Toxicity of sulphonamide-diaminopyrimidine combinations: implications for future use

Numerous reasons were originally found to justify the use of sulphanethoxazole and trimethoprim in combination. Wide spectrum bactericidal activity and in-vitro synergy had been demonstrated and a plausible mechanism of action proposed. The matched serum pharmacokinetics of the constituents were believed to result in optimally synergistic concentration ratios in tissues and clinical trials had shown high efficacy in a variety of bacterial infections. Similar arguments were advanced for subsequent sulphonamide-diaminopyrimidine combinations, and some, for example cotrimazine, were partly promoted on the suggestion of even greater pharmacokinetic compatibility.

Currently none of these concepts remain unchallenged. It is appreciated that optimal ratios are rarely attained in tissues and urine (Reeves & Wilkinson, 1979) and significant resistance has emerged, calling in question the usefulness of sulphonamide in preventing resistance emergence to trimethoprim (Lacey, 1982). Additionally, as discussed by Burchall (1979), the sequential blockade hypothesis of sulphonamide-diaminopyrimidine action and synergy has been disputed in favour of the alternative hypothesis: that the activity of cotrimoxazole results from the action of both constituents, but largely that of trimethoprim, on dihydrofolate reductase. If, as is thought, trimethoprim optimally inhibits this enzyme (Poe, 1976) then addition of sulphonamide may be of no value. Thus, although some laboratory studies demonstrate synergy in the presence of sub-optimal concentrations of each constituent, others have found that synergy cannot be demonstrated if the concentration of trimethoprim alone is inhibitory (Anderson et al., 1974). Some comparative clinical trials, which show trimethoprim monotherapy to be as effective as co-trimoxazole, support the assertion that laboratory synergy is irrelevant in vivo. For example, trimethoprim alone is as effective as co-trimoxazole in urinary and respiratory tract infections (Lacey et al., 1980; Trimethoprim Study Group, 1981), in suppression of bacteriuria (Kasanen et al., 1974), in enteric fever (A. M. Geddes, personal communication) and in travellers' diarrhoeas (Dupont et al., 1982).

Therefore the continued use of sulphonamide-diaminopyrimidine antibacterials must surely be questioned. Under these circumstances the wide variety of toxic effects attributable to the combinations, mostly typical of the sulphonamide moiety, cannot enhance their reputation.

The recent communication from the Committee on Safety of Medicines (CSM) (1985) has spotlighted the latter problem. The safety of these combinations was subsequently addressed by Lacey et al. (1985) who, drawing attention to the 'toxicity and fatalities associated with sulphonamides'... 'would urge the Committee on Safety of Medicines to consider removing the (co-trimoxazole) product licence for many indications'. This view of sulphonamides is not new for, 20 years ago, Murdoch (1965) considered that 'there is today almost invariably a suitable, effective and less toxic alternative to any sulphonamide'. What then of the 'toxicity and fatalities' associated with sulphonamides? In the 1950s Hawking and Lawrence (quoted by Murdoch, 1965) considered the major adverse effects to be (a) crystalluria (b) sensitisation, producing drug fever and rashes, and (c) marrow toxicity. Although crystalluria is no longer a problem with modern, more soluble sulphonamides, the problems of idiosyncratic hypersensitivity and marrow effects remain.

The sulphonamides used in the combinations are medium- to long-acting derivatives. As these agents rarely achieve optimal synergy ratios with trimethoprim in tissues and appear more likely to produce hypersensitivity effects, their choice can be criticised. The high incidence of skin reactions to long-acting sulphonamides has been recognized for many years. Rallison and his colleagues reported (Rallison, O'Brien & Goode, 1961) a 2.7% incidence (35 of 1302 patients) of serious, usually cutaneous, reactions to sulphamethoxypyridazine; six patients died, mostly of the Stevens-Johnson syndrome. Subsequently the FDA investigated the association of this syndrome with long-acting sulphonamides. A total of 116 cases was identified between 1957 and 1965, 79 of which occurred in children in whom the mortality was 25% (O'Carroll, Bryan & Robinson, 1966). This incidence far exceeded that previously associated with short-acting agents. With co-trimoxazole, skin eruptions typical of sulphonamides occurred in 1.6-8.0% of recipients (Salter, 1973) and one-third of all adverse reports referred to cutaneous eruptions (Frisch, 1973). The current CSM report attributes 14 deaths to co-trimoxazole skin reactions. The majority of deaths (50 of 110 patients) reported by the CSM, however, were caused by co-trimoxazole-related blood dyscrasias. Long-term toxicity reports on co-trimoxazole and ampicillin were compared. Co-trimoxazole was associated with a seven-fold greater incidence of deaths (1.42 per million prescriptions;
ampicillin 0.18 per million prescriptions), with a 15-fold greater incidence in the elderly than in patients aged less than 40 years. In their subsequent critique, Lacey et al. (1985) considered that 'an immediate withdrawal of (co-trimoxazole) in the elderly seems warranted', a view which may attract support.

Previously Havas, Fernex & Lennox Smith (1973) had noted that 0.35% of 37,000 patients suffered haematological reactions to co-trimoxazole and Frisch (1973), analysing 2151 adverse reaction reports, found that 9% were of blood dyscrasias, of which neutropenia and thrombocytopenia comprised 56% and anaemias 24%. In a mixture of white and black children, Asmar, Maqbool & Dajani (1981) found that the incidence of co-trimoxazole induced neutropenia was seven times as great as that caused by ampicillin \( (P<0.001) \) and that thrombocytopenia occurred in 12% of those treated with co-trimoxazole, compared with none receiving ampicillin \( (P<0.01) \). However, a subsequent study in negro children found no significant difference in the incidence of neutropenia caused by co-trimoxazole and amoxycillin (Feldman et al., 1985). These authors criticized the original study on the grounds of its definition of neutropenia, as a significant proportion of healthy black children have neutrophil counts lower than the accepted normal range in white children.

The effects of trimethoprim and sulphonamide combinations on haematopoiesis result from inhibition of human, 1-carbon-unit-dependent purine metabolism, secondary to interference with folate synthesis. However, the literature is confusing, some human studies demonstrating measurable falls in available serum folate levels (Jenkins, Hughes & Hall, 1970) and others finding no significant changes (Davis & Jackson, 1973). Subsequently Bateson, Hayes & Pendharkar (1976), using an isotope folate assay, found no changes and suggested that previously reported reductions were caused by interference with co-trimoxazole with microbiological folate assays.

The CSM report attributed only three deaths from blood dyscrasia to trimethoprim but commented that, as experience of trimethoprim monotherapy was limited to two to three million prescriptions, it would be 'unwise to assume that it (trimethoprim) is substantially less liable to cause fatal adverse reactions'. However, although trimethoprim may impair the response to haematinic therapy in patients with megaloblastic anaemia (Chanarin & England, 1972), it is much less likely to affect haematopoiesis than co-trimoxazole (Golde, Bersch & Quan, 1978). Trials comparing trimethoprim with co-trimoxazole have usually shown a much reduced incidence of adverse reactions in the groups receiving monotherapy (Kasanen et al., 1974; Lacey et al., 1980). In Finland, where trimethoprim has been extensively used alone, Kasanen et al. (1978) found no cases of serious skin reactions and, in patients receiving chronic urinary prophylaxis, no haematological side effects other than an insignificant reduction in serum folate. Unfortunately, no studies to date have compared sufficient patients either to encounter serious haematological or cutaneous reactions, or to show a significant difference in their incidence following treatment with co-trimoxazole or with trimethoprim alone.

Therefore, although the CSM article causes additional concern over the continued use of sulphonamide-diaminopyrimidine combinations, there remains no objective proof that the substitution of trimethoprim alone would significantly reduce serious adverse reactions. At the recent meeting on 'Fifty years of sulphonamides' a short questionnaire was distributed to attending members of the British Society for Antimicrobial Chemotherapy. Only 34% returned the questionnaire, but 75% of respondents had read the CSM documents; 53% of these considered that the report would decrease their use of co-trimoxazole and 78% felt that it should have contained more positive comment. Of the latter group, 73% suggested that criticism of co-trimoxazole would have been appropriate and 89% of all those sampled considered trimethoprim alone to be significantly less toxic than co-trimoxazole. However, only 36% of those responding considered trimethoprim to be as effective as co-trimoxazole overall, although a further 32% felt the two to be equivalent in urinary tract infection. The survey was rather small and judicially, in Scotland at least, evidence based on these data would necessitate a verdict of 'not proven'. It will be interesting to observe future trends in the use of trimethoprim sulphonamide combinations in the U.K.

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References
Leading articles


These three leading articles derived from the meeting of the British Society for Antimicrobial Chemotherapy: Fifty Years of Sulphonamides, held in London on 1 November 1985. The first paper on the treatment of puerperal sepsis with Prontosil, by Colebrook & Kenny, appeared in the Lancet of June 6th, 1936.