EMERGING SODIUM FUSIDATE RESISTANCE IN WESTERN AUSTRALIAN METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) continues to be a major cause of nosocomial infection in Australia. In Western Australia, a new type of MRSA (WA MRSA) appeared some years ago and has become endemic in the community. While initially susceptible to most antibiotics, WA MRSA has begun to acquire additional resistance determinants, including trimethoprim and mupirocin resistance, prompting a review of emerging resistance to other antibiotics. Resistance to sodium fusidate, which remained at around 1 - 2% of isolates for many years, rose to 3% in 1993, 5% in 1994 and 9% in 1995. These findings suggest that the use of sodium fusidate in both hospital and community medicine may require review. ***Comm Dis Intell* 1996;20:492-494.**

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) continues to be a major cause of nosocomial infection, often resulting in prolonged hospitalisation and increased morbidity. MRSA first emerged as a problem in eastern Australia in the early 1980s, and these strains are sometimes referred to as Eastern Australian MRSA (EA MRSA)[1]. EA MRSA is now endemic in hospitals in most States and Territories of Australia, with the notable exception of Western Australia, where these strains are referred to as imported MRSA[1,2,3,4]. The reason that imported MRSA has not become established in Western Australian hospitals is believed to be due to a combination of geographical isolation and the screening and control program implemented in 1982[1,3,5]. In the late 1980s a genetically different, less resistant strain of MRSA (now known as WA MRSA) was isolated from patients living in the Kimberley region of Western Australia[6,7]. WA MRSA has since spread to most areas of Western Australia and some strains have acquired additional resistance determinants including trimethoprim and high level mupirocin resistance[1,6,7].

Sodium fusidate is the salt of fusidic acid, a steroid antibiotic produced by the mould *Cephalosporium acremonium*[8]. Sodium fusidate exerts a high degree of antibacterial activity against Gram-positive bacteria, with *Staphylococcus aureus*, including MRSA, being particularly susceptible[8]. Sodium fusidate acts by inhibiting bacterial protein synthesis[8]. Resistance to sodium fusidate is readily generated in the laboratory by growing *Staphylococcus aureus* in increasing concentrations of antibiotic, and the emergence of resistance during treatment has been reported[8]. The development of resistance to sodium fusidate is due to the survival of a high proportion (10%) of the bacterial population after exposure to an inhibitory concentration of sodium fusidate, and a high mutation rate[9]. To help prevent the emergence of resistance, sodium fusidate is usually given in conjunction with another antibiotic, such as rifampicin, when administered orally or intravenously. Topical sodium fusidate has been used for the treatment of skin lesions and burns infected with staphylococci. However, topical use of sodium fusidate is no longer recommended as it encourages the emergence of resistant strains, thereby compromising its value for the treatment of systemic infections[8].

Recently an apparent increase in incidence of sodium fusidate resistance in WA MRSA has been noted. Topical sodium fusidate has been available for community use in Australia for several years. Whether its use in the community should be restricted or not, or whether widespread use of topical sodium fusidate promotes resistance in *Staphylococcus aureus* has been the subject of much debate in Western Australia. We therefore reviewed the emergence of resistance to sodium fusidate in MRSA isolated in Western Australia during the period 1986 to 1995.

Methods

Infection or colonisation with MRSA has been notifiable in Western Australia since 1985. All MRSA isolates in Western Australia are sent to the Infection Control Laboratory at the Western Australian Centre for Pathology and Medical Research, where their identity is confirmed by standard procedures, and antimicrobial resistance pattern determined. Case demographic details as well as details of the isolate are entered into a database.

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WA MRSA was defined on the basis of criteria used previously as MRSA susceptible to gentamicin and also to erythromycin and / or tetracycline[1,6,10]. Imported MRSA was defined as MRSA resistant to gentamicin and / or to both erythromycin and tetracycline.

Results

The Figure shows the total number of MRSA notifications in Western Australia for the period 1986 to 1995. MRSA notifications began to rise in 1991 and reached 204 in 1993, 327 in 1994, and 493 in 1995. The number of imported strains of MRSA has remained relatively stable over the past ten years, and the higher number of notifications is a result of the significant increase in WA MRSA. WA MRSA continues to make up an increasing proportion of all MRSA notifications - 14% in 1989, 78% in 1993, and 88% in 1995. There had been 355 MRSA notifications by the end of June 1996, 93% of which were classified as Western Australian strains.

Resistance to sodium fusidate in MRSA isolated in Western Australia remained around 1 - 2% until 1993. Since then resistance has risen from 3% of MRSA notifications in 1993 to 5% in 1994 and 9% in 1995 (Table). Preliminary analysis of the 1996 MRSA database indicates that 44 out of 355 (12%) isolates (January to June) are sodium fusidate resistant.

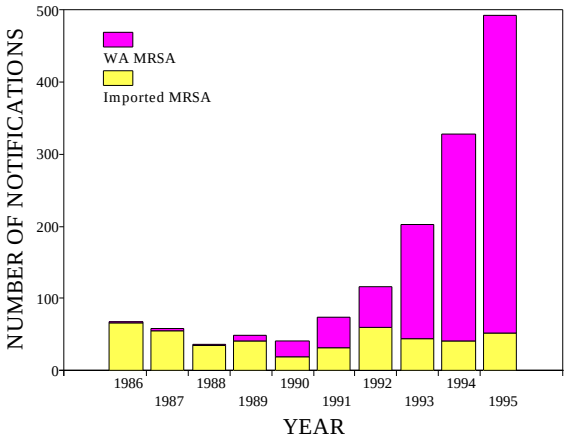
Discussion

In Australia, resistance to sodium fusidate has, until recently, been fairly stable at around 2% of all MRSA isolated. A survey of methicillin-susceptible *Staphylococcus aureus* and MRSA in Australian teaching hospitals between 1986 and 1994, found only 1.1% to 2.6% of isolates resistant to sodium fusidate[11]. The authors suggested that resistance to sodium fusidate developed less easily than was originally thought. These findings supported an earlier Danish study of 8,176 strains of *Staphylococcus aureus* recovered from blood cultures from 1963 to 1987. Sodium fusidate resistance never occurred in more than 1% of the Danish strains during the 24 year period investigated. The majority of sodium fusidate-resistant strains were hospital acquired, and the authors suggested that there were not a large number of sodium fusidate-resistant strains in the community[12]. During the same period the total Danish consumption of sodium fusidate increased from 0.008 to 0.029 defined daily doses / 1000 inhabitants / day. The authors concluded that the increased Danish consumption of sodium fusidate, either as systemic combination therapy or as local treatment with sodium fusidate alone, had not resulted in the development of resistance during the observation period. It should be noted however that the strains in this survey were isolated from cases of bacteraemia only and these findings may not reflect resistance patterns in the wider *Staphylococcus aureus* population. Of the 44 sodium fusidate-resistant MRSA isolated so far this year in Western Australia, only one (2.3%) was recovered from a bacteraemic patient.

Table. Sodium fusidate resistance in MRSA isolated in Western Australia, 1991 to 1995

Year	Number tested	Number resistant (%)
1991	73	1 (1)
1992	116	2 (2)
1993	203	5 (3)
1994	327	15 (5)
1995	493	43 (9)

Figure. Notifications of MRSA in Western Australia, 1986 to 1995



The emergence of sodium fusidate resistance in WA MRSA may be analogous to the earlier problem of mupirocin resistance[10]. The development of mupirocin resistance in WA MRSA was of particular concern as topical 2% mupirocin ointment is used very effectively for clearing nasal carriage of MRSA from hospital staff and patients. Mupirocin had been used empirically and frequently in the north of Western Australia to treat infected skin lesions, resulting in the emergence, selection, and amplification of a mupirocin-resistant strain of WA MRSA, which then spread throughout Western Australia[7,10]. Mupirocin resistance in Western Australia peaked in 1993, when 18% of WA MRSA isolates demonstrated high level mupirocin resistance[10]. As a result of this finding, the Health Department of Western Australia proposed guidelines recommending that mupirocin not be used without prior laboratory susceptibility testing; its use not exceed ten days; and at least one month elapse before a prescription is repeated for the same patient[10]. Since the implementation of these guidelines in 1993, mupirocin resistance (low level) fell to 6.9% of WA MRSA isolates in 1994, and 4.8% in 1995. Preliminary analysis of 1996 MRSA database indicates only 3% of MRSA isolates are mupirocin resistant. However, it is not clear whether this reduction in the prevalence of mupirocin resistance is due to the change in policy, and hence usage, or to other as yet undetermined factors.

The increase in sodium fusidate resistance in MRSA in Western Australia raises two important issues. The first of these is the possibility that increased resistance is related to increased usage, perhaps as a result of the implementa-

tion of guidelines to restrict the use of topical mupirocin. Gathering data on the usage of topical sodium fusidate in Western Australia over the last few years, in an effort to answer this question, has been difficult. A total of 435 fifteen-gram tubes of sodium fusidate ointment were supplied to pharmacies in Western Australia from May 1995 to May 1996 (L. Fry, Pharmaceutical Services, Health Department of Western Australia, personal communication). Previous usage figures are not currently available, and so no comparison with earlier years can be made. Although the total number of tubes supplied is apparently low, continued use in an area where fusidic acid-resistant MRSA are prevalent is likely to exacerbate the problem by maintaining selective pressure on these strains. The second issue concerns whether sodium fusidate resistance has emerged in a single clone that has spread, or has arisen independently in several communities. Genetic investigations are being undertaken to resolve this issue.

The increasing incidence of sodium fusidate resistance in WA MRSA has sparked discussion in Western Australia over whether the availability of topical sodium fusidate in the general community should be controlled. Emergence of resistance to topical antimicrobials has been clearly documented for almost every agent used during outbreaks of MRSA infection[13]. We have seen a significant increase in sodium fusidate resistance in MRSA in Western Australia over the past three years, and perhaps it would be prudent to review the issue of restricting the use of topical sodium fusidate in the community.

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