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STUDY OF HAEMATOLOGICAL PARAMETERS IN CHILDREN ON ANTIEPILEPTIC DRUGS

Paediatrics

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ABSTRACT

Background: Seizures constitute one of the most common neurological problems in children. Several studies have documented changes in haematological parameters in patients treated with antiepileptic drugs. But most of these studies are on adults and studies in children from India are sparse.

Methods: Eighty seven children aged 4-13 years, receiving AED monotherapy (carbamazepine, Phenytoin and valproate) were enrolled and divided in three groups based on the drug given. Hematological parameters studied were compared with age and sex matched controls.

Results:.Compared with controls children taking valproate had statistically significant higher packed cell volume, total leucocyte count and lower platelet count. Erythrocyte sedimentation rate was significantly higher in children taking carbamazepine. No significant difference was observed in Mean corpuscular volume (MCV) and Mean Corpuscular Hemoglobin (MCH) and Mean corpuscular haemoglobin concentration (MCHC) between the control subjects and children taking any of the antiepileptic drugs.

Conclusion: antiepileptic drugs tend to alter haematological parameters and hence may require regular monitoring

KEYWORDS

AED, Hematological parameters, adverse effects

Introduction

A seizure or convulsion is a paroxysmal, time limited change in motor activity and/or behaviour that results from abnormal electrical activity in the brain. Seizures are common in the pediatric age group and occur in approximately 10% of children.(1)Children with seizures are commonly treated with an antiepileptic drug (AED). Majority of patients can be treated with conventional drugs like phenytoin (PHT), phenobarbitone (PB), valproate (VPA) and carbamazepine (CBZ). Many new drugs like levetiracetam (LEV), lamotrigine (LTG) and topiramate (TPR), tiagabine (TBG) etc. are currently used as add-on or alternative therapy (2) Although efficacy for some specific seizure types sometimes drives drug selection, the side effect profile of drugs and the potential for toxicity are important considerations (3)

Antiepileptic drugs may have hematotoxic effects i.e. there is decrease in haemoglobin concentration, RBC & WBC counts after long term antiepileptic therapy (4). However Such alterations may be subtle and insidious in onset, thereby taking years to become clinically apparent (5). Identifying, screening and monitoring for adverse effects of these drugs is still not incorporated into the clinical practice, Also the potential of adverse events in children is greater than in adults because young children have immature detoxification mechanisms and a greater variability in dosing owing to a wider range of body size and weight(6).Moreover data is lacking on hemotoxic effects of antiepileptic drugs in children(7).

Hence this study was planned to explore alteration in haematological parameters in children with AED.

Material and methods

This study was conducted in Department of Paediatrics Hindu Rao Hospital in 2013. Eighty seven children aged between four years and thirteen years on one of antiepileptic drugs, Phenytoin/ Valproate/ Carbamazepine for more than 3 months were enrolled in the study and study subjects were divided into three groups based on the antiepileptic drug they were receiving. Twenty age and sex matched children visiting out patient department were taken as controls. Children on polytherapy or having ever received any antiepileptic other than Phenytoin, carbamazepine or valproate, or with any change in antiepileptic drug or dosage in previous 3 months, and children with diagnosis of either neonatal seizures, tubercular meningitis, congenital birth defects, cerebral palsy or mental retardation were excluded from the study.

The present study was cleared by the institutional ethical committee.Informed consent from parents were taken before enrolment. After reviewing previous treatment records, history of adverse effects after starting antiepileptic therapy were asked for. Clinical examination was done and relevant information and findings were recorded. 2 mL of venous blood was collected in relevant vials for various parameters using standard aseptic technique. Hemoglobin (Hb), Total Leucocyte count (TLC), Differential Leucocyte Count (DLC), Platelet count (PC), Peripheral blood smear (PS), Packed cell volume (PCV), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin concentration (MCHC), ESR (erythrocyte sedimentation rate) and APTT (activated partial thromboplastin time) were assessed by automated counters and analyzers (Sysmex KX 21)

Statistical analysis was performed using the SPSS statistical package version 17.0. ANOVA with post hoc Bonferroni test was used to analyze the differences between various groups and to compare the difference between individual drugs and controls. A $p<0.05$ was considered statistically significant.

Results and Observations:

Data of one hundred seven children were analysed finally after excluding14 children for not turning up for sampling or sampling errors. Finally 87 (M/F: 40/47) children were analysed in the study group and 20(M/F:10/10) formed the control group. Of the study group, 32 children were taking carbamazepine, 25 were taking phenytoin and 30 children were taking valproate for mean (sd) duration of 12.78(4.9) months, 14.9(5.9) months and 14.9(7.2) months respectively. Demographic and baseline parameters of all the study and control groups in terms of sex, age, and duration of therapy were comparable.

The haematological profile of children on AED's for more than 3 months is given in Table No 1

Table No. 1 :Haematological Profile of Children on AED's

Parameter	Control grp (n= 20)	Carbamazepine Grp (n=32)	Phenytoin grp (n=25)	Valproate Grp (n=30)	p value
Hb (g/dL) mean ±SD	11.3±1.1	12.24±1.2	11.7± o.7	11.9±1.2	0.056
PCV (%)mean ±SD	35±3.5	36.1±2.5	37.1±2.6	37.9±3.1*	0.004*
MCV (fL) mean ±SD	83.3±6.9	84.5±11.2	84.6±5.9	86.5±6.3	0.538
MCH (pg) mean ±SD	28.97±0.69	28.28±1.171	27.93±1.261	27.99±2.148	0.0399
MCHC (g/dL) mean ±SD	30.8±0.9	31.0±1.8	30.1±2.5	33.6±9.9	0.079

TLC(/dL) mean ±SD	7911±1546	9498±2920	8476±1686	10050±2530*	0.003*
PLC(/dL) mean ±SD	287961±94693	270906±62728	282280±93430	220400±93430	0.009*
ESR (mm AEFH) mean ±SD	8±3	11±3*	11±4	11±3	0.028*
PT (seconds) mean ±SD	14.02±1/27	13.68±1.65	14.52±2.56	14.09±1.25	0.349
APTT (seconds) mean ±SD	32.37±2.52	33.98±2.99	34.76±1.97	35.37±5.27*	0.013*

*p <0.05

No statistically significant difference was found in the level of hemoglobin (Hb), mean corpuscular volume (MCV), Mean Corpuscular Hemoglobin (MCH) or Mean corpuscular haemoglobin concentration (MCHC) between the controls and any of the 3 antiepileptic drugs groups. Statistically significant difference was however seen in PCV, TLC, PLC, ESR and APTT between the controls and any of the 3 antiepileptic drugs groups.

The post hoc comparison of individual drugs with controls is given in Table No 2.

Table no. 2: Individual Drug Comparison with Controls (Post hoc Analysis)

Test	Control	Carbamazepine	p value	Phenytoin	p value	Valproate	p value
Hb (g/dL) mean ±SD	11.1±1.2	12.24±1.2	0.085	11.7± 0.7	0.254	11.9±1.2	0.035*
PCV (%) mean ±SD	35±3.5	36.1±2.9	0.20	37.1±2.6	0.207	37.9±3.1	0.014*
TLC Count (/dL) mean ±SD	7911±1546	9498±2920	0.062	9498±2920	1.000	10050±2530	0.005*
PLC (/dL) mean ±SD	287961 ±94693	270906 ±62728	1.000	270906±62728	1.000	220400± 93430	0.017*
ESR (mm AEFH) mean ±SD	8±3	11±3	0.043*	11±3	0.081	11±3	0.144
APTT	32±2.86	33.98±2.30	0..503	37.55±4.66	0.097	35.37±5.27	0.011*

*P<0.05

In the valproate group, on comparison with the control group; Packed cell volume (PCV) was statistically significant higher (37.9±3.1% vs 35±3.5%); Total leucocyte count was also significantly higher (10050±2530 /dLvs 7911±1546 /dL); Platelet counts (PLC) was significantly lower (220400±93430 /dL vs 287961±94693) /dL). Activated plasma thromboplastin time (APTT) had also significantly higher values in children taking valproate as compared to the control subjects (35.37±5.27 sec vs 32.37±2.52 sec) . Children taking carbamazepine had significantly higher erythrocyte sedimentation rate AEFH (11±3 mm) as compared to the control subjects (8±3 mm). Rest all parameters were comparable.

Discussion

Antiepileptic drugs are associated with changes in haematological parameters in adults; however very few studies are available on children. It has been postulated that anti-folic acid activity of antiepileptics like CBZ, oxaCBZ, PHT, PB, LTG andVPA etc. is responsible for bone marrow depression that results in blood dyscrasias like thrombocytopenia, leucopenia and aplastic anemia.(8).This moreover is dependent on the dose and duration of the AED administered.

Hematological parameters of 87 children on Carbamazepine, phenytoin and Valproate monotherapy for a duration of more than 3 months were compared amongst themselves and with age and sex matched controls. The dosage of phenytoin, carbamazepine and valproate administered in this study were lower as compared to study by Herranz et al. (9) but were similar to those used by Thillothamal et al. (10).

This study, in consonance with that of Dae Hun Pee et al. (11) revealed no significant difference in the values of Haemoglobin, MCV, MCH, and MCHC in children receiving antiepileptic drug monotherapy. . Hauser et al .(12) reported a gradual rise in MCV in children on valproate therapy which was not seen in our study. However significantly higher values of TLC was observed as also by Dae Hun Pee et al (11) who reported higher (but not statistically significant) TLC values. Four (13%) of the children receiving valproate had lower than the lower normal platelet count. The mean values of platelet was also significant lower in children receiving valproate monotherapy. This finding is similar to and supported by a previous study by Hauser et al.(13). The children on carbamazepine had higher ESR as compared to controls. This has not been seen in previous studies. Children receiving Phenytoin were not detected to have significant haematological changes.

There are however certain limitations of the study. Despite the strength of the study being a large sample size, a higher number of children on AED's need to be recruited. The children also need to be followed up after having received the AED's for 6 mnths and an even larger duration.

Conclusion:

From the above study, it can be concluded that AEDs are potentially toxic agents and produce varying degrees of haematological alterations .Challenge lies in the correct balance between the drug dosage so that it can effectively control seizure and produce minimal and tolerable side effects. In children taking antiepileptic drugs these effects should be actively looked for and haematological parameters should be monitored.

Contributions: PJ, RK: conception and design of the study and data collection. RK, PJ: Acquisition , analysis & interpretation of the data. PJ will act as guarantor for the paper

Compliance with Ethical standards: Yes
Conflict of interest: None.

Source of funding: None. The study is original thesis work of RK under guidance of PJ

REFERENCES

1) Michael V. Johnston. Seizures in childhood. In :Kleigman RM, Behrman RE, Jenson HB, Stanton BF, editors. Nelson textbook of Pediatrics. 18th ed. Philadelphia: Saunders; 2007. p.2457.
2) ShobhanaMathur, Sumana Sen, L Ramesh, Satish Kumar M. Utilization pattern of anntiepileptic drugs and their adverse effects, in a teaching hospital. Asian Journal of Pharmaceutical and Clinical Research. 2010;3(1):55-9.
3) WillmoreLJ, Wheless JW, Pellock MJ. Adverse Effects of Antiepileptic Drugs. In: Pellock JM, Bourgeois BFD, Dodson WE, editors. Pediatric Epilepsy Diagnosis and Therapy. 3rd ed. USA: Demos; 2008. p 449
4) Jawad S, Mercer A, Jamil N, Richens A. Haematological values of epileptic patients entering drug trials. International Journal of Clinical Pharmacology Research. 1988;8(5):363-6.
5) Annegers, J.F.; Hauser, W.A. & Shirts, S.B. Heart disease mortality and morbidity in patients with epilepsy. Epilepsia. 1984;25:699-704.
6) Moore TJ, Weiss SR, Kaplan S, Blaisdell CJ. Reported adverse events in infants and children under 2 years of age. Pediatrics, E53-E57 (2002).
7) Mathis LL, Iyasu S. Safety monitoring of drugs granted exclusively under the Best Pharmaceuticals for Children Act: what the FDA has learned. Clin.Pharmacol.Ther. 82,133-134 (2007)
8) KobyBrosh, IlanMatok, EyalSheiner, Gideon Koren, ArnonWiznitzer, Rafael Gorodischer, Amalia Levy. Teratogenic Determinants of First- Trimester Exposure to Antiepileptic Medications. J PopulTherClinPharmacol. 2011;18(1):e89-98.
9) Herranz JL, Armijo JA, Arteaga R. Clinical side effects of phenobarbital, primidone, phenytoin, carbamazepine, and valproate during monotherapy in children. Epilepsia 1988; 29:794–804.
10) Thilothammal N, Banu K, Ratnam RS. Comparison of phenobarbitone, phenytoin with sodium valproate: randomized, double-blind study. Indian Pediatr 1996; 33: 549–555.
11) Pee DH, Park YK, Eun BL, Park SH, Kim SK. The hematologic effect of antiepileptic drug. Korean J Pedoatr. 1997 Feb; 40(2): 217-224.
12) Hauser E, Seidl R, Freilinger M, et al. Hematologic manifestations and impaired liver synthetic function during valproate monotherapy. Brain Dev. 1996;18:105–109.