentin
Primidone	Lamotrigine	Pregabalin
Ethosuximide	Perampanel	Vigabatrin
	Retigabine	
	Rufinamide	
	Clonazepam;	
	Diazepam;	
	Lorazepam;	
	Clobazam	
	Oxcarbazepine;	
	Eslicarbazepine	
	Acetate	
	Zonisamide	
	Topiramate	

The modality of treatment of epilepsy also varies with the type of epilepsy and for each individual type of epilepsy the use of drug is different. The study have shown 60-70% seizures are well controlled by anti- epileptic drugs [5,10,11]. Those who do not respond to medications, requires surgery and neuro stimulation [5]. Rehabilitation care and lifelong medications may be required in long term epileptic patients that depends on patient follow up to hospital and regular drug intake as prescribed and care [11-14].

1.5 Oxcarbazepine

Oxcarbazepine (10,11-dihydro-10-oxo-5H-benz (b.f) azepine-5-carboxamide;OXC) belongs to Mino stilbene group of antiepileptic drug, structurally derived from carbamazepine, rapidly metabolized to active 10-monohydroxy metabolite(MHD) [15]. It was introduced in 1990 as a safe and effective monotherapy as well as adjunctive therapy for treatment of partial seizures (simple/complex/partial seizures with secondary generalization); newly diagnosed epilepsy; anticonvulsant, mood stabilizing drug, treat anxiety, motor tics, bipolar disorders; BECTs; etc. [16,17] OXC blocks voltage dependent sodium channels by modulating different types of sodium channels. It is oxidized by cytochrome P-450 system and undergoes biotransformation mediated by cytosolic aryl ketone reductase enzyme to form MHD in liver, eliminated further by conjugation with glucuronic acid, glucuronidated and excreted in urine [18, 19]. Bioavailability of OXC is >95%; 1 to 5hour half- life. OXC has low potential for drug

Table 1. Localization-related (focal, generalized) epilepsies and syndromes

(1) Idiopathic with age-related	(2) Symptomatic	(3) Cryptogenic
onset: a. Childhood epilepsy with occipital paroxysms b. BECTs	a. Chronic progressive epilepsia partialis continua of childhood b. Syndromes characterized by seizures with specific modes of precipitation: Parietal lobe epilepsies Occipital lobe epilepsies Frontal lobe epilepsies Temporal lobe epilepsies	

Table 2. Generalized epilepsies and syndromes

(1) Idiopathic, with age-related onset (listed in order of age)	**(2) Idiopathic /symptomatic (listed in order of age)**	**(3) Symptomatic** **Nonspecific etiology**
a. Benign neonatal familial convulsions b. Benign neonatal convulsions c. Benign myoclonic epilepsy in infancy d. Childhood absence epilepsy (pyknolepsy) e. Juvenile absence epilepsy f. Juvenile myoclonic epilepsy (impulsive petit mal) g. Epilepsy with grand mal seizures on awakening h. Other generalized idiopathic epilepsies not defined above i. Epilepsies with seizures precipitated by specific modes of activation	a. West syndrome (infantile spasms) b. Lennox-Gas taut syndrome c. Epilepsy with myoclonic-astatic seizures d. Epilepsy with myoclonic absences	a. Early myoclonic encephalopathy b. Early infantile epileptic encephalopathy with suppression burst c. Other symptomatic generalized epilepsies not defined above **Specific etiology** Epileptic seizures may complicate many disease states

Table 3. Epilepsies and syndromes undetermined as to whether they are focal or generalized

- *With both generalized and focal seizures*	*-Without unequivocal generalized or focal features*
Neonatal seizures	
Severe myoclonic epilepsy in infancy	
Epilepsy with continuous spike waves during slow-wave sleep	
Acquired epileptic aphasia (Landau-Kleffner syndrome)	
Other undetermined epilepsies not defined above	

interaction with other antiepileptic drugs. It is an inducer of CYP3A4 and CYP3A5, weak inhibitor of CYP2C19, may increase the serum concentration of phenytoin and phenobarbital and decrease plasma hormone levels of oral contraceptives. The considerable variation of therapeutic ranges of MHD falls between 10-35 microgram/ml. Various pharmacological agents like oxcarbazepine, lamotrigine, levetiracetam, topiramate, zonisamide has been widely undergone rapid liquid chromatography-tandem mass spectrometry method and MHD in human serum. HPLC is simple, accurate and effective method helps us to determine relation between the active metabolite of different drugs like OXC and its concentration and the dose adjusted, dose clearance or adverse effects on combination of drugs [20,21]. The common side effects of OXC are nausea, vomiting, dizziness, headache, diplopia, ataxia, somnolence, symptomatic hyponatremia (<125 mmol/l), neurotoxicity, cutaneous hypersensitivity reactions [15,22]. The narrow therapeutic ranges of AEDs have more serious side effects. Bipolar disorders like manic depression, fibromyalgia, trigeminal neuralgia, or migraine headaches are more common with older AEDs signifying importance of TDM to assess the drug compliance and toxicity. The factors that favor TDM: auto induction with chronic dosing, liver failure, variable metabolism, potential for severe toxicity, renal failure, extensive first-pass metabolism, high serum protein binding, drug-drug interactions, well

defined toxic concentrations, use in pregnancy. The factors that limit the use of TDM are: active metabolite, unclear toxic concentrations, wide range of clinically effective serum concentrations, low incidence of drug toxicity, short half-life, high serum protein binding that may complicate total drug concentration interpretation. Optimal therapeutic effect and minimal toxicity is achieved through MHD monitoring. OXC is rapidly absorbed after oral administration and reached peak concentration within about 1-3 hours after single dose. The peak MHD occurs within 4-12 hours. At steady state, the peal of MHD occurs about 2-4 hours after drug intake. About 40% are plasma bound. Cerebral fluid concentration of MHD are in same range as unbound plasma concentration of MHD. Typical dose of OXC is 600-2400 mg/day in divided doses. As a monotherapy 2400 mg/day is effective in treatment of refractory partial seizures in adult patients. As an adjunctive therapy, OXC 600, 1200 and 2400 mg/day is effective to reduce frequency of seizure and refractory partial seizures. In children (6-18years) initially 8-10 mg/kg increasing weekly by similar doses to maximum 46mg/kg in divided doses. [17] At low to moderate doses, OXC is effective for treatment of patients with newly diagnosed, previously untreated partial epilepsy, and a longer time interval from the onset of epilepsy to start of treatment significantly predicted poor seizure control. OXC widely used in patient with Dravet syndrome, however drug withdrawal is risky and close monitoring is beneficial. Child with BECTs under OXC maintenance therapy induced genetic polymorphisms (SCN1, UGT2B7 and ABCC2) are associated with OXC maintenance doses and useful for personalization of OXC therapy in epileptic patients. The tentative therapeutic range of OXC is 12-24 mg/l (48-95µmol/l). Study done by Striano, 2006 #82, have shown that MHD serum concentration > or = 30 mg/l are at greater risk of developing adverse side effects and the adverse effects are found to be fluctuating with serum MHD, thus TDM can help in analysis and management of OXC therapy.

The purpose of this study is to investigate TDM that helps to measure and interpret its concentration to optimize drug therapy and its clinical outcome to minimize the risk of drug induced toxicity. Use of TDM in drugs with narrow therapeutic index, protein bound drugs, drug interaction and toxic metabolites is highly beneficial. It will help us to decide whether adverse effects are dependent on MHD concentrations. However, more systematic studies exploring the concentration-effect relationship are required.

2. MATERIALS AND METHODS

2.1 Patient sample

Thirty-three children were enrolled in this clinical study conducted in the inpatient and outpatient department of epilepsy and rehabilitation in Jiamusi Central hospital between Jan 2016 to May 2016, evaluated clinically and included for study if they met the eligibility criteria for the study, in accordance with the definition of the International League Against Epilepsy. Informed consent was obtained from all parents of participants approved by institutional review boards.

2.2 Clinical Evaluation Criteria

Inclusion criteria:	**Exclusion criteria:**
1. Age of onset between 3 to 12 years, able to give informed verbal consent either themselves or parents. 2. Study group includes status epilepticus, febrile/nonfebrile convulsions, generalized seizure, simple/complex partial seizures, temporal lobe epilepsy, BECT, absence seizure or any other epileptic conditions who receive AEDs for at least six months or more. Normal developmental and neurological examination. 3. Principal characteristics: speech arrest, drooling of saliva, lip and lateralization, twitching of angle of mouth, facial numbness, generalized tonic clonic movements. Classical	1. Acute epilepsy caused by intracranial disease 2. Severe mental illness or other systemic diseases such as cognitive dysfunction, neurological disease 3. Systemic diseases (heart, lung, liver, hematological) rule out. 4. Patient who refused to give informed consent for the study. 5. Patient who are unable to follow up. ***Evaluation and outcome standards:*** *Control*: No attack *Effective*: Reduced seizure frequency by 50% or above

	BECTs: orofacial pharyngeal sensorimotor symptoms with speech abnormality and hyper salivation. Patient with at least 2 EEGs consistent with spikes in one or both centrotemporal region and normal background.	*Aggravated*: Seizure frequency not subsided *Treatment Failure*: Ineffective seizure control or intolerable adverse drug reactions or both or combined with other antiepileptic drugs.
4.	Suggestive EEG findings for epilepsy. Patient with normal neuroimaging that excluded alternative structural, inflammatory or metabolic causes for seizures.	*Treatment of seizure control/ attack control*: When aby form of epilepsy in childhood does not occur with at least 1 year.

2.3 Materials

HPLC (API 3200 series): MDH standard (Jiuhou pharmaceutical in Shanghai Bell Company limited, purity greater than 99%), a vortex mixer, centrifuge: Denver Instruments, constant temperature water bath, 4ºC refrigerator, microwave oven (MO-2270M1), 721 spectrophotometers, refrigerator, micropipette, test tube and kits.

2.4 Blood Sampling, Processing and Data Analysis

Thirty three blood samples was obtained after 2 hours of medicine intake for estimation of serum levels of OXC (after dose stabilization), creatinine, alanine transaminase, aspartate transaminase and albumin 100 µl venous blood was extracted from vein in heparinized 5ml tube, 10% 50 microliter perchlorate added, vortex mixing done and kept at room temperature 60 minutes, then centrifuged at 12000 rpm for 15 minutes, 20 µl supernatant fluid injection taken, centrifugal clear liquid stored in EP tube seal at 4ºC in a freezer for measurement and send for HPLC determination of MHD serum concentrations. The chromatography 18 columns (4.6 mm × 100, 5 µm), the mobile phase for methanol: 0.1% acetic acid (38:62), flow rate 1ml/min with a run time of 6min, oven temperature set at 25ºC, chromatograph was read at a detection wavelength 215 nm, MDH peak time 5-6 minutes. From the result obtained from all subjects, descriptive analysis was done using SPSS 20.0 statistical software to mean, *P* value, correlation with linear correlation analysis, $0.01 \leq P < 0.05$ statistically significant, $P < 0.01$ is highly statistically significant.

3. RESULTS

From blood samples of 33 (18 girls & 15 boys) epileptic patients, our result showed the mean OXC dose given to the patient was 20.32 mg/kg/day (range 5.5 mg/kg/day to 32 mg/kg/day) for 3 weeks to 6 months mean serum concentration level of MHD was 11.9 mg/l (range 3.4 mg/l to 17.04 mg/l) prescribed with mean oxcarbazepine dose. The minimum effective concentration of drugs found to be 3.44 mg/l and maximum safe concentration found to be 17.04 mg/l. OXC was well tolerated and no significant side effects were identified. There was a significant linear relationship between dose/weight and plasma concentration found to be ($r = 0.0728$, $P < 0.01$); independent of age and sex. Despite of administration of effective antiepileptic drug dose, poorly controlled epilepsy is considered to have poor prognosis. However, none of our cases suggested poor prognosis. In our study, the OXC serum drug concentration preferably at lowest effective concentration level is capable of controlling symptoms. 2 cases (0.06%) were found to be drug resistant, 11 cases (0.33%) achieved complete remission/ seizure free, 10 cases (0.30%) showed >50% reduction in seizure frequency per week.

4. DISCUSSION

TDM for AEDs are likely to benefit to measure individual therapeutic concentration in order to assess potential cause for change in drug response; long term observation for any therapy for seizure control has clinical benefit; diagnosis of clinical toxicity; to assess the clinical efficacy of AEDs; to check the compliance in patients with uncontrolled seizures or breakthrough seizures; helps us to guide dose adjustment whenever there exists pharmacokinetics, pharmacodynamics and therapeutic range variability. The pharmacokinetics variability depends on impaired organ function (kidney or liver), Pharmacogenetics or drug/substance interaction. OXC pharmacokinetics are altered in patients with renal insufficiency since clearance of drugs or metabolites and dialysis procedure clears OXC which has low degree plasma protein binding. Hence, we are concerned about OXC serum concentration measurement which is a monotherapy or adjunctive therapy for various epilepsy. Monitoring of OXC in saliva is easy in

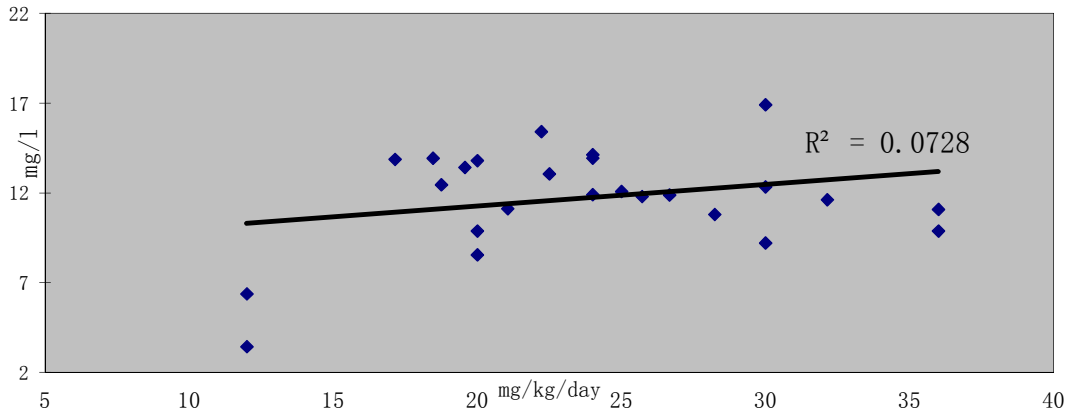

Fig. 1. OXC serum concentration measurement

pediatric population however due to short half-life and low concentration 5-10% less compared to serum, serum was preferred in our study. Since the serum concentration are affected by tolerance of drug, irreversibility of drug action and active metabolites, measurement of active metabolites or pro drug or both can be done. We measured a major metabolite, 10-hydroxycarbazepine concentration.

TDM in our study helped us to establish individual patient's serum optimal plasma concentration range. We identified at what serum concentrations, seizures are restrained or AEDs adverse effect could possibly occur.

Based on our study, routine analysis of AEDs monitoring has high significance in clinical settings. Out of 33 cases, 2 cases were found to be drug resistant. 1 case was absence seizure and was diagnosed with bilateral temporal lobe epilepsy, while the other was hypoxic brain injury and kept for further evaluation. Few cases presented with common side effects like nausea, vomiting and headache; were managed conservatively. The serum concentration of these patients was within or below the normal tough levels of serum OXC and had no correlation with these side effects. No patients showed signs of toxicity. TDM aided our clinical management for BECTs who were under OXC maintenance therapy. No cases of BECTs documented OXC induced genetic polymorphisms. Based on TDM, the OXC dose was adjusted. The duration of time window determination of appropriate management was increased with TDM, frequency of seizures was controlled, complete control of epileptic seizures was attained among eleven patients, with no serious adverse effects.

The normal therapeutic range of OXC is 12-24 mg/l (48 to 95 µmol/l). A previous study determined the relationship between serum MHD and adverse effects in series of patients taking OXC for treatment for drug-resistant epilepsy. In this study, we found that the serum MHD concentration > or equal to 30 mg/l was associated with higher risk to develop adverse effects. In our study, the mean therapeutic range was 3.44 mg/l to 17.04 mg/l with mean OXC dose 5.5 mg/kg/day to 32 mg/kg/day. Within this range of OXC therapy patient had an optimal therapeutic response to drugs, seizure was well controlled with minimal or no serious adverse effects. Further studies on large population sample may be requires to elicit adverse effects associated with high dose OXC. We found a linear relationship between drug dose/ weight and serum OXC concentration. Sex and age did not influence the serum OXC concentration. For newly diagnosed patients, previously untreated partial epilepsy, and in poorly controlled seizures of longer duration from the onset of epilepsy to start of treatment, seizures were well controlled now even with low to moderate doses of OXC in our study group. In our study, low dose 5.5 mg/kg/day achieved seizure control in newly diagnosed cases. We believe patients under OXC therapy are suitable for routine use of TDM in clinical practice as it provides a better trough level for effective control of seizure and minimize toxicity. There is a need for monitoring the serum levels of newer AEDs like OXC considering the various parameters like dose, gender, dosage forms, clinical efficacy, adverse drug reactions and drug toxicity to help appropriate prescribing.

Our study was the hospital based observation with small sample to explore clinical base for TDM and optimal drug prescription with a hope to make an easy and early decision on plan of management. We were able to ensure the quality life, good prognosis and better rehabilitation on our patient. Drug resistant epilepsy was easily determined. This study only helped us to know insufficient seizure control due to inadequate dosing or drug overdose. Adverse side effects may occur even at lower concentrations; however, it did not occur in our study. We evaluated only thirty-three children and our study maintained the therapeutic drug range for their effective treatment with no adverse effects. Clinical decision should not be made on the basis of drug concentration alone. However, further research in the large number of epileptic children may require to evaluate the effectiveness of the routine practice of TDM of OXC. The importance of measuring routine therapeutic serum concentration might be useful in patients with newly diagnosed epilepsy, in special situations and in selected patients.

5. CONCLUSION

Based on our study and results, TDM of OXC enabled us to make decisions and effective optimization of therapy for our patients. OXC exhibits a linear relationship between drug dose/ weight and serum OXC concentration; sex and age being independent. At a lower serum concentration of OXC, the seizure was well controlled, drug resistant epilepsy was diagnosed. We hereby hypothesize that the routine practice of measuring OXC serum concentration can provide us a better trough level for effective control of seizure and reduces drug toxicity in patients with newly diagnosed, drug resistant epilepsy, in special situations and in selected patients; to know the progression of disease and management; ensure quality life, good prognosis and rehabilitation.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying data.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by appropriate ethics committee and have therefore been performed in accordance with the ethical standard fade down in the 1964 declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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