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Short communication

Evaluation of the activity of fusidic acid tested against contemporary Gram-positive clinical isolates from the USA and Canada

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ABSTRACT

We evaluated the antimicrobial activity of fusidic acid (CEM-102) against 1140 clinical strains of Gram-positive bacteria obtained from patients with bacteraemia or skin and skin-structure infections collected in more than 30 medical centres in the USA and Canada over a 10-year period (1997–2006). Fusidic acid was very active against meticillin-susceptible *Staphylococcus aureus* (MSSA), meticillin-resistant *S. aureus* (MRSA) and coagulase-negative staphylococci (CoNS), with MIC_{90} values (minimum inhibitory concentration encompassing 90% of isolates tested) at 0.12 μg/mL for US strains of MSSA, MRSA and CoNS and 0.25 μg/mL for Canadian strains of MSSA and MRSA. A progressive increase in fusidic acid resistance was observed among Canadian strains of *S. aureus* (12.2% in 2005–2006) and among Canadian strains of CoNS. In contrast, no fusidic acid resistance was detected among US *S. aureus* strains and only 1.5% among CoNS. Fusidic acid was equally active against community-acquired MRSA and linezolid-resistant staphylococci. Fusidic acid exhibited equal or greater potency against staphylococci compared with vancomycin, daptomycin and linezolid.

1. Introduction

Several new agents with activity against multidrug-resistant (MDR) Gram-positive pathogens have been introduced into clinical practice [1]. Those currently available include quinupristin/dalfopristin, linezolid and daptomycin, and the antibacterial pipeline includes additional drugs at advanced stages of development, including new glycopeptides (dalbavancin, oritavancin and telavancin), new anti-meticillin-resistant *Staphylococcus aureus* (MRSA) β-lactams (ceftobiprole and ceftaroline) and a new diaminopyrimidine (iclaprim) [1]. Unfortunately, cost and toxicity issues may restrict the use of some newer agents, and concerns of emerging resistance among staphylococci to daptomycin and linezolid are already being raised [1,2]. Such issues have prompted clinicians throughout the world to reconsider the use of older agents with proven potency against Gram-positive cocci, particularly those with anti-MRSA activity, in order to obviate the broad use of daptomycin or linezolid, thus delaying the inevitable development of resistance to these agents [3]. One such agent with proven antistaphylococcal (including MRSA) activity is fusidic acid (CEM-102) [3,4].

Fusidic acid has been used in Europe and Australia since 1962 and in Canada since 1986–1987 [4,5]; however, it has not been licensed by the US Food and Drug Administration (FDA) and it is not currently available in the USA. This belated introduction of fusidic acid into the USA may now be viewed as positive in that it provides an additional antistaphylococcal agent with low toxicity and a unique mechanism of action that is devoid of cross-resistance to other classes of antibacterial agents [4–6]. Furthermore, the extensive foreign experience with fusidic acid in the treatment of serious staphylococcal infections over the past four decades provides a wealth of information regarding the optimal use of this agent, particularly with regard to the implementation of strategies to delay or avoid the development of resistance [5].

In the present study, we summarise the 1997–2006 results of a US and Canadian in vitro sampling programme comparing the activity of fusidic acid and currently marketed topical and systemic antistaphylococcal agents against clinical isolates of *S. aureus*, coagulase-negative staphylococci (CoNS) and Group A streptococci obtained from patients with skin and skin-structure infections (SSSIs) or bloodstream infections (BSIs). A total of 1140 bacterial strains, including 50 community-associated MRSA (CA-MRSA) and 10 linezolid-resistant (LZD-R) staphylococci, were tested using reference Clinical and Laboratory Standards Institute (CLSI) methods, with susceptibilities to comparator agents interpreted by CLSI breakpoint criteria [7,8].

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2. Materials and methods

2.1. Isolates

A total of 1080 non-duplicate clinical isolates of *S. aureus* (727 strains), CoNS (228 strains) and Group A β-haemolytic streptococci (β-HS) (125 strains) were collected from 30 hospitals (25 US hospitals and 5 Canadian hospitals) between 1997 and 2006. Isolates from SSSIs or BSIs deemed clinically significant by the local site investigators were shipped to the monitoring laboratory (JMI Laboratories, North Liberty, IA) for subsequent identification confirmation and reference antimicrobial susceptibility testing [9]. This collection was supplemented by the inclusion of 50 US strains of CA-MRSA [USA300 and Panton–Valentine leukocidin (PVL)-positive] and 10 LZD-R staphylococci (1 strain of *S. aureus* and 9 strains of CoNS). Trends in susceptibility to fusidic acid among *S. aureus* were assessed in the USA and Canada by testing 101–106 US strains and 40–54 Canadian strains in each of five 2-year sample periods from 1997 to 2006.

2.2. Susceptibility test methods

All strains were tested by the broth microdilution method [8] using commercially prepared and validated panels (TREK Diagnostics, Cleveland, OH) in cation-adjusted Mueller–Hinton broth (with 2–5% lysed horse blood added for testing streptococci). Fusidic acid (CEM-102) was obtained from Cempra Pharmaceuticals (Chapel Hill, NC) and the comparator agents, including ciprofloxacin, clindamycin, daptomycin, doxycycline, erythromycin, gentamicin, linezolid, mupirocin, neomycin, oxacillin, penicillin, trimethoprim/sulfamethoxazole and vancomycin, were obtained from the respective manufacturers. Interpretation of minimum inhibitory concentration (MIC) results was in accordance with published CLSI criteria [7]. Quality control strains utilised included *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619 [6,7].

3. Results

3.1. Activity of fusidic acid against clinical isolates

A total of 727 strains of *S. aureus* were obtained from hospitals in the USA (510 strains; 49.2% MRSA) and Canada (217 strains, 46.5% MRSA). Fusidic acid MIC values were not influenced by meticillin resistance, with MIC_{90} values (MIC encompassing 90% of isolates tested) of 0.12 μg/mL for MSSA and MRSA strains from the USA and 0.25 μg/mL for Canadian MSSA and MRSA isolates (Table 1). All US strains of *S. aureus* were susceptible to fusidic acid at a MIC of ≤0.5 μg/mL compared with 93.5% of Canadian strains. Although CLSI breakpoints for fusidic acid have not yet been established, susceptibility is generally defined as a MIC of ≤0.25 μg/mL or ≤0.5 μg/mL and resistance as a MIC of ≥2 μg/mL [5,10]. A total of 14 Canadian strains of *S. aureus* (7 strains each of MSSA and MRSA) were resistant to fusidic acid using these criteria.

Similar to *S. aureus,* fusidic acid activity against CoNS was not influenced by resistance to meticillin (Table 1). Although meticillin-susceptible CoNS strains from Canada appear to be more susceptible to fusidic acid than meticillin-resistant CoNS strains, this is likely due to the small number of meticillin-susceptible CoNS tested. Resistance to fusidic acid was detected among CoNS both from the USA (3 isolates; 1.5% of total) and Canada (6 isolates; 24.0% of total strains over 10 years). Although data on fusidic acid resistance among CoNS were limited, the prevalence of such resistance in *Staphylococcus epidermidis* appears to be greater than that observed in *S. aureus*, suggesting that CoNS have been subjected to more fusidic acid selection pressure [10].

Fusidic acid was 32-fold less active against β-HS compared with the two groups of staphylococci (Table 1). Fusidic acid MIC values were distributed across a narrow range (2–8 μg/mL) with minimal variations in the country-specific antibiograms.

3.2. Trends in susceptibility to fusidic acid among staphylococci

The MIC distributions for the US strains were tightly grouped between 0.03 μg/mL and 0.5 μg/mL,with a modal MIC value of 0.12 μg/mL in each of the 2-year time periods. The modal MIC for Canadian isolates was also 0.12 μg/mL in each of the five time periods; however, resistant strains were noted in each period, constituting 3.7% in 1997–1998, 5.0% in 1999–2000 and 2001–2002, 7.1% in 2003–2004 and 12.2% in 2005–2006. This progressive increase in resistance of these isolates is in contrast to the absence of fusidic acid resistance observed in the USA.

Fusidic acid (CEM-102) trends among CoNS isolates were assessed by testing 10 USA strains and 5 Canadian strains from each of the 2-year samples (Table 2); the number of US isolates collected in 2005–2006 was increased to 163 to provide a broader spectrum of CoNS species. No resistant CoNS strains were detected in Canada from the initial 4 years; however, 24.0% of the Canadian sampling from 1997 to 2006 were resistant to fusidic acid (6 of 25 strains). None of the US isolates from 1997 to 2002 were resistant to fusidic acid, but when a larger collection of isolates from 2005 to 2006 was evaluated three strains (1.8%) for which MIC values were >2 μg/mL were detected.

3.3. In vitro activity of fusidic acid and comparators

The fusidic acid MIC_{90} values for MSSA, MRSA and CoNS were 2- to >66-fold lower than all comparator agents, including daptomycin and linezolid (Table 3). Among the staphylococci collected, only one MRSA strain exhibited decreased susceptibility to daptomycin (MIC = 2 μg/mL). The fusidic acid MIC for this strain was 0.12 μg/mL. There were no staphylococcal isolates for which linezolid MIC results were >2 μg/mL. Ciprofloxacin, erythromycin, clindamycin and gentamicin all exhibited limited activity against MRSA and CoNS. Doxycycline (94.6% susceptible), trimethoprim/sulfamethoxazole (91.2% susceptible) and vancomycin (100.0% susceptible) were most active against MRSA. The topical agents mupirocin and neomycin (component of triple antibiotic ointment) were comparably active both against MSSA and MRSA. High-level resistance to both of these agents was <5%.

Among the β-HS, 92.0% and 97.6% were susceptible to erythromycin and clindamycin, respectively, and 100.0% of strains were susceptible to daptomycin, linezolid, penicillin and vancomycin (Table 3). Fusidic acid was less active against β-HS compared with all other tested agents with the exception of gentamicin.

3.4. In vitro activity of fusidic acid against special organism populations

Additional strains of MRSA characterised as CA-MRSA (50 strains) were tested, each having staphylococcal cassette chromosome *mec* (SCC*mec*) IV, PVL and a USA300 pulsed-field gel electrophoresis pattern. As with all other MRSA strains tested, all fusidic acid MIC values ranged from 0.06 μg/mL to 0.12 μg/mL. Non-β-lactam resistances were only found for ciprofloxacin (4.0%) and erythromycin (100.0%).

Given the lack of LZD-R staphylococcal strains among the sampled clinical isolates (Table 3), an additional 10 strains of