Leading article

Mupirocin ('pseudomonic acid')—a promising new topical antimicrobial agent

Ever since 1867, when Joseph Lister applied carbolic acid to the open fracture of a 13-year-old boy in Glasgow, new antiseptics have been used with enthusiasm and often extravagance. They have not always been subjected to the same scrutiny for efficacy as systemic antimicrobials. The recent introduction of the novel non-systemic antibiotic, mupirocin, has again revived interest in the topical approach for the treatment of infection.

The antimicrobial activity of fermenting cultures of *Pseudomonas fluorescens* was first recorded in 1887, some 20 years after Lister introduced his theory of antisepsis, but it was not until the late 1960's that Fuller and his colleagues isolated and purified a monocarboxylic acid, first called 'pseudomonic acid', from *P. fluorescens* NCIB 10586 (Fuller et al., 1971). Because this name might wrongly imply activity against *Pseudomonas* species the British Pharmacopoeia and World Health Organization have agreed the new generic name, mupirocin. Mupirocin shares no structural relationships with other antibiotics and consists of a short fatty acid side-chain ester linked to a larger molecule, monic acid (Chain & Mellows, 1974, 1977), the tail end of which appears to mimic the amino acid iso-leucine (Hughes & Mellows, 1978) (Figure 1).

Mupirocin binds reversibly to the iso-leucyl tRNA synthetase and thus, by preventing the incorporation of iso-leucine into growing protein chains, arrests protein synthesis.

For *Staphylococcus aureus*, including methicillin-resistant strains, MICs of mupirocin are less than 0.1 mg/l and are often as low as 0.015 or 0.03 mg/l (Leigh & Tighe, 1984; Casewell & Hill, 1985a,b; Dahl & Bint, 1985; Smith & Gould, 1985; White et al., 1985). Naturally occurring relatively resistant variants of *S. aureus* with MICs of 2 mg/l occur at a frequency of only $10^{-9}$, and exposure to numerous small incremental concentrations of mupirocin produces unstable tolerance to 40 mg/l (Casewell & Hill, 1985a). Kinetic studies show that in liquid media the molecule is stable and that its action is slowly bactericidal (Casewell & Hill, 1985a, b). We have also demonstrated that the pH of the test medium can influence MICs, as can the inoculum size and the presence of blood (Casewell & Hill, 1985a, b). These effects and slight variations in technique probably account for the higher MICs of about 1.0 mg/l that have been reported by a few workers (White, Masters & Sutherland, 1983; White et al., 1985). *S. epidermidis* and streptococci (with the exception of enterococci) are similarly sensitive with MICs of 0.06–1 mg/l and 0.015–1 mg/l, respectively (Leigh & Tighe, 1984; Dahl & Bint, 1985; Smith & Gould, 1985; White et al., 1985) and mupirocin has good activity against *Neisseria gonorrhoeae, Haemophilus influenzae* and *Mycoplasma* spp. (White et al., 1985). MICs for enterococci of 1–2 mg/l (Leigh & Tighe, 1984), 4–16 mg/l (Dahl & Bint, 1985) and 32–64 mg/l (White et al., 1985) have been recorded. For Enterobacteriaceae the MICs are 8–256 mg/l, and for *P. aeruginosa* 6,400 mg/l (Leigh & Tighe, 1984; White et al., 1985). Although mupirocin appears to be able to bind to both procaryotic and eucaryotic iso-leucyl tRNA synthetase (Hughes & Mellows, 1980), MICs for *Candida* spp. are > 256 mg/l (Hill & Casewell, unpublished observations).

The in-vitro activity of mupirocin increases with decreasing pH and this effect is significant at the skin pH of 5.5 (Casewell & Hill, 1985a, b). It is stable in physiological concentrations of skin fatty acids (Hill &
Figure 1. \( R = (\text{CH}_2)_8 \text{COOH} \): mupirocin (pseudomonic acid); \( R = \text{H} \): monic acid.

Casewell, unpublished observations) and after occlusion on normal skin, where it is active against the normal flora (Jackson et al., 1985) and against inoculated Gram-positive bacteria (Aly, 1985). Mupirocin is bound by a variety of body fluids including blood, serum, albumin and pus but, interestingly, its activity is not significantly reduced by nasal secretions (Hill & Casewell, unpublished observations).

Mupirocin seems to be a non-toxic, non-sensitizing agent in animals and man and appears to be free of teratogenic or mutagenic potential (Cockburn, Jackson & White, 1985; Leyden, 1985a). It absorbs ultraviolet light poorly (Clayton et al., 1979) and does not produce photosensitive irritant reactions (Leyden, 1985a). After topical application less than 0.24% is absorbed across intact normal human skin (Cockburn, Jackson & White, 1985). Once mupirocin enters the blood it is rapidly eliminated by hydrolysis of the ester link by non-specific esterases; its plasma half-life in man is less than 30 min (Baines et al., 1984). Mupirocin is therefore unsuitable for systemic use. However, as it is stable for at least 24 h in citrated blood at 37°C (Hill & Casewell, unpublished observations) hydrolysis is probably mediated by hepatic and renal esterases.

The recently commercially available 2% formulation in polyethylene glycol, 'Bactroban', is not intended for use on broken skin or mucous membranes (e.g., intranasally or in the eyes) as the polyethylene glycol base is irritant and causes dysplasia in animal models and in cell cultures. In addition, it seems sensible not to apply any polyethylene glycol-based preparation to sites such as extensive open wounds or burns in patients who have renal impairment because of the risk of nephrotoxicity (Bruns et al., 1982). An experimental formulation in white soft paraffin with anhydrous lanolin has proved suitable for intranasal use, and a similar new formulation is being developed by Beecham Research Laboratories.

Mupirocin formulated as Bactroban has been approved for the treatment of primary skin infections; however, early clinical trials included the treatment of secondary infections. The results of these early studies are presented in two symposium proceedings (Dobson et al., 1985; Wilkinson & Price, 1985) which, when considered with the in-vitro and pharmacokinetic studies, suggest three potentially useful clinical applications.

Firstly, the difficulties of eliminating nasal carriage of \( S. \) aureus, especially during outbreaks caused by methicillin-resistant strains (MRSA), are well known (Casewell, 1986). In a controlled trial, nasal carriage of methicillin-sensitive strains was eliminated in all 32 volunteers during the first two days of a five day course. Nasal clearance of \( S. \) aureus was sustained for several weeks and when re-colonization eventually occurred it was usually with a different phage type (Casewell & Hill, 1986). Elimination of nasal carriage of MRSA from staff and patients was achieved in at least three MRSA outbreaks and was associated with epidemiological control (Dacre, Emmerson & Jenner, 1983; Casewell, Hill & Duckworth, 1985; Shanson, Johnstone & Midgley, 1985). The prompt identification of nasal carriage and its elimination by mupirocin may prove to be a standard requirement for the control of these difficult and expensive outbreaks (Report, 1986).

Secondly, staphylococcal and streptococcal primary infections of the skin, such as impetigo, are an obvious target for topical mupirocin which, after five to seven days of therapy, seems to eliminate these organisms from superficial lesions (Reilly & Spencer, 1984; Wuite et al., 1985). However, most clinical trials have either lacked suitable controls or used polyethylene glycol ointment as a placebo. This base has antibacterial activity (Chirife et al., 1983) and this may explain why the placebo itself has given such good cure rates. For example, when patients with impetigo were treated three times a day for up to 12 days, 54% (Rojas et al., 1985) and 63% (Rojas & Zaias, 1985) were cured or improved when treated with the base alone, compared with cure rates of 90% and 96%, respectively, for treatment with mupirocin. When the base alone produces such good
results the additional effect of the mupirocin is difficult to assess and the polyethylene glycol is not a true placebo. These trials have been usefully reviewed by Ward and Richards (1986). In contrast, a bacteriological cure rate of 87.5% for mupirocin ointment compared to 35% for polyethylene glycol has been reported for 52 patients, 35 of whom had impetigo (Milidiú da Silva & Silva, 1985). In a double-blind controlled trial in patients with well-defined impetigo, Kennedy, Watts & Speller (1985) found mupirocin to be as effective as topical neomycin.

Thirdly, mupirocin has been used for secondary infection of skin lesions including eczema, psoriasis, ulcers, wounds and burns. Many of these trials did not adequately match patients’ lesions for analysis, or failed to control for concomitant use of baind emollients or corticosteroids. For skin infections, within-patient studies can be complicated by the transfer of active ointment between treatment and control sites. Again, the proportion of patients cured or improved with mupirocin often approached that for the base alone, with bacteriological eradication rates of 73–100% for mupirocin and 19–89% for polyethylene glycol alone (Ward & Richards, 1986). In a comparison with chlorotetracycline (3%) cream, 7 days of treatment for primary and secondary infections resulted in bacteriological elimination rates of 83 and 90% for chlorotetracycline and mupirocin, respectively (Huskisson & Wainscott, 1984). In general, S. aureus and streptococci are uniformly eliminated (Dahl & Bint, 1985; Leyden, 1985b; Wuite et al., 1985), whereas Gram-negative bacilli are not (Leyden, 1985). In atopic dermatitis, Alyiffe (1984) found that mupirocin applied twice daily for seven days reduced the skin count of S. aureus from a mean of 33,250 to 20 cfu/cm^2 and was as effective as neomycin. Similarly, in patients with dermatitis 14 days of mupirocin reduced colonization with S. aureus at both maximally affected and control sites when compared with the base, and this was accompanied by significant clinical improvement (Dr Kay Hadley, personal communication). In addition, Simpson et al. (1985) successfully treated the clinical flare of atopic dermatitis in 16 of 20 patients and for eight patients there was loss of pruritis within 24 h.

The effect of mupirocin on wounds and ulcers has yet to be clarified as mupirocin has not shown convincing advantages over placebo in terms of clinical efficacy (Ward & Richards, 1986). Elimination of MRSA from lesions such as bed sores and ulcers is uncertain although in one study MRSA were eliminated from 23 of 24 burns (Rode et al., 1985). In guinea pigs, twice daily application for five days was as effective as the use of fusidic acid cream in reducing the number of viable S. aureus inoculated into a superficial wound (Boon, Beale & Sutherland, 1985). Mupirocin does not seem to delay healing (Mertz, Dunlop & Egstein, 1984) and there is tenuous evidence that low concentrations may actually promote healing, despite the finding that at 100 mg/l it is cytotoxic to fibroblasts in vitro (Carter et al., 1985). In vitro, protein dramatically reduces the diffusion of mupirocin from its point of application (Hill & Casewell, unpublished observations) and therefore presumably its immediate bio-availability in deeper or weeping wounds. In chronic wounds clinical, but not necessarily bacteriological, improvement has been recorded but when used in dressings mupirocin was superior to hypochlorite (Huizinga et al., 1985).

Thus far it seems clear that mupirocin is the drug of choice for the elimination of nasal staphylococci. The results of further clinical trials, preferably including a blank control and measurement of both clinical and microbiological end points, for primary and secondary skin infections, wounds, burns and ulcers seem likely to extend the indications for this interesting new topical agent.

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References


