Evaluation of Nail-fold Capillary Structures (Diameter and Tortuosity) in Carbamazepine-Treated Patients

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Abstract

Carbamazepine is an anti-epileptic drug and used for treatment of several diseases such as epilepsy, neuropathic pain (neuralgia) and bipolar affective disorders. Several reports have shown vascular adverse drug effects of anti-epileptic drugs, including carbamazepine. Very few reports have been involved with micro-vascular (capillary) structural changes, which may be related to potential adverse drug reactions in patients with long-term therapy. The aim of this observational study was to evaluate nail-fold capillary structural changes in carbamazepine-treated patients in relation to serum carbamazepine concentrations and its apparent adverse drug reactions. Patients from Chiangmai Neurological Hospital (N=60) were recruited and enrolled according to specific inclusion and exclusion criteria. All patients were treated with monotherapy of carbamazepine. Calibrated nail-microscope Dino-Lite® was employed to measure nail-fold capillary structural changes (i.e. arterial and venous diameters and tortuous index) at the proximal nail-fold. The measurement was performed in ¹st and ²nd month after starting the treatment. Serum carbamazepine concentrations were also measured by fluorescene polarization immunoassay (Abbot Axsym System®). Results showed that after one and two months of treatment the arterial loop diameters of the capillary were significantly decreased (9.05±1.07 [baseline] vs 8.88±1.10 and 8.78±1.15 µm, p<0.001, respectively). Tortuous index was also found to be increased from baseline after treatment for one and two months; 1.64±0.32 µm vs 1.86±0.38 µm vs 1.94±0.36 µm, p<0.001, respectively. Correlation between % arterial loop diameter changes of the capillary and serum carbamazepine concentrations existed (r=-0.406, p<0.05), but not the turtuos index. Although frequency of adverse drug reactions was greater in patients whose serum carbamazepine concentrations ≥8 µg/mL, there was no established association of both % arterial loop diameter changes of capillary and tortuous index with apparent short-term adverse drug reactions.

Keywords: nail-fold capillary, carbamazepine, adverse drug reaction
การประเมินโครงสร้าง (เส้นผ่าศูนย์กลางและความคด) ของหลอดเลือดแดงที่ฐานเล็บในผู้ป่วยที่ได้รับยาคาร์บามาซีปีน

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บทคัดย่อ

คาร์บามาซีปีนเป็นยาต้านโรคลมชักที่ใช้ในการรักษาโรคร่วมหลายระเภท เช่น โรคลมชัก โรครักษาปวดประสาท และโรคร้ายทางจิตแบบสองขั้ว รายงานหลายฉบับได้แสดงผลไม่พึงประสงค์ต่อระบบหลอดเลือดของยาต้านโรคลมชักซึ่งรวมทั้งยาคาร์บามาซีปีน รายงานนี้มีวัตถุประสงค์เกี่ยวกับการเปลี่ยนแปลงโครงสร้างหลอดเลือดแดงซึ่งอาจเกิดขึ้นกับอาการอันไม่พึงประสงค์ที่เป็นไปได้สูงในผู้รับยาได้รับการรักษาระยะยาว วัตถุประสงค์ของศึกษาเชิงสังเกตุนี้เพื่อประเมินการเปลี่ยนโครงสร้างหลอดเลือดแดงที่ฐานเล็บที่สัมพันธ์กับความเข้มข้นของยาคาร์บามาซีปีนในซีรั่ม และอาการอันไม่พึงประสงค์ของยาที่ปรากฏในผู้รับยาได้รับยาคาร์บามาซีปีน ในการศึกษาครั้งนี้มีผู้ป่วยจำนวน 60 รายจากโรงพยาบาลประสาท เชียงใหม่ ได้รับการเกณฑ์และคัดเลือกตามเกณฑ์การคัดเข้าและออกที่เจาะจง ผู้ป่วยทุกรายได้รับการรักษาด้วยยาคาร์บามาซีปีนแบบเดี่ยว การวัดการเปลี่ยนแปลงโครงสร้างหลอดเลือดแดงที่ฐานเล็บใช้กล้องจุลทรรศน์ส่องเล็บ (Dino-Lite®) และดำเนินการวัดที่เดือนที่ 1 และ 2 หลังจากเริ่มการรักษา และความเข้มข้นของยาคาร์บามาซีปีนในซีรั่มได้รับการตรวจโดยวิธี fluorescene polarization immunoassay (Abbot Axsym System®) จากการศึกษาพบว่าหลังจาก 1 และ 2 เดือนของการรักษา เส้นผ่าศูนย์กลางของวงหลอดเลือดแดงมีค่าลดลงอย่างมีนัยสำคัญทางสถิติเมื่อเทียบกับเส้นผ่าศูนย์กลาง ก่อนการรักษา (9.05±1.07 ไมโครเมตร [ค่าก่อนได้รับยา] เทียบกับ 8.88±1.10 และ 8.78±1.15 ไมโครเมตร ตามลำดับ, p<0.001) ทำให้ความคดมีค่าเพิ่มขึ้นทั้งเดือนที่ 1 และ 2 เมื่อเทียบกับก่อนได้รับยา (1.64±0.32 [ค่าก่อน] เทียบกับ 1.86±0.38 [เดือนที่ 1] กับ 1.94±0.36 [เดือนที่ 2] ไมโครเมตร, p<0.001) ได้ความสัมพันธ์ระหว่างการเปลี่ยนแปลงของเส้นผ่าศูนย์กลางวงหลอดเลือดแดงอยู่กับความเข้มข้นของยาคาร์บามาซีปีนในซีรั่มโดยมีค่าสัมประสิทธิ์สี่เหลี่ยมที่ r=-0.406 (p<0.05) ไม่มีความสัมพันธ์ระหว่างค่าความคดกับความเข้มข้นของยาคาร์บามาซีปีนในซีรั่มมากกว่าหรือน้อยกว่า 8 ไมโครกรัม/มิลลิลิตร แต่มีความสัมพันธ์ระหว่างร้อยละการเปลี่ยนแปลงของเส้นผ่าศูนย์กลางวงหลอดเลือดแดงอยู่กับการเปลี่ยนแปลงของเส้นผ่าศูนย์กลางวงหลอดเลือดแดงและค่าความคดกับอาการอันไม่พึงประสงค์ที่ปรากฏ

คำสำคัญ: หลอดเลือดแดงที่ฐานเล็บ, คาร์บามาซีปีน, อาการอันไม่พึงประสงค์
Introduction

Carbamazepine is an antiepileptic drug and used for the treatment of several diseases such as epilepsy, neuropathic pain (neuralgia) and bipolar affective disorders. Reports of adverse drug reactions can range from concentration-related CNS effects and hypersensitivity reactions.\textsuperscript{1-3} Several reports have also shown vascular adverse drug effects of anti-epileptic drugs, including carbamazepine.\textsuperscript{4,5} Very few reports have been involved with micro-vascular (capillary) structural changes, which may be related to potential cardiovascular adverse drug reactions in patients with long-term therapy with carbamazepine. Gerstner et al. (2006) used capillary microscope and reported changes of nail-fold capillary structures and hemorheology in pediatric patients with epilepsy who were treated with either carbamazepine or valproic acid.\textsuperscript{6} They found significant differences in capillary density, tortuous index of the capillaries, capillary diameter and flow rate of erythrocytes for both antiepileptic drugs. Additionally, there were changes in plasma-viscosity and the aggregation of erythrocytes.

The aim of this observational study was to investigate nail-fold capillary structural changes, i.e. arterial and venous loop diameters and tortuos index, in relation to serum carbamazepine concentrations and apparent adverse drug reactions.

Methods

Subjects

This prospective observational study was carried in patients, who were treated by monotherapy of carbamazepine, from Chiangmai Neurological Hospital (N=60). The patients were recruited and enrolled according to inclusion and exclusion criteria. The inclusion criteria were 1) male or female age between 18-60 years 2) monotherapy of carbamazepine 3) patients giving their consents. The exclusion criteria were 1) patients identified by doctors to be at risk if participating in the study 2) patients not giving their consents 3) patients whose treatment regimen was added with other antiepileptics 4) co-administration with other drugs such as erythromycin, clarithomycin, isoniazid, fluoxetine, fluvoxamine, verapamil, diltiazem, lamotrigine, ketoconazole and fluconazole 5) co-administration with drugs which affect vacular vessels, such as calcium channel blockers, nitrates, alpha-1 blocker, pseudoephedrine, phenylephrine 6) consumption of herbal or dietary supplement, such as pomegranate, ginkgo biloba, grape fruit, St.John’s wort, evening primrose 7) patients who were diagnosed with congestive heart failure, COPD, Turner’s syndrome, schizophrenia, systemic lupus erythematosus (SLE), Familial Mediterranean fever (FMF), scleroderma, dermatomyositis, polycythaemia, which can influence nail-fold capillary changes 9) patients having scar or wound or rough skin of the ring finger.

The study protocol was approved by the ethic committee of Chiangmai Neurological Hospital.
**Instrument and data collection**

The measurements were performed at baseline, the 1st and 2nd month after starting the treatment with monotherapy of carbamazepine. Compliance of medication for all enrolled patients was also tested for each visit.

**Nailfold capillary measurement:** Calibrated nail microscope Dino-Lite® (Chosen Technology, Thailand) was employed to measure the change in arterial and venous loop diameters of capillary at the proximal nail-fold. Patients were asked to take a rest for 20 minutes at room temperature of 25°C before the measurement. Microscopic photographs of 5 measurements from each patient were recorded for each visit. Computer-aided software (DinoCapture) accompanied with the microscope was used to measure the arterial and venous loop diameters, together with estimation of tortuous index, the ratio between a widest part over a narrowest part of the capillary loop.

**Serum carbamazepine concentrations:** Blood samples were collected 12 hrs from last dose at 1 and 2 months after treatment and stored at -20°C before analysis. Abbott AxSYM System (Automated Immunoassay analyzer) based on fluorescence polarization immunoassay was used for analysis of serum carbamazepine concentrations. The assay accuracy is 99.8% with sensitivity of 0.50 µg/mL to 80 µg/mL and specificity ≥90 %.

**Adverse drug reactions:** Detection of adverse drug reactions was carried out by Naranjo’s algorithm.

**Statistical data analysis**

Data were presented as mean±SD, otherwise stated. Continuous data with normal distribution were tested using parametric statistical method (i.e. repeated ANOVA), while categorical data or non-normal distributed data was tested with Chi-square test. Correlation test was performed by parametric Pearson’s correlation test. SPSS 11.5 was used for statistical analysis.

**Results**

Table 1 shows characteristics of patients with monotherapy of carbamazepine. The majority of patients were female and all patients were age between 22-59 years. Their compliance was accounted for over 90% with average daily dose of 342.50±139.56 mg/day. The patients were diagnosed to have epilepsy or hemi facial spasm or trigeminal neuralgia (or neuralgia), whose average serum carbamazepine concentration was 4.88±2.43 (µg/mL).

**Arterial, venous loop diameters and tortuous index**

Significant decrease in arterial loop diameters was found after 2 months of treatment compared with those of baseline (9.05±1.07 µm [baseline] vs 8.88±1.10 and 8.78±1.15 µm, p=0.001) (Figure 1). In contrast to the arterial loop diameters, the venous loop diameters were not significantly changed after the same period of treatment (9.89.00±1.27 µm [baseline] vs 9.78±1.31 µm and 9.72±1.23µm, p=0.16) (Figure 2)
Table 1. Characteristics of patients with monotherapy of carbamazepine

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 (36.67%)</td>
</tr>
<tr>
<td>Female</td>
<td>38 (63.33%)</td>
</tr>
<tr>
<td>Age (yr) (range)</td>
<td>50.02±8.62</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>56.22±9.92</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.57±8.71</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.68±2.49</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>7 (11.67%)</td>
</tr>
<tr>
<td>Hemi facial spasm</td>
<td>13 (21.67%)</td>
</tr>
<tr>
<td>Trigeminal neuralgia, neuralgia</td>
<td>40 (66.66%)</td>
</tr>
<tr>
<td>Compliance (%)</td>
<td>99.21±1.40</td>
</tr>
<tr>
<td>Dose/day (mg/day)</td>
<td>342.50±139.56</td>
</tr>
<tr>
<td>Dose/kg/day (mg/kg/day)</td>
<td>6.29±3.01</td>
</tr>
<tr>
<td>Serum carbamazepine concentrations (µg/ml)</td>
<td>4.88±2.43</td>
</tr>
<tr>
<td>Brand</td>
<td></td>
</tr>
<tr>
<td>Tegretal CR® 200 mg</td>
<td>33 (55.00%)</td>
</tr>
<tr>
<td>Carmapine® 200 mg</td>
<td>27 (45.00%)</td>
</tr>
</tbody>
</table>

Figure 1. Change of arterial loop diameters after two months of the monotherapy of carbamazepine. Values are mean, N=60.
**Figure 2.** Change of venous loop diameters after two months of the monotherapy of carbamazepine. Values are mean, N=60.

Tortuous index, as the ratio between the widest part over the narrowest part of the capillary loop, was found to be 1.86±0.38 and 1.94±0.36 at the first and second month after treatment, respectively, and these values were significantly greater than that of baseline (1.64±0.32) \( (p<0.001) \) (Figure 3).

**Figure 3.** Tortuous index of the capillary loop after two months of the monotherapy of carbamazepine. Values are mean, N =60.
Relationship between serum carbamazepine concentrations and nailfold capillary structural change

Percentages of arterial loop diameter changes of the capillary, but not tortuous index, and serum carbamazepine concentrations were significantly correlated (r=−0.406, p<0.05)

Adverse drug reactions and their relationship with the nail-fold capillary changes

Possible adverse drug reactions, as detected by Naranjo’s algorithm, were obtained from all 60 patients whose adverse drug reactions were recorded two times. Therefore, there were the total visits of 120. When using 8 μg/mL as a cutoff concentration, the concentrations at which frequent adverse drug reactions usually found, 11 visits belonged to those with the concentrations ≥8 μg/mL (10.66±3.12 μg/mL) whereas 109 visits belonged to those with the concentrations <8 μg/mL (4.28±1.88 μg/mL). Table 2 shows number of adverse drug reactions in relation to the cutoff concentrations. It is evident that about or greater than twice adverse drug reactions were found when the concentrations ≥8 μg/mL. There was no clear evidence of any correlation between these apparent adverse drug reactions with detected nail-fold capillary changes

Table 2. Adverse drug reactions in relation to serum carbamazepine concentrations at the cutoff concentrations of 8 μg/mL.

<table>
<thead>
<tr>
<th>Adverse Drug Reactions</th>
<th>&lt; 8 μg/mL (109 visits)</th>
<th>≥ 8 μg/mL (11 visits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Somnolence</td>
<td>53* (48.62%)</td>
<td>10 (90.91%)</td>
</tr>
<tr>
<td>2. Dizziness</td>
<td>48 (44.04%)</td>
<td>8 (72.73%)</td>
</tr>
<tr>
<td>3. Nausea</td>
<td>15 (13.76%)</td>
<td>5 (45.45%)</td>
</tr>
<tr>
<td>4. Impair cognition</td>
<td>9 (8.26%)</td>
<td>3 (27.27%)</td>
</tr>
<tr>
<td>5. Lost of appetite</td>
<td>3 (2.75%)</td>
<td>3 (27.27%)</td>
</tr>
<tr>
<td>6. Ataxia</td>
<td>0 (0%)</td>
<td>3 (27.27%)</td>
</tr>
</tbody>
</table>

*unit as visit

Discussion

This present study is the first of its kind to investigate changes in nail-fold capillary structure in adult patients with monotherapy of carbamazepine. The decrease in diameter of the arterial loop of nail-fold capillary was detected together with the increased change in tortuous index. The mechanism involved in the decreased diameter of the arterial loop can be explained by inhibition of sodium voltage gated channel which is found both in the neuron system and on cell membrane of endothelial cells. The endothelial cells are present at the arteries to the arterioles\(^7\), as well as they also exist at the vein.\(^8\) Inhibition of the sodium
voltage gated channel by carbamazepine at the capillary loop, especially the arterial loop, causes the vessel to dilate, and thus increase the diameter, and subsequently a drop in blood pressure for a short-term manner. The event is also enhanced by inhibition of the central nervous system via sympathetic pathway by the drug. However, auto-regulatory blood pressure via the renin-angiotensin system later plays a role in compensating the drop in blood pressure by stimulating the contraction of arterioles and thus reducing the diameter of the arterial loop as shown in this present study. On the contrary, for a long-term inhibition of sodium voltage gated channel remodeling of neural cells occurs and leads to increase more tetrodotoxin resistant sodium voltage gated channels. As a result, hyperexcitable neurons exists and promotes more gradual transmission of sympathetic pathway in the long run. This remodeling explains discrepancy found between this present study and that of Gerstner et al. (2006) showing that capillary diameters, especially the venous loop, were increased as the subjects were treated with carbamazepine for a longer period ranging from 9 months to 4.5 years.

For the tortuous index, results from this present study are in accordance with those of Gerstner et al. that the index increases together with elevated capillary density. Mechanisms that can possibly explain these changes may be involved with influence of catecholamine change in the sympathetic pathway. Catecholamine affects endothelial capillary via cAMP associated receptors through catecholamine-sensitive cyclase, which are found to be abundant at the endothelial capillary. As a result, catecholamine then leads not only to capillary structural changes, but also their chemical composition changes as well. Currently, catecholamine, but not its analogues, is found to stimulate endothelial cell via IFN-gamma, which activates dibutyryl-cAMP. Other possible mechanisms may be involved with elevated homocysteine by anti-epileptic drugs (AEDs). Homocysteine and homocysteiene-related products has been shown to act as oxidants that are potential inducers of endothelial injury. Therefore, vascular damage, including tortuosity changes found with the nail-fold capillary, can possibly be observed after treatment by AEDs. Further research is needed to confirm these possible mechanisms.

This present study also show that at least percentage changes in arterial loop diameter are correlated with serum carbamazepine concentrations in a concentration-dependent manner. However, no established correlation between percentage changes in arterial loop diameter and concentration or dose-dependent apparent CNS adverse drug reactions. Further investigations concerning using and detecting appropriate outcomes of vascular adverse drug reactions in relation to nail-fold capillary structural changes are of interest.

Some limitations of this present study exist as follows: 1) This study was observational in nature, thus variation of doses could not be avoided, and the sample size was relatively small, other study designs with relative large sample size may be required to confirm these findings, 2) The disease effects on the findings could not clarify in this study due to not enough sample size for subgroup analysis, 3) Other outcomes such as flow rate and aggregation of erythrocytes, plasma-viscosity could not be measured due to limited capability of the nail microscope used. Higher capability of the instrument may be employed for further investigation, 4) Using only one operator without blinding to subject’s visit is a
potential bias of this study. However, one can find practical use of this finding, particularly in the field of pharmacokinetics and therapeutic drug monitoring (TDM). For the pharmacokinetics field, the changes in arterial loop diameters can be used as a covariate for population pharmacokinetics in order to estimate more accurate population pharmacokinetic parameters such as a clearance of carbamazepine. For the TDM field, practitioners can apply the established correlation between the percentage changes in arterial loop diameters and serum carbamazepine concentrations to estimate the steady-state concentrations of the drug. At the moment, ongoing research is being carried on to investigate a possibility in the population pharmacokinetics field.

In conclusion, this study demonstrates that there are changes in the nail-fold capillary structures, i.e. the arterial loop diameter and tortuous index. The possible mechanisms are discussion and are warranted for further investigations. Although there are some limitations of the study, the findings can be applied for a practical use such as for TDM or for further research in population pharmacokinetic study.

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References


