allowing us access to data of such high quality, to Dr Lucy Carpenter for her valuable comments and advice, and Ms Sarah Jones for typing the drafts of this manuscript.

The three adverse outcomes studied here are not independent measures of prematurity. Low birthweight and preterm delivery are highly correlated, and RR estimates for each are often similar in the same occupational group. Small-for-gestational age is a composite measure of birthweight and gestational age. It is noteworthy that the risk of this adverse outcome hardly varied between occupational groups; this suggests that occupational factors act by increasing the risk of preterm delivery, rather than by slowing intrauterine growth.

In conclusion, these data indicate that neither maternal nor paternal occupational exposures have strong effects on the risk of prematurity. Where there is evidence of adverse effects, they are associated with maternal rather than with paternal exposures.

We thank Dr Susan Cole, Scottish Information Services Division, for allowing us access to data of such high quality, to Dr Lucy Carpenter for her valuable comments and advice, and Ms Sarah Jones for typing the drafts of this manuscript.

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HYPOTHESIS

Adverse reactions to co-trimoxazole in HIV infection

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The origin of the increased frequency of side-effects to co-trimoxazole in HIV-positive patients is unknown. Data on plasma concentrations of the parent compounds are inconclusive. Evidence points to the hydroxylamine derivatives of sulphonamethoxazole as the reactive metabolites that cause adverse reactions to co-trimoxazole. HIV-positive individuals have a systemic glutathione deficiency, and therefore a reduced capacity to scavenge such metabolites. This process would lead to an increased exposure to toxic intermediates and would explain the high frequency of adverse reactions to co-trimoxazole in these patients.


Pneumocystis carinii pneumonia is an important opportunistic illness in patients with the acquired Immunodeficiency syndrome (AIDS). Treatment with a high dose of co-trimoxazole—20 mg/kg trimethoprim (TMP) and 100 mg/kg sulphonamethoxazole (SMX)—is recommended. The frequency of adverse reactions to co-trimoxazole in patients with AIDS (40-80%) is much higher compared with other patients, even those who are immunodeficient.1,4 The explanation for this increased side-effect profile is unknown.

Trimethoprim and possible side-effects

Controversy exists as to whether side-effects depend on serum concentrations of TMP.4,7 Serum concentrations above 25 mg/l in patients with AIDS may be associated with leucopenia, and dose reduction to maintain serum concentrations between 5 and 8 mg/l may reduce the risk of bone marrow suppression while preserving antimicrobial efficacy.7 Other studies have shown that the serum concentration of TMP was 48% higher in patients treated with TMP and dapsone compared with patients treated with TMP and SMX, whereas adverse events were more common in the TMP/SMX group.4,8 TMP inhibits dihydrofolate reductase and can cause megaloblastic anaemia and neutropenia in patients whose folate stores are deficient. In some patients, megaloblastic changes in bone marrow have been found despite normal serum folate concentrations.6 However, other studies have

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either failed to find megaloblastic changes or report no therapeutic benefit with folic acid. A different mechanism that explains the haematological changes has been described. Antibodies to polymorphonuclear cells have been found in untreated HIV-infected patients and were shown to increase according to the degree of neutropenia in co-trimoxazole-treated AIDS patients. Therefore no convincing data show that TMP is the main cause of the side-effects in such patients, although a contributory role cannot be excluded.

**Sulphamethoxazole and possible side-effects**

The relevance of serum concentrations of SMX to the development of adverse reactions in AIDS patients is also controversial. Some workers do not believe that high serum SMX concentrations are a contributory factor, whereas other groups do share this belief. Other mechanisms may be more important, such as formation of sulphamamide metabolites.

Sulphamethoxazole is metabolised (figure) by N-acetyltransferase (50-70%) to N4-acetylsulphamethoxazole (N4-SMX), and by the cytochrome-P450 system (10-15%) to 5-hydroxysulphamethoxazole (SMX-50H). SMX can also be oxidised on the N4 position to form a hydroxylamine derivative. The rate of production of this reactive intermediate may be influenced by the rate of acetylation of the parent compound, which suggests that acetylator status is important. Inherited differences in the rate of production of this reactive metabolite may also contribute to this process. The hydroxylamine metabolite is an electrophilic, reactive compound that can bind covalently to macroglobulins; it must be scavenged by the oxidant-buffering capacity of glutathione before it is excreted in the urine. In-vitro studies show that hydroxylamine metabolites lead to increased cytotoxicity towards lymphocytes of patients with a clinical history of sulphamamide hypersensitivity compared with control lymphocytes of non-allergic individuals. The cytotoxicity of these hydroxylamine derivatives diminished after coincubation with glutathione or N-acetylcysteine. Hydroxylamine derivatives may have a direct cytotoxic action because of the ability of these electrophilic species to bind to macroglobulins. This process may lead to formation of haptons that can stimulate an immune response. Scavenging of these hydroxylamine derivatives by glutathione might be crucial for prevention of covalent binding and toxicity. Hypersensitivity may be due to increased production of a reactive metabolite together with the relative inability of tissues to detoxify such a substance.

**Glutathione concentrations in HIV-positive individuals**

Glutathione is an important antioxidant. In patients with AIDS, as well as in symptom-free HIV-positive individuals, glutathione concentrations in both serum and bronchoalveolar lavage fluid were significantly reduced. The mechanisms that lead to this systemic glutathione deficiency are unknown. Decreased glutathione synthesis, increased catabolism, and increased use could all be involved. The reactive metabolites of sulphamethoxazole are scavenged by glutathione. The formation and scavenging of hydroxylamine derivatives takes place throughout the body, since both the cytochrome-P450 system and glutathione are widely distributed.

**Hypothesis**

The hydroxylamine derivatives of sulphamethoxazole are the reactive metabolites that cause adverse reactions to co-trimoxazole. HIV-positive individuals have a systemic glutathione deficiency, and therefore a reduced capacity to scavenge such reactive metabolites. This process would lead to an increased exposure to toxic intermediates and would explain the high frequency of adverse reactions to co-trimoxazole in these patients. When adverse reactions to co-trimoxazole do occur, dose reduction will often diminish the severity of these events. This observation suggests a dose-related toxicity rather than true hypersensitivity but, as discussed above, measurements of serum concentrations of the parent compounds TMP and SMX do not clearly support this relation. Toxicity may be caused by the metabolite rather than the parent compound. Inherited differences in the rate of production of these (toxic) metabolites, like acetylator status, could add to an individual's susceptibility to adverse events and would explain the lower frequency of side-effects reported in African, Haitian, and black American patients with AIDS. The observation that side-effects occur after 8 to 12 days might suggest a role for a metabolite, either by slow accumulation or by an immune response that the metabolite could initiate.

Although our hypothesis seems attractive because the formation of hydroxylamine derivatives is theoretically likely, detection of these reactive species by methods such as high-performance liquid chromatography, has never been reported. Furthermore, hydroxylamine derivatives can have either a direct toxic effect or function as a hapten, but which of the side-effects of sulphamethoxazole in HIV-positive patients are toxic or immunological remains unclear. In addition, a possible contributory role of TMP cannot be excluded. Like sulphamethoxazole, TMP has a para-aminogroup that could be oxidised to form hydroxylamines. Glutathione synthesis requires sulphur-containing aminoacids and their metabolism is linked to folic acid and cobalamin; TMP could influence this synthetic pathway.

There are two ways to substantiate this hypothesis. Firstly, N-acetylcysteine could be added to co-trimoxazole treatment. N-acetylcysteine replenishes cysteine and sustains glutathione synthesis when demand for glutathione is increased. Secondly, by selecting sulphamidines that are not easily N-hydroxylated, the generation of reactive metabolites might be prevented. With these modifications of the standard regimens of prophylaxis against *Pneumocystis carinii* pneumonia, side-effects could be largely eliminated.

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