Hospitalization for serious blood and skin disorders following use of co-trimoxazole

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Aims
The objective of this study was to quantify the risk of serious blood and skin disorders associated with co-trimoxazole.

Methods
We conducted a population-based cohort study of serious blood and skin disorders requiring hospitalization among otherwise healthy users of co-trimoxazole at Group Health Cooperative and Puget Sound (GHC).

Results
During the years 1987 to 1993 we found six cases of co-trimoxazole-associated blood 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
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 60 years or older. Sixty-five percent were women and 57% received only one prescription for the drug. 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.

Results
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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, polymyositis, 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. 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.

Blood disorders
Among the six patients with blood disorders, 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.)
in three—one case each of pancytopaenia, leukopaenia and thrombocytopaenia. The time from first use was 5 weeks, 6 days and 2 weeks respectively. Co-trimoxazole was discontinued and all patients improved and were discharged from the hospital within 7 days.

Three patients had a newly-diagnosed blood disorder where a causal relation was considered clinically only possible—two with a diagnosis of neutropaenia and one with thrombocytopaenia. All three patients recovered promptly after discontinuing the drug.

Overall the estimated risk of probable or possible blood disorders among users of co-trimoxazole was 6/107 689 or 5.6/100 000 (95%CI 2.6–12.2) (Table 2).

**Skin disorders**

Three patients had a diagnosis of either erythema multiforme or Stevens Johnson syndrome—none with toxic epidermal necrolysis. A causal connection between the skin disorder and co-trimoxazole was considered to be probable in two cases—both with a diagnosis of Stevens Johnson syndrome. In both patients co-trimoxazole was discontinued with prompt recovery. A causal connection with co-trimoxazole seemed possible in one patient diagnosed with erythema multiforme. The duration of hospitalization in this case was only 1 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). The age distribution of the nine cases is similar to the distribution in the study population. Five patients (55%) were male.

**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/10^6</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>3</td>
<td>2.8</td>
<td>0.9, 8.2</td>
</tr>
</tbody>
</table>

**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.

Newly-diagnosed blood disorders occurred in six patients. There were two cases of neutropaenia, two cases of thrombocytopaenia, one case of leukopaenia and one case of pancytopaenia. 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 to co-trimoxazole was considered to be possible, but an alternative aetiology could not be ruled out. Assuming that all cases were caused by the study drug, the incidence of co-trimoxazole-associated blood disorders was estimated to be 5.6/100 000 (95%CI 2.6–12.2). 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 0.9/100 000 [5]. The somewhat higher risk estimate in the current study may have been due to chance or to differences in criteria for hospitalization in the two study populations. In the current study four of the six cases were hospitalized for less than 3 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 2.8/100 000 (95%CI 0.9–8.2). These results are consistent with an earlier study based on GHC 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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