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RESEARCH ARTICLE

BIOCHEMISTRY

THE CONVENTIONAL ANTIEPILEPTIC DRUG USE WHEN COMPARED TO A COMBINATION THERAPY REGIME IN A TEACHING HOSPITAL IN INDIA.

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ABSTRACT

Epilepsy is a common chronic neurological disorder characterized by seizures. The recurrent seizures which pose a significant psychosocial and medical risk to the patient can be prevented by antiepileptic drugs (AED). The majority of patients achieve seizure control by effective monotherapy only. Among the antiepileptics phenytoin, phenobarbitone and carbamazepine remain the stalwarts, either as monotherapy or in combination with other drugs. We tried to determine the pattern of these conventional antiepileptics use, the degree of epileptic control achieved and the therapeutic drug levels achieved by the epileptics in Armed Forces Medical College, Pune. A total of 123 patients attending OPD were randomly included in the study. Phenytoin was found to be the most frequently used AED. Monotherapy was used on 68.3% of subjects. 40 (32.5%) subjects on monotherapy and 12 (9.75%) subjects on polytherapy were free of seizures with the AEDs they were receiving from the clinic. Only 19.5 % of patients achieved therapeutic drug levels measured only for the conventional drugs. This study shows that most of the epileptics can be effectively managed with the conventional AEDs with clinical monitoring with judicious use of monitoring in special circumstances.

KEYWORDS

Epilepsy, antiepileptic, therapeutic drug levels, monotherapy and polytherapy.

INTRODUCTION

Epilepsy is one of the most common neurological disorders which is characterized by an enduring predisposition to generate seizures and affect the patient by its neurobiological, cognitive, psychological, and social consequences [1].The prevalence and incidence of epilepsy are higher in developing countries than in developed countries[2].A review indicates incidence of 38.0-49.3 per 100000 persons-years in India [3].

The number of new cases in India is estimated to be closer to half a million. Epilepsy thus is a cause of heavy burden on the economy of our country in spite of the fact that care for epileptics is marginalized and that many people receive no pharmacologic treatment at all. The fundamental principle of managing epilepsy simply involves making an accurate diagnosis and choosing the most effective antiepileptic drug (AED) for the seizure type. Also it entails an effort on the part of physicians to first try out monotherapy regimes, exhausting possibilities and then only using polytherapy or nonmedical therapies. Because conventional drugs like phenytoin, carbamazepine and phenobarbital are available and inexpensive, they are the drugs most often used in developing countries [4].The ultimate goal of antiepileptic therapy should be to achieve a seizure free state. However in some clinical trials a 50% or more reduction in seizure frequency is considered as a surrogate measure in determining the efficacy of AEDs [5].Since two of the major problems associated with drug treatment of epilepsy are polypharmacy and chronic toxicity. Many studies indicate that polypharmacy should be avoided in the first place if possible [6, 7].

Therefore we thought it was important to determine the pattern of AED use in a teaching hospital in Pune, the degree of epileptic control achieved and the therapeutic drug levels achieved in order to make useful suggestions on management of epileptics to improve their quality of life.

The objectives of this study were to determine: the frequency of using the three conventional (phenobarbital, phenytoin, carbamazepine) AEDs either as monotherapy or combination polytherapy in the outpatients' clinic managing epileptics at the Armed Forces Medical College, Pune, the degree of seizure control achieved by the patients with the treatment given from the clinics and also measure the serum levels of the three conventional AEDs using High Pressure Liquid Chromatography [8].

MATERIALS AND METHODS

This was a cross sectional descriptive and analytical study. The study population was selected from the epileptic patients attending medical neurology clinic of the Armed Forces Medical College, Pune. The criteria for including a subject in the study were that he/she has been diagnosed to have epilepsy by a Consultant Neurologist with a clinical history, examination and relevant investigations including an EEG, has been on AED/s for more than eight weeks, not on any other medication and consented to take part in this study. The present study was cleared by the institutional ethical committee.

There was one Neurology clinic run at the Armed Forces Medical College, Pune for patients. One Consultant Neurologist and three Consultant Physicians were responsible for giving care to patients attending these clinics. A questionnaire was designed according to the objectives of the study. It composed of questions administered in Marathi/Hindi and later recorded in English. Further details were taken from patients' clinical records. 5 ml blood samples were collected in

the morning during OPD hours in red top vacutainers. Serum was separated and was analyzed for drug levels using High Pressure Liquid Chromatography.

RESULTS

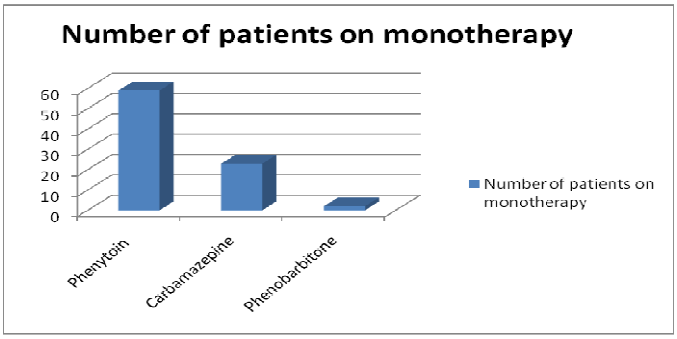
The study group comprised of 123 subjects: 98 (79.7%) males and 25 (20.3%) females. The mean age of the subjects was 19.2 years: range 14-60 years. The patients were divided into two main groups

Group 1: Those on monotherapy with conventional drugs viz phenytoin, phenobarbitone and carbamazepine.

Group 2: Those on polytherapy with one or more of the above mentioned conventional drugs and/or with other drugs.

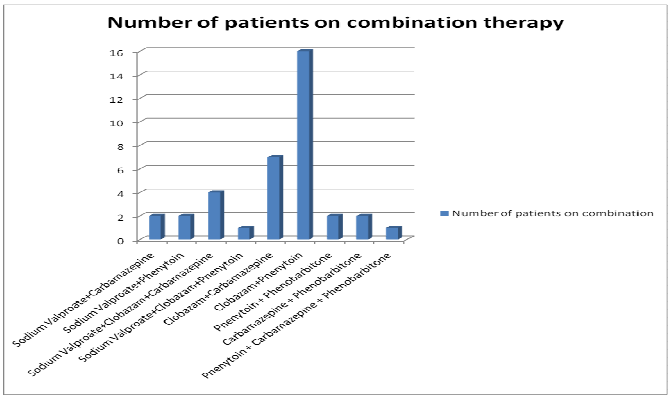
84 subjects (68.3%) were on monotherapy and 39 (31.7%) were on polytherapy. [Graph: 1, 2] shows the frequency of using different AEDs, showing separately their use as monotherapy and in polytherapy regimes. Phenytoin was found to be the most frequently used AED, being used on 65.8% of the subjects as monotherapy or in combination. (Table 1) shows the number of subjects on different AEDs as monotherapy who reported seizure control. There were 9 different AED combinations used in group 2 of epileptics (Table 2) and the most frequently used AED combination was clobazam + phenytoin.Table 2 also shows the different AED combinations and the corresponding number of subjects reporting different degrees of seizure control. 40 (32.5%) subjects on monotherapy and 12 (9.75%) subjects on polytherapy were free of seizures with the AEDs they were receiving from the clinics. 60.8% getting carbamazepine, 50 % getting phenobarbitone and 42.3% getting phenytoin sodium as monotherapy were free of seizures. Out of the 123 subjects a total of 52 (42.2%) were free of seizures with the treatment received from clinics. The outcome of therapeutic drug monitoring (table 3) done as per recommended guidelines[9] of at least 4-5 weeks of steady drug intake without dose change and taking pre dose samples is complied in a tabular format.

Graph 1
Number of patients on monotherapy



Graph 1: This column chart shows the frequency of using different AED. Each column shows the total number of patients taking each monotherapy regime.

Graph 2
Number of patients on combination therapy



Graph 2: This column chart shows the frequency of using different AED. Each column shows the total number of patients taking each Polytheraphy regime.

Table1
Degree of seizure control in patients on notheraphy

Drug	Number of patients	Free of seizures	50% or more reduction in seizure frequency
Pnenytoin	59	25	11
Carbamazepine	23	14	10
Phenobarbitone	2	1	0

Table2
Degree of seizure control in patients on various combinations

Serial number	Combination	Number of patients	Free of seizures
1	Clobazam+Pnenytoin	16	5
2	Clobazam+Carbamazepine	7	3
3	Sodium Valproate+Clobazam+Carbamazepine	4	2
4	Sodium Valproate+Carbamazepine	2	1
5	Sodium Valproate+Phenytoin	2	0
6	Sodium Valproate+Clobazam+Pnenytoin	1	0
7	Pnenytoin + Phenobarbitone	2	1
8	Carbamazepine + Phenobarbitone	2	0
9	Pnenytoin + Phenobarbitone+ Carbamazepine	1	0

Table3
Outcome of plasma antiepileptic drug monitoring

Group	Antiepileptic Drug Levels			
	Therapeutic	Sub Therapeutic	Toxic	Not detectable
Group 1	11	54	4	15
Group 2	13	24	2	2

DISCUSSIONS

The number of male epileptics who sought treatment from the clinics was higher as compared to females (79.7% males and 20.3% females). 68.3% of subjects were on monotherapy. In keeping with the recommended principles of antiepileptic therapy, the practice of polytherapy was relatively low (31.7%) in this teaching hospital. The most frequently prescribed AED in these clinics as monotherapy and in combinations was phenytoin followed by carbamazepine. The most frequently prescribed AED combination was phenytoin + clobazam. Phenobarbitone has been used as monotherapy only on 02 subjects in this study group and was used in polytherapy in 5 patients on three different combinations. This observation is in close accordance with the views expressed by Lerman and Lerman [10]. They have shown that even though phenobarbital is the oldest of the currently available AEDs, it has lost its popularity in this era. Phenobarbitone is seldom used after infancy in developed countries.Out of the epileptics on monotherapy 47.62% were free of seizures and another 25 % showed 50% decrease in seizure frequency. The total percentage (72.62%) closely tallies with the statement given by Guberman [11] who has inferred that 70-80% of patients can be efficiently controlled with monotherapy. Even though our center of study was a teaching hospital there were no facilities for measuring the plasma concentration of AEDs on routine basis, and dosage was adjusted and determined on clinical grounds. In this particular study all included patients had their levels checked for phenytoin, phenobarbitone and carbamazepine. Considering the percentage of epileptics who have achieved significant control of epilepsy in our study (see results), together with the results of Therapeutic drug monitoring (table 3) we suggest that with the AEDs most commonly used, monitoring the serum levels of these drugs in selected patients and in special situations is likely to be more useful than routine measurements in large clinic populations. While the measurement of drug concentrations can aid in minimizing adverse effects, there is also a danger of overtreatment resulting from inappropriate interpretation of drug concentration data [12].

This suggestion of basing the treatment on clinical interpretation and not therapeutic drug monitoring is more important in view of the fact that epilepsy is one of the most important non communicable neurological illnesses which is particularly under resourced and undertreated in the developing world [13]. It is more important to make the AEDs available to more patients, than to have extensive facilities for therapeutic monitoring.

In this study of patients only 43.24% of subjects on polytherapy (group 2) were free of seizures or had 50% reduction in seizure frequency in contrast to the 72.62% on monotherapy (group 1). This low percentage of either seizure free subjects or those having 50% reduction in seizure frequency in the polytherapy group would have been probably due to most of them suffering from difficult to control epileptic

syndromes. 9 different AED combinations with conventional epileptics and other drugs have been used on them. A review by Perucca [14] also states that when new AEDs are added to preexisting therapy in patients with refractory epilepsies, they improve seizure frequency in 15% to 40% of cases, but only rarely freedom from seizures is achieved. Perucca [14] reports that new AEDs are not free of severe adverse effects and in newly diagnosed patients, the efficacy is similar to that of older agents. 72.62% of the whole study group had achieved effective control of epilepsy with a 50% or greater reduction in seizure frequency. Of them 68.3% were those on monotherapy using conventional drugs like carbamazepine, phenytoin sodium or phenobarbitone. Valproate and clobazam were used in combination therapy. These facts on new AEDs considered together with our results raise the question whether the clinicians should promote the use of new AEDs in developing countries where one should be concerned about the cost of drugs, in order to reduce the burden on the patients and economy of a country, when effective control of epilepsy can be achieved with the less costly conventional AEDs. The new antiepileptic drugs may be a useful contribution in challenging epilepsy, but because of limited clinical experience and cost considerations their first line use cannot be recommended in most situations. The use of new AEDs should be reserved for use on epileptics not responding to conventional AEDs.The most frequently prescribed AED in these clinics as monotherapy and in combinations was phenytoin followed by carbamazepine. The most frequently prescribed AED combination was phenytoin + clobazam. Similar drug use profile has been established by a pharmacoeconomic study done in a secondary level hospital in North India indicating that phenytoin is the most prescribed among AEDs [15]. In US also the first choice AED was found to be phenytoin (48%) and carbamazepine (31%) whereas it was found to be more variable across Europe (generally valproate acid and carbamazepine were preferred [16]).Dan Chisholm reported that older first line AEDs (Phenobarbital and phenytoin) were more cost effective on account of their similar efficacy but lower acquisition costs [17].

CONCLUSION

Results of another Indian study by Anand Krishnan et al[15] taken together with our results, strongly suggest making conventional AEDs, phenytoin, phenobarbitone and carbamazapine more available at a lesser cost by increasing their production locally in developing countries. The use of the costly new AEDs in developing country like India needs to be weighed against benefits in efficacy, adverse reactions and improved quality of life. If steps are taken to cut down the acquisition costs of new AEDs and improve the local production of commonly used efficacious conventional AEDs, quality of life of many epileptics in developing countries may be improved.

REFERENCES

1. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE).Epilepsia, 46: 470–472, (2005).
2. Carpio A and Hauser W A. Epilepsy in developing world. Current Neurology Neuroscience Reports, 9: 319-326, (2009).
3. Ray BK, Bhattacharya S, Kundu TN, et al. Epidemiology of epilepsy-Indian perspective. J Indian Med Assoc, 100: 322–326, (2002).

4. Sridharan R, Murthy BN. Prevalence and pattern of epilepsy in India. Epilepsia, 40(5):631-636, (1999).
5. Walker MC and Sander J W A S. The impact of new antiepileptic drugs on the prognosis of epilepsy: Seizure freedom should be the ultimate goal. Neurology, 46:912-914, (1996).
6. Shorvon S D, Reynolds E H. Reduction in polypharmacy for epilepsy. British Medical Journal, 2: 1023-1025, (1979).
7. Reynolds EH, Shorvon SD. Monotherapy or polytherapy for epilepsy? Epilepsia, 22:1-10, (1981).
8. Naithani M, Chopra S, Somani B L, Singh R K. Studies on adverse metabolic effects of antiepileptics and their correlation with blood components. Current Neurobiology, 1 (2): 117-120, (2010).
9. Warner A, Privitera M, Bates D. Standards of laboratory practice: antiepileptic drug monitoring.Clinical Chemistry 44:51085–1095, (1998).
10. Lerman-Sagie T, Lerman P. Phenobarbital still has a role in epilepsy treatment. J Child Neurol., 14(12):820-821, (1999).
11. Guberman A. Monotherapy or polytherapy for epilepsy? Can J Neurol Sci., 25:S3-S8, (1998).
12. Perucca E, Patrick K. Overtreatment in Epilepsy: How It Occurs and How It Can Be Avoided CNS Drugs, 19(11):897-908, (2005).
13. Scott R A, Lhatoo S D., Sander JWAS. The treatment of epilepsy in developing countries: where do we go from here? Bulletin of the World Health Organization, 79 (4):344-350, (2001).
14. Perucca-E. The spectrum of the new antiepileptic drugs. Acta-Neurol-Belg, 99:231-238, (1999).
15. Krishnan A, Sahariah SU, Kapoor SK. Cost of epilepsy in patients attending a secondary-level hospital in India. Epilepsia, 45(3): 289-291, (2004).
16. Anand Krishnan R, Chowdhury D. Cost of antiepileptic drugs in India. Neurology Asia, 12 (Supplement 1): 42 – 43, (2007).
17. Chisholm D. WHO-CHOICE. Cost effectiveness of first-line Anti-epileptic drug treatments in the developing world: A population level analysis. Epilpesia, 46(5): 751-759, (2005).