


Evolution of the bacterial dihydrofolate reductase inhibitors

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Sir,

Numerous pyrimidine and purine analogues were synthesized in the late 1940s as potential nucleic acid antagonists. Particular interest was devoted to antagonists of thymine. It was quickly realized that the 2,4-diaminopteridines inhibit folic acid utilization and that this was a general property of all of these compounds (Hitchings *et al.*, 1950; Hitchings, 1989).

It was recognised that the 3,4,5-trimethoxydiaminopteridine-derivative was outstanding for its breadth of antibacterial activity. Consequently it was selected for detailed study and clinical trials in 1959 (Roth *et al.*, 1962) and given the name trimethoprim. Subsequently a 3,4-dimethoxy-5-bromo derivative was also found to be active. The role of bromine substitution on the benzyl-ring of trimethoprim was later confirmed with an analogue in which the 4-methoxy group, instead of being in the 5 position, was substituted by this halogen; the compound was synthesized in 1972 (Kompis *et al.*, 1980) and named brodimoprim. The effect of this substitution was to improve the trimethoprim binding to bacterial DHF R (Then & Hermann, 1984), providing equivalent or better antibacterial activity, improving lipid solubility and the pharmacokinetic behaviour, and to achieve sufficiently high concentrations at the infection site (Weidekamm, 1993).

Trimethoprim was put forward as a potential for sulphonamides for the treatment of bacterial infections: sulphamethoxazole was chosen as the sulphonamide owing matched half-life of trimethoprim. It was argued that the combination of sulphamethoxazole and trimethoprim, later given the name co-trimoxazole in Europe, offered several antimicrobial advantages (Hitchings, 1989).

Since its introduction in 1968 co-trimoxazole is still widely used for the treatment of a wide variety of bacterial infections, toxoplasmosis and in particular *Pneumocystis carinii* pneumonia. However, in many circumstances, it is the trimethoprim moiety of this combination that is responsible for its clinical effectiveness owing to increasing bacterial resistance to the sulphonamide. In fact, the sulphonamide moiety of the mixture may be disadvantageous because of a number of adverse reactions and drug interactions which are more common in the elderly and chronically ill patients, or in those receiving prolonged high dose treatment (Reeves, 1982; Kucers, Bennett & Kemp, 1987; British National Formulary, 1993; Brumfitt & Hamilton-Miller, 1994). Trimethoprim became available for use as a single drug in 1973 and brodimoprim 20 years later (Periti *et al.*, 1993).

Trimethoprim alone has been shown in clinical trials to be as effective and better
tolerated than the combination with sulphamethoxazole. The advantage of co-trimoxazole over trimethoprim has been proven in a limited number of infections; among these pneumocystosis, remains an extremely important indication for the use of co-trimoxazole at high dose (Reeves, 1982; Braunsteiner & Fisinger, 1993; Brumfit & Hamilton-Miller, 1994).

Bacteria have been shown to acquire resistance to antifolates through the acquisition of one of several types of R factors, which code for a wide variety of DHFRs which have a lower affinity for antifolates than the chromosomal bacterial DHFR (Schweitzer, Dicker & Bertino, 1990). There is little evidence that the use of trimethoprim alone has resulted in an increase in the incidence of trimethoprim-resistant organisms (Grüneberg, 1979; Lacey, 1982).

In the last 20 years the evolution of strains resistant to trimethoprim from among the target bacterial species has been sporadic within the developing world (Aymes & Towner, 1990) and equivalent (3% to 11%) to that of most antibiotics in Europe and the USA (Goldstein & Acar, 1993; Thomson, 1993).

On the basis of the bacteriological, pharmacological and clinical data published in the last 15 years, there are few valid advantages to support the indiscriminate use of co-trimoxazole in comparison to monotherapy with trimethoprim or brodimoprim (Brumfit & Hamilton-Miller, 1994). Brodimoprim has in-vitro activity similar to that of trimethoprim (Aymes, 1993; Benoit-Lemercier, Bergogne-Bérézin & Joly-Guillou, 1993). However, brodimoprim's ability to inhibit the dihydrofolate reductase of Bacteroides fragilis is almost four-fold greater than that of trimethoprim (Then & Herman, 1984). Moreover, brodimoprim is decidedly superior to trimethoprim in vivo in the mouse acute intraperitoneal infection model due to its lipophilicity, much longer elimination half-life and better tissue diffusion (Böhn & Then, 1982).

Acute and subacute toxicity tests in conventional laboratory animals show there to be little difference between brodimoprim and trimethoprim; brodimoprim lacks teratogenic, embryotoxic and mutagenic activity (Stephan-Güldner, 1993).

The primary physicochemical differences between trimethoprim and brodimoprim are represented by their degree of hydrophobicity. Brodimoprim is about twenty times more lipid soluble and 240 times less water soluble than is trimethoprim (Then & Hermann, 1984). Brodimoprim also has some advantages over trimethoprim in terms of oral bioavailability (greater than 80%), diffusion into the extra-vascular compartment, and elimination half-life which allows once daily dosing, which is supported by pharmacokinetic studies in animals and man (Weidekamm, 1993).

A comparative pharmacokinetic evaluation in young, healthy, fasting volunteers after a single 160 mg dose of trimethoprim and 150 mg dose of brodimoprim provides the following respective data: $C_{\text{max}}$ 2.1 ± 1.2 and 1.5 ± 0.1 mg/L; $T_{\text{max}}$ 1–2 and 3.6 ± 2.3 h; half-life 7.49 ± 1.9 and 33.8 ± 11.4 h; plasma clearance 145 ± 5.1 and 37.1 ± 9.7 mL/min; renal clearance 92.9 ± 47.6 and 2.3 ± 0.8 mL/min; urinary recovery of the parent molecule 41.4 ± 8.3% (0–24 h) of dose and 7.0 ± 2.2% (0–72 h) of dose. The relative protein bindings are 44% for trimethoprim and 89.4% for brodimoprim (Bushby & Hitchings, 1968; Alhmen & Bronson, 1982; Weidekamm, 1993). The high protein binding of brodimoprim, and total body clearance no higher than 40 mL/min, explains its long half-life of 35 h, allowing once daily administration instead of twice daily with trimethoprim (Weidekamm, 1993). Brodimoprim concentrations in bronchial mucosa (peak of 9.7 ± 5.3 mg/kg), bronchial secretions (peak of 4.57 ± 1.0 mg/L) and middle ear effusion (peak of 3.9 ± 2.0 mg/L) support the likely efficacy in the treatment of respiratory tract infections (Scaglione et al., 1993).

The concentrations of trimethoprim alone or as co-trimoxazole in the urine are high and sufficient to inhibit most urinary pathogens. For these pharmacokinetic reasons trimethoprim or co-trimoxazole have been widely used in the treatment of urinary tract infections (Brumfit & Hamilton-Miller, 1994).

In an analysis of 66 published clinical studies comparing brodimoprim to other antimicrobial agents, including trimethoprim (in the form of co-trimoxazole) a total of 3770 patients, 2624 of whom were adults and 1146 were children, all of whom suffered from upper or lower respiratory tract infections, have been treated. The response to brodimoprim was similar to those treated with other types of antimicrobial agents. In 704 adults with upper respiratory tract infections treated with brodimoprim for 7 to 12 days, 90.9% were cured or improved and 72.7% had negative bacterial culture. In 799 adult patients with lower respiratory tract infections, 88% responded favourably and 83% had negative post-treatment bacterial cultures. Treatment was interrupted on account of adverse events in 2.06% of 1503 brodimoprim patients and
1.56% of 1121 patients administered the comparator drug.

Of 1056 paediatric patients treated for upper respiratory tract infections, 80% of 524 treated with brodimoprim were cured whereas only 67% (P < 0.01) of 532 were cured in the control group. Treatment interruption occurred in 2.4% of brodimoprim patients and in 3.5% of control patients. The main adverse event in both adults and children was gastrointestinal in nature and did not differ significantly in incidence between the brodimoprim and control drug groups (Periti, 1993; Periti et al., 1993).

In conclusion, trimethoprim and brodimoprim have a similar spectrum of activity and tolerability. They differ notably in their physicochemical and pharmacokinetic characteristics, allowing trimethoprim to be administered twice daily and remaining appropriate for urinary tract infections. Brodimoprim can be given once daily and may be more suited for the treatment of bacterial ear, nose and throat and lower respiratory tract infections which is supported by the comparative studies of ear, nose and throat infections in children (Periti, 1993). The confirmation of these observations must await more widespread experience from those countries in which brodimoprim is licensed.

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References


