Hospitalization for serious blood and skin disorders following co-trimoxazole

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Aims: To quantify the risk of serious blood and skin disorders requiring hospitalization among otherwise healthy users of co-trimoxazole.

Methods: We conducted a population-based cohort study at Group Health Cooperative of Puget Sound (GHC).

Results: During the years 1987 to 1993 we found six cases of co-trimoxazole-associated blood disorders and three cases of co-trimoxazole-associated skin disorders yielding risks of 5.6/100,000 (95% CI 2.6–12.2) and 2.8/100,000 (95% CI 0.9–8.2) respectively. In all cases found there was prompt recovery after discontinuation of co-trimoxazole. We found no cases of toxic epidermal necrolysis.

Conclusions: We conclude that the risk of blood and skin disorders associated with the use of co-trimoxazole leading to hospitalization is low.

Keywords: co-trimoxazole, adverse drug reactions, blood disorders, skin disorders, toxic epidermal necrolysis, Stevens-Johnson syndrome

Introduction

Serious blood and skin disorders associated with co-trimoxazole have been described in numerous reports [1–4]. We have previously published the results of a population-based cohort study providing quantitative information on the risk of co-trimoxazole-associated serious blood and skin disorders using data from the General Practice Research Database (GPRD) in the United Kingdom [5]. In order to provide further quantification of this risk, we performed a similar study based on information obtained from Group Health Cooperative of Puget Sound.

Methods

Group Health Cooperative (GHC) is a consumer-owned organization that provides medical care at clinics and hospitals in the Seattle, Washington area [6]. As of 1994 it had more than 380,000 members. The plan covers the cost of ambulatory and inpatient medical care and most prescriptions. Automated files of drugs dispensed to individual members have been maintained since July 1975. Information on admissions to Group Health hospitals, including discharge diagnoses, have been recorded on computer since 1972 [6].

For the current study we identified all persons in the Seattle area, who filled at least one prescription for co-trimoxazole between January 1, 1987 and December 31, 1993 and identified those hospitalized with a diagnosis of a potentially serious blood disorder [7] (ICD-8 codes 2839, 2849, 2871, 2880, 2881, 2889, 2899) or skin disorder [4] (ICD-8 695x) within 45 days of a prior prescription for co-trimoxazole. Patients with a diagnosis of cancer or acquired immunodeficiency syndrome (AIDS) prior to the event were excluded from the study cohort.

Hospital discharge summaries together with available consultation reports were obtained for all patients to identify a potentially drug-inducible illness. Case histories were reviewed by the authors who gave strong consideration to the clinical diagnoses made by the physicians who cared for the patients.

Results

We identified 107,689 eligible subjects who filled 229,386 prescriptions for co-trimoxazole. Thirty-one percent were below age 20 years, 45% were age 20–59, and 24% were age 60 years or older. Sixty-five percent were women and 57% received only one prescription for the drug.

We identified and reviewed the clinical records of 24 patients with a coded hospital discharge diagnosis of a blood or skin disorder. After review fifteen patients were excluded: four diagnosed with idiopathic thrombocytopenic purpura, three with a viral illness, one each with AIDS (not documented on the computer record), infection, plasma cytosis, collagen vascular disease, and undocumented study drug exposure; two had the illness prior to receipt of co-trimoxazole, and in one the diagnosis was not confirmed.

There remained nine patients with an illness for which a causal connection with co-trimoxazole could not be ruled out. Six had a newly-diagnosed blood disorder and three patients had a newly-diagnosed skin disorder, (see Table 1 for details).

Blood disorders

Among the six patients with blood disorders, a causal connection to co-trimoxazole was considered to be probable in three—one each of pancytopenia, leukopenia and thrombocytopenia. The time from first use was 5 weeks, 6 days and 2 weeks respectively. Co-trimoxazole was
Table 1 Details of cases of co-trimoxazole-associated blood and skin disorders.

<table>
<thead>
<tr>
<th>Age/Sex (years)</th>
<th>Diagnosis</th>
<th>Duration of use</th>
<th>Causal assessment</th>
<th>Duration of hospitalization</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 M</td>
<td>Pancytopenia</td>
<td>5 weeks</td>
<td>Probable</td>
<td>7 days</td>
<td>Recovered</td>
<td>Attributed clinically to co-trimoxazole.</td>
</tr>
<tr>
<td>33 F</td>
<td>Leukopenia</td>
<td>6 days</td>
<td>Probable</td>
<td>2 days</td>
<td>Recovered</td>
<td>Attributed clinically to co-trimoxazole.</td>
</tr>
<tr>
<td>66 M</td>
<td>Thrombocytopenia</td>
<td>2 weeks</td>
<td>Probable</td>
<td>2 days</td>
<td>Recovered</td>
<td>Attributed clinically to co-trimoxazole.</td>
</tr>
<tr>
<td>26 F</td>
<td>Neutropenia</td>
<td>4 days</td>
<td>Possible</td>
<td>2 days</td>
<td>Recovered</td>
<td>Clinical diagnosis—viremia or reaction to co-trimoxazole.</td>
</tr>
<tr>
<td>5 F</td>
<td>Neutropenia</td>
<td>4 days</td>
<td>Possible</td>
<td>2 days</td>
<td>Recovered</td>
<td>Clinical diagnosis—viral or co-trimoxazole cause</td>
</tr>
<tr>
<td>57 M</td>
<td>Thrombocytopenia</td>
<td>Uncertain</td>
<td>Possible</td>
<td>3 days</td>
<td>Recovered</td>
<td>Concomitant exposure to mefloquine.</td>
</tr>
<tr>
<td>Skin disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 M</td>
<td>Stevens Johnson</td>
<td>20 days</td>
<td>Probable</td>
<td>6 days</td>
<td>Recovered</td>
<td>Attributed clinically to co-trimoxazole. Prior exposure to ceftriaxone, gentamicin, doxycycline.</td>
</tr>
<tr>
<td>28 F</td>
<td>Stevens Johnson</td>
<td>10 days</td>
<td>Probable</td>
<td>4 days</td>
<td>Recovered</td>
<td>Attributed clinically to co-trimoxazole.</td>
</tr>
<tr>
<td>3 M</td>
<td>Erythema multiforme</td>
<td>10 days</td>
<td>Possible</td>
<td>1 day</td>
<td>Recovered</td>
<td>Exposure to erythromycin.</td>
</tr>
</tbody>
</table>

The age distribution of the nine cases is similar to the distribution in the study population. Five patients (55%) were male.

Discussion

This population-based follow-up study was designed to estimate the risk of hospitalization for blood and skin disorders among users of co-trimoxazole at GHC in otherwise healthy patients. In the more than 100,000 users identified we found only a small number of blood or skin illnesses in hospitalized patients that were considered to be probably or possibly causally related to co-trimoxazole.

Several cases of neutropenia, two cases of thrombocytopenia, one case of leukopenia and one case of pancytopenia. Of these, three patients had an illness where co-trimoxazole was clinically implicated as the cause of the illness. In the remaining three patients a causal connection with co-trimoxazole seemed possible in one patient diagnosed with erythema multiforme. The duration of hospitalization in this case was only one day with subsequent recovery.

The estimated risk of probable or possible skin disorders among co-trimoxazole users was 3/107,689 or 2.8/100,000 (95% CI 0.9–8.2). In all patients co-trimoxazole was discontinued and all had a complete recovery. In a previously published cohort study using data from the GPRD in the UK we estimated the risk of hospitalization for important blood illnesses among those exposed to co-trimoxazole to be 5.6/100,000 (95% CI 2.6–12.2).

Table 2 Risk of blood and skin disorders associated with co-trimoxazole.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Number of patients</th>
<th>Rate/100,000</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>6</td>
<td>5.6</td>
<td>2.6–12.2</td>
</tr>
<tr>
<td>Skin</td>
<td>5</td>
<td>2.8</td>
<td>0.9–8.2</td>
</tr>
</tbody>
</table>

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days (see Table 1). In our prior study such patients may well have been treated as outpatients.

We found three cases of skin disorders that were hospitalized. Importantly, there were no cases of toxic epidermal necrolysis. In two cases co-trimoxazole was implicated as the cause of illness and in one case the causal relation was considered possible yielding a risk estimate of 2.6/100,000 (95% Cl 0.9–8.2). These results are consistent with an earlier study based on GHR which reported the incidence of hospitalizations for skin disorders among users of co-trimoxazole to be 2.6/100,000 [4] and with our prior study based on the GPRD [5], which yielded a risk estimate of 1.7/100,000 for skin disorders associated with the drug.

In summary, the results of the present study provide further quantitative evidence that the risk of newly-diagnosed blood and skin disorders requiring hospitalization among users of co-trimoxazole is low. Our findings together with the results of previous studies provide reassurance about the safety of this antibiotic.

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References


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