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

Shweta Siraslewala*, Sushma Malik**, Surekha Joshi***, +Renuka Kulkarni+, Urmila Thatte++

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 therapeutics 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. 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
and in a few cases home-based collection is possible.\textsuperscript{3} 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.\textsuperscript{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\textsuperscript{1} and analysis was done by high performance liquid chromatography (HPLC).

The norms for therapeutic range in the serum\textsuperscript{4} were – Phenytoin = 10-20 µg/mL and CBZ = 4-12 µg/mL and for saliva\textsuperscript{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 ≤ 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>
<thead>
<tr>
<th>Serum Levels</th>
<th>Saliva Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically Controlled</td>
<td>Clinically Not Controlled</td>
</tr>
<tr>
<td>Sub therapeutic</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Supra-therapeutic</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
</tr>
</tbody>
</table>

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

**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**
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,
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 al13 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

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

<table>
<thead>
<tr>
<th>Serum Levels</th>
<th>Clinically Controlled</th>
<th>Clinically Not Controlled</th>
<th>Saliva Levels</th>
<th>Clinically Controlled</th>
<th>Clinically Not Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub therapeutic</td>
<td>3 (10%)</td>
<td>5 (83%)</td>
<td>4 (13.3%)</td>
<td>6 (100%)</td>
<td></td>
</tr>
<tr>
<td>Therapeutic</td>
<td>25 (83%)</td>
<td>1 (7%)</td>
<td>14 (46.7%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Supra-therapeutic</td>
<td>2 (7%)</td>
<td>0</td>
<td>12 (40%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>6</td>
<td>30</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>
seizure control better than serum phenytoin levels.

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

References


STATIN SHOWN TO REDUCE BLOOD PRESSURE

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.