Cutaneous reactions in patients with solitary cysticercus granuloma on phenytoin sodium

G Singh, S Kaushal, M Gupta, S Chander Chopra

Several medical conditions are believed to be associated with an increased risk of cutaneous adverse reactions to antiepileptic drugs. The aim of this study was to study the frequency and nature of cutaneous reactions in a cohort of patients being treated with phenytoin sodium for seizures, who were divided into those with a solitary cysticercus granuloma (SCG) and those with a condition other than SCG, to determine if the presence of SCG increases the risk of cutaneous adverse reaction to phenytoin. A cohort of 117, consecutively begun on treatment with phenytoin for seizure control, were followed up prospectively for the development of cutaneous reactions. There were 63 patients with SCG upon imaging and 54 patients to whom phenytoin was administered for seizures due to causes other than SCG or multiple neurocysticercosis. Cutaneous reactions were significantly more common (p=0.02) in patients with SCG (9/63 patients; 14.3%) than in controls (2/54 patients; 3.7%). The spectrum of skin reactions in patients with SCG included benign skin rash (n=3), anticonvulsant hypersensitivity syndrome (n=4), Stevens-Johnson syndrome (n=1), and urticaria (n=1). Individuals with seizures due to SCG have a high incidence of cutaneous adverse reactions to phenytoin. This fact should be kept in mind when initiating them on treatment with this anti-epileptic drug.

S solitary cysticercus granuloma (SCG) is one of the most common presentations of neurocysticercosis. It manifests with seizures in young persons and presents upon computed tomography (CT) as a single enhancing lesion with surrounding oedema. The mainstay of management of patients with SCG is the administration of anti-epileptic drugs (AEDs) until such time as the granuloma resolves. Phenytoin sodium is perhaps the most frequently administered AED to individuals with SCG, on account of its reasonable cost, convenience of administration, and rapid achievement of therapeutic blood levels with oral or intravenous loading doses. Cutaneous adverse reactions significantly undermine the effectiveness of several AEDs, including phenytoin. A number of concomitant illnesses such as acquired immune deficiency syndrome, the application of cranial irradiation to patients with brain tumours, and certain viral infections, notably herpesvirus and cytomegalovirus, predispose to cutaneous adverse reactions to phenytoin. We have observed a high frequency of skin reactions among patients with SCG who are administered AEDs, most frequently phenytoin, for control of their seizures. Therefore, patients who were treated with phenytoin were prospectively followed up for the development of cutaneous reactions in order to determine if the presence of an underlying SCG predisposed them to allergic skin phenomena.

MATERIALS AND METHODS

Patient population

The study was conducted at the neurology outpatient and inpatient departments of the Dayanand Medical College, Ludhiana, India following institutional review board approval. The patient population comprised of 117 patients with a seizure disorder who were consecutively begun on treatment with phenytoin between 1 September 2000 and 31 October 2001 for control of seizures. Patients with multiple neurocysticercosis (n = 5), who were begun on phenytoin treatment were excluded from the study. The decision to institute phenytoin treatment was based upon indications and contraindications of the agent relative to other available AEDs. Young women on oral contraceptives were excluded from the study. Patients were then classified on the basis of the aetiology as determined by clinical, electroencephalographic, imaging, and other data into two groups: (a) SCG, and (b) others (those patients with seizures due to causes other than SCG and multiple neurocysticercosis).

Study design

All patients received a single brand of phenytoin sodium (Eptoin; Magnus, Mumbai, India). The mode of initialisation of treatment, including whether a loading dose was given or not, and intravenous oral route for the loading dose was recorded. In addition, prior histories of allergy (including drug allergy), atopy, and asthma, and current or recent helminthiasis were also recorded. An attempt was made to keep administration of concomitant medications to the minimum; all such medications and their doses and durations of administration were noted. Routine haemogram including an absolute eosinophil count was performed in all patients at the initial visit and at 3 weeks. Stool examinations for parasites were also performed at the first visit. Routine follow ups were scheduled at 3, 6, and 8 weeks following initiation of treatment, although patients could make unscheduled visits when required. Patients were counselled regarding the possibility of allergic reactions to phenytoin and were instructed to report any skin or mucous membrane lesion (transient or persistent skin rash in any form or itching or oral ulcers) or fever at the earliest opportunity.

Endpoints

The primary outcome measure was the development of a skin or mucous membrane reaction during first 8 weeks of treatment. Patients who developed a cutaneous reaction were evaluated by a dermatologist (M G). The reactions were classified into benign skin rash, anticonvulsant hypersensitivity syndrome (AHS), Stevens-Johnson syndrome (SJS).
toxic epidermal necrolysis, and skin condition that was not causally related to phenytoin administration (for example, urticaria) according to criteria described elsewhere.4

The nature and extent of the cutaneous reaction and its onset relative to initiation of phenytoin treatment, duration in days, presence or absence of fever, hepatomegaly, lymphadenopathy, and thyromegaly, laboratory (haematological, renal, hepatic, and thyroid function) abnormalities, and treatment given for the skin condition were noted.

Statistical analysis
The frequency of cutaneous reactions in cases and controls were compared using Fisher’s exact test. Student’s t test was used for categorical variables. p<0.05 was considered statistically significant.

RESULTS
Treated with phenytoin sodium was given to 117 patients. Included were 63 patients with an involuting SCG upon imaging studies (either magnetic resonance imaging or CT) and 54 patients with conditions other than SCG or multiple neurocysticercosis. Baseline characteristics of the two groups of patients including age (mean (SEM) (SD), 95% CI), gender, duration of seizures, mode of initiation of phenytoin treatment (oral or intravenous loading or maintenance doses), reported frequencies of prior allergy of any type, prior drug treatment (oral or intravenous loading, maintenance doses), medications apart from phenytoin at the time of or just prior to initiation of treatment was 20 (21) days (range 1–60 days) and duration was 11 (10) days (range 1–34 days). One patient who developed a skin rash within 1 day of initiation of phenytoin treatment had previously developed a phenoxyt rash, but this fact had not been disclosed to the treating physician at time of entry into the study; this individual was considered to be previously sensitised to the drug. In addition, she was also on concomitant treatment with sertraline and dothiepin. Apart from this patient, no patient who developed a cutaneous reaction was on any additional medications apart from phenytoin at the time of or just prior to onset of skin rash. Discontinuation of phenytoin treatment because of severe cutaneous reaction was undertaken in six patients with SCG. Clobazam (1 mg/kg as loading dose followed by 0.5 mg/kg maintenance doses) were used as an alternative AED in these patients. In three remaining patients (including one patient with urticaria) it was possible to continue phenytoin treatment. In at least six patients with

<p>| Table 1 | Comparison of selected demographic, clinical and laboratory parameters in patients who were initiated on phenytoin sodium treatment for seizures due to an underlying SCG and those with conditions other than SCG |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>SCG n=63</th>
<th>Others n=54</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SEM) (SD) 95% CI</td>
<td>23 (2) (14) 19–25</td>
<td>28 (2) (17) 23–32</td>
<td>0.03</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>49</td>
<td>44</td>
<td>NS</td>
</tr>
<tr>
<td>Females</td>
<td>14</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Duration of seizures (in months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SEM) (SD) 95% CI</td>
<td>7 (2) (14) 0–21</td>
<td>19 (5) (38) 9–29</td>
<td>0.02</td>
</tr>
<tr>
<td>Prior allergies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>4</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Drug rash</td>
<td>13</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Helminthiasis</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Initial phenytoin treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous loading</td>
<td>12</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Oral loading</td>
<td>47</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Oral maintenance</td>
<td>4</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Baseline hematological parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total leucocyte count (/mm³)</td>
<td>6601 (266) (2106)</td>
<td>6870 (294) (2157)</td>
<td>NS</td>
</tr>
<tr>
<td>Range 3900–15130</td>
<td>3800–12900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute eosinophil count (/mm³)</td>
<td>340 (47) (372)</td>
<td>180 (29) (216)</td>
<td>0.019</td>
</tr>
<tr>
<td>Range 20–2020</td>
<td>0–1010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematological parameters at 3 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total leucocyte count (/mm³)</td>
<td>5303 (349) (2762)</td>
<td>5471 (3520) (2586)</td>
<td>NS</td>
</tr>
<tr>
<td>Range 4500–11600</td>
<td>4400–12900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute eosinophil count (/mm³)</td>
<td>300 (37) (293)</td>
<td>164 (36) (264)</td>
<td>0.024</td>
</tr>
<tr>
<td>Mean (SEM) (SD)</td>
<td>20–1700</td>
<td>0–1400</td>
<td></td>
</tr>
</tbody>
</table>

SEM, standard error of mean; SD, standard deviation; 95% CI, 95% confidence intervals; SCG, solitary cysticercus granuloma; NS, not significant
SCG and two non-SCG patients, cutaneous reactions were considered to be causally related to phenytoin because they improved upon drug withdrawal. Two patients in whom the skin rash disappeared in spite of persisting with phenytoin treatment were considered to have a benign drug rash,15 while one patient was determined to have urticaria. When patients with SCG were arbitrarily divided on the basis of duration of seizures, it was noted that 8/47 (17.0%) patients with a seizure duration of <3 weeks and 1/16 (6.3%) with duration of seizures of >3 weeks developed cutaneous reactions (NS).

**DISCUSSION**

This preliminary, prospective, observational study demonstrates a significantly increased frequency of cutaneous reactions in patients with SCG. The reasons for this increased incidence are conjectural at present. Drug induced cutaneous adverse reactions clearly have an immune basis, with possible genetic predisposition. There is evidence for involvement of both CD4+ and CD8+ cells and of both Th1 and Th2 pathway related cytokines in the generation of adverse cutaneous reactions.9–11 The role of Th1 and Th2 pathways and of different cytokines in the natural history of neurocysticercosis is also being actively studied.9 For instance, Evans et al recently documented an increased expression of eosinophil selective mediators, eotaxin and interleukin-5, in treatment naive individuals with cysticercosis.8 Thus, molecular pathways leading to increased recruitment of eosinophils, which in turn may further release pro-inflammatory cytokines and mediators may be surmised to underlie the predisposition of patients with SCG to phenytoin induced cutaneous adverse reactions. In contrast, suppression of both the Th1 and Th2 arms of the immune response through activation of tumor necrosis factor β may occur in patients with head trauma (A Clinton White, personal communication, 2001). This may in turn protect head injured patients from AED induced cutaneous adverse reactions. This is important in view of that individuals with head trauma often receive phenytoin treatment for seizure prophylaxis.

Pertinent to any conclusions from this study is an analysis of the differences between the two groups. There were significant differences between mean age and seizure duration between the SCG and non-SCG groups (table 1). In addition, co-medications may be a confounding factor by either predisposing to or protecting individuals from drug rash. The inclusion of one patient with urticaria may be justified on the grounds of presenting the complete spectrum of cutaneous reactions in patients with SCG, although this does not imply that phenytoin was causal in this case.

From the point of view of treatment, discontinuation of phenytoin in the event of cutaneous reaction remains an important decision, although as shown in our study, it may be possible to continue with phenytoin treatment in certain patients under careful observation. In those instances where discontinuation is undertaken, it is important to avoid substitution with another aromatic AED because of the high frequency of cross reactions that are known to occur.9 In the present study, patients who were discontinued from phenytoin treatment were treated with clobazam. The latter was found to be effective for seizure control and did not cause cutaneous adverse reactions in any of the patients to whom it was given.

In conclusion, patients with SCG have a high frequency of cutaneous adverse reactions to phenytoin. This phenomenon needs to be confirmed by more systematic, controlled studies of similar nature in other geographical locations as it may represent a regional or ethnic phenomenon. Moreover, the issue needs to be addressed with greater depth to include monitoring of serum cytokine and immunoglobulin levels, patch and lymphocyte stimulation tests, and drug rechallenge.14 15

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