Comparison of Salivary versus Serum Carbamazepine and Phenytoin Levels in Epileptic Children

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Abstract

Aims and Objectives **: To compare serum versus salivary carbamazepine and phenytoin levels in children with seizure disorder and correlate them with clinical seizure control.**

Material and Methods **: A prospective study of 61 epileptic children, (4 to 15 years of age) attending OPD or wards was carried out at a tertiary centre in Mumbai, over a period of one year. Only those children on monotherapy, either phenytoin or carbamazepine (CBZ), for at least 3 months duration were included in the study. This included 25 on phenytoin (PHY) and 36 on CBZ. All these patients underwent clinical examination and relevant investigations (EEG, neuroimaging). Fasting paired serum and saliva samples were collected for AED trough levels and assayed by high performance liquid chromatography (HPLC). The norms for therapeutic range in the serum were – Phenytoin=10-20 μg/mL and CBZ = 4-12 μg/mL and for saliva were- Phenytoin=1-2 μg/mL and CBZ=1.4-3.5 μg/mL. The results were analyzed by Pearson Chi square test.**

Results **: The male : female ratio was 1.9 : 1 with 56% patients in 8-12 years and 28% in 4-8 years age group. In the phenytoin group, 80% of the controlled patients had their serum levels in the subtherapeutic range as compared to 73.3% salivary levels in the therapeutic range, but in the poorly controlled PHY patients both the sera and saliva were in the subtherapeutic range. In the CBZ group 83% of the controlled patients had their serum levels in the therapeutic and 17% were subtherapeutic range, while 46.7% had their salivary CBZ levels in the therapeutic and 40% in the supratherapeutic range.**

Conclusions **: Salivary phenytoin levels have a good statistical (P = 0.00029) correlation with clinical seizure control, as compared to serum levels. Both serum and saliva CBZ levels correlate with clinical seizure control (P ≤ 0.001). It is recommended that saliva AED estimation; a non-invasive painless test can be used for monitoring epileptic patients.**

Introduction

Epilepsy is one of the most common and important neurological disorder encountered in children. The use of antiepileptic (AED) is an important facet of treatment. Serum AED levels normally indicate free drug as well as the protein bound fraction, but it is the free drug level which is important for determining the efficacy and toxicity of the drug.[1] Blood collection for therapeutic drug monitoring (TDM) is an invasive and painful procedure, hence for long term monitoring of epileptic children non invasive methods like salivary estimation can be tried. Advantages of salivary sampling are: non painful, low cost, free drug estimation

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and in a few cases home-based collection ispossible.[2] The present study was performed to compare the serum versus salivary levels of carbamazepine and phenytoin and their correlation with clinical control of seizures in epileptic children.

Subject and Methods

This prospective study was conducted over a period of one year, in the department of paediatrics of a tertiary care centre in Mumbai, after obtaining the requisite approval of the Ethics Committee and prior informed consent from the parent/guardian. The study included 61 epileptic children (4-15 years), attending OPD or wards. The inclusion criteria consisted of epileptic children on monotherapy of AED, either phenytoin or carbamazepine (CBZ), for at least 3 months duration with good compliance. Exclusion criteria consisted of children on polytherapy, poor compliance, and inability to cooperate for saliva collection. The study group included 25 patients on phenytoin, and 36 on CBZ.

All subjects underwent clinical examination and relevant investigations like EEG, neuroimaging and BERA. Collection method consisted of early morning salivary sample after an overnight fasting was collected to get the through levels in the saliva. Simultaneously a paired serum sample was also collected. Saliva secretion was stimulated by placing a few crystals of citric acid on the patient's tongue.[2] Three ml of saliva was collected in sterile glass bulbs after prior rinsing of the mouth with water. The saliva was then immediately drawn in a sterile syringe, care being taken to expel the excess air so as to avoid any pH or drug level alteration[3] and analysis was done by high performance liquid chromatography (HPLC).

The norms for therapeutic range in the serum[4] were – Phenytoin = 10-20 μg/mL and CBZ = 4-12 μg/mL and for saliva[5-7] were – Phenytoin = 1-2 μg/mL and CBZ = 1.4-3.5 μg/mL. The results were recorded and analyzed by the Pearson chi square test, P value was used to measure the strength of the result of a test, ($P \leq 0.05$), was considered significant. The coefficient of correlation 'r' was employed to test the strength of an association ('r' towards 1 signifies high correlation).

Results

The demographic profile revealed male preponderance (M : F = 1.9 : 1). There were 56% patients in the 8-12 year age of group, followed by 28% in 4-8 year age group. Generalized seizures were seen in 21 patients (84%) in phenytoin group and in 20 children (55%) in the CBZ group. Partial seizures were seen in 4 patients (16%) in the phenytoin group and in 16 patients (45%) in the CBZ group. The drug dosage in phenytoin group ranged from 4-8 mg/kg/day and for CBZ ranged from 10-30 mg/kg/day. Duration of treatment ranged from 3 to 84 months, with an average of 21 months for phenytoin and 18 months for CBZ. On analysis we found that the serum phenytoin levels ranged from 0.9-12.8 μg/mL (average of 4.95 μg/mL) and the salivary phenytoin levels ranged from 0.38-1.94 μg/mL (average of 1.10 μg/mL). Similarly the serum levels of CBZ ranged from 1.6-14.5 μg/mL (average of 6.99 μg/mL) and saliva levels ranged from 0.36-11.9 μg/mL (average of 3.08 μg/mL).

We observed a linear correlation between serum and salivary phenytoin levels. The correlation coefficient for salivary to serum phenytoin ratio, 'r' = 0.7 (Fig. 1). Similarly there was a linear correlation between serum and salivary CBZ levels, and correlation of coefficient for salivary to serum CBZ ratio, 'r' = 0.6. (A value of 'r' approaching 1 indicates a very high correlation) (Fig. 2).

On correlation of serum phenytoin levels

with clinical seizure control (Table 1) we observed that as many as 80% patients in the controlled group had sub therapeutic serum levels, indicating a poor association between serum phenytoin levels and clinical seizure control. But the same was not statistically significant (P = 0.132). In contrast we noticed that 73.3% in the controlled group had their salivary levels in the therapeutic range, thus showing an association between the salivary phenytoin levels and clinical seizure control and this was statistically significant, P = 0.000296 (Table 1).

Further on analysis is our seizures we observed, that in the CBZ group (Table 2) those who had a good seizure control (83%) had serum levels I the therapeutic range and this was statistically significant. Thus showing a good association between serum CBZ levels and seizure control (P = 0.00041). Salivary CBZ levels were in therapeutic range for 46.7% patients in the controlled group and in the subtherapeutic range in all (100%) of the poorly controlled patients. Thus showing an association between salivary CBZ levels and clinical seizure control. This observation was statistically significant, P=8.60 E-05 (Table 2).

Discussion

Therapeutic drug monitoring for AED is an important component of management of epileptic children and especially in children and especially in children with resistant seizures and in suspected toxicity. In our study serum levels for phenytoin ranged from

Table 1 : Association of serum and saliva phenytoin levels with clinical seizure control

	Serum Levels		Saliva Levels	
	Clinically Controlled	Clinically Not Controlled	Clinically Controlled	Clinically Not Controlled
Sub therapeutic	12 (80%)	10 (100%)	4 (26%)	10 (100%)
Therapeutic	3 (20%)	0	11 (73.3%)	0
Supra-therapeutic	0	0	0	0
Total	15	10	15	10

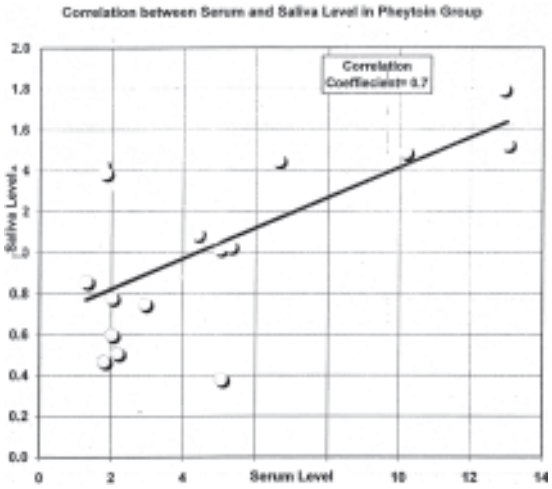

Fig. 1 : Association of serum and saliva AED levels for children on phenytoin

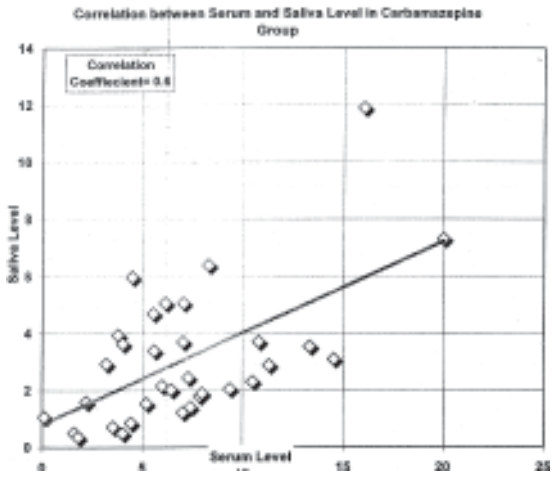

Fig. 2 : Association of serum and saliva AED levels for children on CBZ

Table 2 : Association of serum and saliva carbamazepine levels with clinical seizure control

	Serum Levels		Saliva Levels	
	Clinically Controlled	Clinically Not Controlled	Clinically Controlled	Clinically Not Controlled
Sub therapeutic	3 (10%)	5 (83%)	4 (13.3%)	6 (100%)
Therapeutic	25 (83%)	1 (7%)	14 (46.7%)	0
Supra-therapeutic	2 (7%)	0	12 (40%)	0
Total	30	6	30	6

0.9-12.88 µg/mL and for CBZ ranged from 1.6-14.5 µg/mL. In a similar study by Gorodischer *et al*,[8] the ranges for serum phenytoin levels were 4.5-20.9 µg/mL, and for serum CBZ levels were 1-23.6 µg/mL. The salivary levels of phenytoin in our study ranged from 0.38-1.94 µg/mL, and for CBZ ranged from 0.36-11.9 µg/mL, while according to Mucklow,[5] Miles MV *et al*,[6] and Knott *et al*,[7] the salivary therapeutic ranges for phenytoin were 1-2 µg/mL, and for CBZ were 1.4-3.5 µg/mL. We observed that 80% of the well controlled patients had their serum phenytoin levels in the subtherapeutic range. In an Indian study by Kshirsagar,[9] out of 1000 newly diagnosed cases, 20% were in the subtherapeutic range despite good control. Similarly Lund *et al*[10] reported 48% of those with subtherapeutic range to have good seizure control. We found in our study a poor association of serum phenytoin levels with seizure control. Thus, in clinically controlled epileptic children with low serum phenytoin levels, we need not increase the drug dosages. According to our study serum CBZ levels had a statistically significant association with clinical seizure control. This was also noticed by Vasudev *et al*,[11] noticed that amongst the patients taking CBZ, all patients (100%) of the controlled group were in the therapeutic range. We observed a significant correlation between salivary phenytoin and salivary CBZ levels with seizure control.

A preliminary pilot study was also conducted at our institute which had revealed a highly significant correlation between salivary and serum AED levels for phenytoin and CBZ.[12] Troupin *et al*[13] estimated phenytoin and CBZ levels (also phenobarbitone and primidone levels) in serum, saliva and CSF and found stimulated saliva useful to estimate free phenytoin and CBZ levels. Since 'r' = 0.7 and 0.6 for salivary : serum ratio of phenytoin and CBZ respectively, we conclude that saliva levels can predict and represent serum levels in both groups, however further studies on larger number of children are required.

Conclusions

Serum phenytoin, levels have poor correlation with clinical seizure control in contrast to salivary phenytoin levels, which have excellent correlation with seizure control as depicted in the above study. Therefore clinically well controlled patients on phenytoin do not always need upward dosage scaling. Salivary phenytoin levels can be used to monitor drug levels in the body as 'r'=0.7. In our study both serum and salivary CBZ, had good correlation with seizure control and 'r'=0.6 for salivary: serum ratio of CBZ suggest that salivary CBZ levels can be used to monitor drug levels in the body.

Key messages

- Our study revealed a good correlation between serum and saliva levels of phenytoin and carbamazepine.
- Salivary phenytoin levels correlate with

seizure control better than serum phenytoin levels.

- Both serum and salivary CBZ levels correlate well with clinical control.

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A randomized, controlled trial has demonstrated a small but significant reduction in systolic and diastolic blood pressure with both a lipophilic and a hydrophilic statin.

High baseline blood pressure was defined as systolic > 140 mm Hg or diastolic > 90 mmHg.

The results showed a significant blood pressure reduction with statins compared with placebo.

The Practitioner, 2008; 252 : 6-17.