AN EXPERIMENTAL DESIGN FOR FINDING OF MINIMUM DOSAGE OF CARBAMAZEPINE AND VALPROATE IN PREVENTING OF SEIZURE ATTACKS

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ABSTRACT

Previous studies have shown that physicians use high doses of Carbamazepine (CBZ) and Valproate (VPA) to control of epileptic attacks, while these drugs incur of many side effects include of gastrointestinal, hematologic, psychiatric, cardiac and other side effects. The aim of this study was to determine the minimum therapeutic dose with and an acceptable blood level of these drugs.

This semi-experimental study was done in 56 epileptic patients in during of one year. At the first demographic data including of age, sex, weight and the period of drug taking was recorded. Then the drug CBZ and VPA were prescribed to adults (more than 12 years old) 9-11 mg/kg and 12-14 mg/kg respectively, and in children (less than 12 years old) 12-14 and 12-15 mg/kg respectively. Serum levels of CBZ and VPA were measured monthly by gas chromatography method that is separation technique, is mostly employed in chemical analysis.

The results indicated that serum levels of CBZ and VPA in adult were 7.4 and 74.7 and serum levels of drugs in children were 8.2 and 66.8 respectively. Also patients have not epilepsy attack in during the period of assessment.

These findings showed that with a much lower dosage of the drugs, which is suggested in texts can lead to an appropriate blood level of CBZ and VPA for controlling the epileptic seizures.

Keywords: Epilepsy, carbamazepine, valproate, seizure.

INTRODUCTION

Epilepsy is one of the disorders with chronic, recurrent and sudden changes in neurological function due to electrical abnormalities of cerebrum (Ronen *et al.,* 2003, Kasper *et al.,* 2005). Convulsion is the clinical manifestation of epilepsy that is usually without stimulating factors and is noticed with decreasing level of consciousness with or without abnormal movements. The prevalence of disease is more common among children (Meyer *et al.,* 1990) and elderly, in which men have a little more likelihood of getting seizures. Previous studies have shown that around forty five million through out the world are suffering from epilepsy (Andreoli *et al.,* 2004, Marson *et al.,* 1996) and is estimated that between 0.5 and 2 percent of the population could acquire this disorder at any age (Kasper *et al.,* 2005). Experiments have shown that uncontrolled seizures could be associated with great emotional complications that as a result will increase the percentage of depression, despair and suicide among patient (Andreoli *et al.,* 2004). Experiments have revealed that controlling the seizures can help the patients to pursue the scientific, artistic and business life normally. Therefore taking the seizures under control is the best we can do to help the patients (Ronen *et al.,* 2003; Andreoli *et al.,* 2004). Treating an epileptic patient consists of finding the cause of seizures, preventing the seizures appearance and encountering the psychosocial after math's (Kasper *et al.,* 2005). The aim of therapy is to prevent seizures in protecting normal mental activities, without letting dangerous systemic side effects (Reynolds and Murthy 1989) to appear while the essential treatment is drug therapy (Czapinski and Terczynski 1996; Marson and Chadwick 2001). One of the basic problems of epileptic patients is the steady usage of drugs and at the same time keeping the level of drugs at an acceptable level, in order to prevent seizures. It is also suggested that if possible one drug should be used with its minimal effective dosage and only one drug should be prescribed (Kasper *et al.,* 2005). Among drugs that are being used, CBZ and VPA are noticeable. These two are the first line drugs for most attacks (Czapinski and Terczynski, 1996). VPA is responsive to generalized tonic-colonic seizure (Kasper *et al.,* 2005). These prescribed drugs are effective as Phenytoin yet don't have the side effects of Phenytoin, and still maintain the mental cognitive mechanisms at a good level (Prevey *et al.,* 1996). But these drugs like other drugs have various side effects that can be prevented by keeping an acceptable blood level of these drugs. However returning the blood level to the therapeutically level could retrieve the side effects (Steinborn and Galas-Zgorzalewicz, 2000). Previous studies have shown the probability of the anti-epileptic drugs can be effective for sudden deaths among patients, so the accurate control of drug could reduce this risk (Nilsson *et al.,* 2001). Evidence has shown that in third

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world countries, some of the epileptic children suffering from malnutrition, anemia, hepatic diseases and immune system deficiencies. The physicians should be cautions in prescribing anti-epileptic drugs which otherwise could intensify the disorders (Hemingway *et al.,* 1999). Also previous evidence indicated that often of physicians for reaching to the acceptable serumic level of drugs, they use high doses of them. These drugs are causing different side effects in many systems: [growth, endocrine (Rattya *et al.,* 1999), digestive, neurologic, hematologic, dermatologic, psychologic and hepatic systems] even evidences have shown that toxic levels of drugs could cause complications like drowsiness and confusion in patients (Ramsay *et al.,* 1990). The objective of this study is to reach the least consuming dose while maintaining an acceptable blood level for prevention of seizure attacks.

METHODS

This study has been an imperial case study that endured for one year on epileptic patients. The demographic data like age, sex, marital status and the duration of treatment were considered during the experiment and were recorded in respective questionnaires. Then drug prescription was performed periodically in order to prevent the seizures, while the serumic level of drugs was monitored by gaschromathography method monthly (Hernandez-Fustes *et al.,* 1990). At the end, the data was evaluated with descriptive and analytic statistics, and were compared with proposed data in books, references and articles. Patient divided to two groups: 1- below 12 years old (2-12 yr.) 2-over 12 years old.

The treatment of the patients was approved by recommendation of the declarations of Helsinki of 2003.

STATISTICS ANALYSIS

We used of Kolmogorov-Smirnov test showed normal data distribution. Hence, parametric analysis procedures were used for data analysis. Student t-test was used for comparison of two independent groups. A difference at $P<0.05$ was considered statistically significant.

RESULTS

The results showed that 31% of cases were below of twelve years old and 69% of cases were over of twelve years old. Also results indicated that by the minimal dose of drugs that we use for treatment in various age groups, we could reach an acceptable serumic level. The proposed dose of CBZ in adults varies from 20-30 mg/kg and in children from 10 to 30 mg/kg of body weight. And for VPA, can start with a daily dosage of 15 mg and increase it to 30 mg/kg of body weight and reaching the maximum level of 60 mg/kg of body weight. The consuming dosage for VPA in adults varies from 20-60 mg/kg while the mean consuming dosage in this research for the age of fewer than twelve has been 13 mg/kg of CBZ and 13.3 mg/kg of VPA. These drug levels could maintain the average blood level of CBZ at 7.4 µg/ml and VPA at 74.7 µg/ml; also the mean consuming dosage for the age group of over twelve years old was 10 mg/kg of CBZ and 10.1 mg/kg of VPA. This consuming dosage has been able to keep the blood level of CBZ at 8.2 and VPA at 66.8 µg/ml. Furthermore the results and comparison of the proposed levels are based on the proposed dosage introduced in books, references and articles. The normal blood level for these drugs as discussed in the references comprise of 4-11 µg/ml of CBZ and 50-100 µg/ml of VPA (table). Also follow-up the patients indicated that in 90% or greater of them reduction in frequency of seizures.

DISCUSSION

The most important results show that carbamazepine and sodium valproate, with much lower proposed levels in books can maintain an acceptable blood level for controlling the Epileptic seizures. The previous studies have shown that determination of concentration of anti – epileptic drug in biological fluids and calculation of drug dosage is the fundamental procedure for chronically therapy for epileptic patients. These treatment accommodations will secure the patient health in controlling epileptic seizures and will reduce the risk of side effects (Nilsson *et al.,* 2001, Minkova *et al.,* 2000,

Table: Comparison between results of this research and suggestions in books and references

	Dose suggested in book and references	Mean dosage of used in this research	Blood level of drug in references	Mean blood level drug in this research
CBZ in over of 12 years old	20-30 mg/kg*	10 mg/kg	4-12 µg/ml*	8.2 µg/ml
CBZ in below of 12 years old	10-30 mg/kg*	13 mg/kg	4-11 µg/ml*	7.4 µg/ml
VPA in over of 12 years old	30-60 mg/kg*	10.1 mg/kg	50-100 µg/ml*	66.8 µg/ml
VPA in below of 12 years old	10-60 mg/kg*	13.3 mg/kg	50-100 µg/ml*	74.7 µg/ml

*****All doses and blood level that suggested in book (Andreoli *et al.,* 2004).

and Verrotti *et al.,* 2002). The past decade studies show that the best results in epileptic treatment could result from pharmacokinetic data used in patient's drug therapy and it has been observed that the increased serumic level of drugs could be associated with the increase side effects (Miura 1990, Miura 2000). In clinical surveys, anti seizure drug serumic level controls are the most effective techniques in reaching an acceptable treatment (Jannuzzi *et al.,* 2000).

The mentioned drugs if used in high doses could have toxic neurological affects. Nistagmus is prevalent with therapeutically dosages but ataxia, confusion, tremor, mental retardation, amnesia and even stupor could be observed in high blood levels (Reynolds and Murthy, 1989). The last studies have proposed that full awareness of the kind of epilepsy, its wide spectrum of existing anti-epileptic drugs effects and conscious of pharmacokinetic principles could lead to complete control of seizures among high percentages of patients. In case the appropriate drug is not selected in relation to the kind of seizure or an appropriate dosage is not prescribed, many patients show resistance to drugs or may suffer side effects (Kasper *et al.,* 2005; Aminoff *et al.,* 2005). Availability of equipment's to measure the anti-seizure serumic levels, adjust drug dosage and controlling the usage of the drug could make it possible to prescribe a drug. There fore we can prescribe a drug and after a suitable duration, measure the blood level of drug and then compare it with the standard therapeutically dosage of every drug. Then we can adjust the drug dosage with the absorption changes or drug metabolism in each patient (Kasper *et al.,* 2005). On the other hand past experiences show that we can control most seizures with one single drug, so beginning the treatment with multiple drugs could expose the patient to the more risk of toxicity, without adding to the benefits of therapy (Aminoff *et al.,* 2005). Also patients who are using multiple drugs are exposed to drug interaction risk. Furthermore, because the usage of these drugs will lower the level of consciousness especially in driving, so the aim should be to use the minimal dosage of drugs.

CONCLUSION

The above finding show that the proposed and consumed levels of CBZ and VPA in this case study is capable of controlling the epileptic attacks and keeping an acceptable blood level in patients.

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