Effect of medium composition on the MIC breakpoint for gentamicin


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Sir,

In 1991 the BSAC published its Guide to Sensitivity Testing.1 Included in this document were in vitro breakpoint concentrations for interpretation of sensitivity. These breakpoints were derived by means of a formula,1 incorporating pharmacokinetic parameters and in vitro activity data based on MIC distributions for the ‘wild’ population, with the facility to adjust the breakpoint in cases where a mechanism of resistance was not detected. Pivotal to the selection of these breakpoints were the data from MIC determinations using BSAC methodology.1

Like all other reference methods, the BSAC method for determining MICs1 relies on consistent performance of the components of the procedure. If a significant change occurs the MIC distribution may be affected. This has little consequence for drug–organism combinations where the distribution is bi-modal and the breakpoint sits between the susceptible and resistant populations, but may cause problems when MIC distributions for the susceptible population and strains with reduced susceptibility merge. In this latter case a minor change in the MIC distribution can significantly increase or decrease the proportion of organisms on the resistant side of the MIC breakpoint.

It is of concern to the BSAC Working Party on Sensitivity Testing that the performance of Iso-Sensitest Agar (ISA), the medium used to derive the original MIC distribution data and breakpoints may have changed since 1991, with consequences for susceptibility tests for aminoglycosides against Pseudomonas aeruginosa. Independent data, mainly MIC values for the P. aeruginosa control strain NCTC 10662, using ISA from four sources: St Thomas’ Hospital in London, the Swedish Reference Group on Antibiotics, City Hospital in Birmingham and Oxoid Ltd, have been evaluated by the Working Party to establish if, indeed, there has been a change in performance.

In 1991, MIC determinations for P. aeruginosa NCTC 10662 with 0.1 mg/L increments of gentamicin were undertaken on 19 separate occasions. MICs ranged from 0.7 to 1 mg/L, with 10 observations at 0.8 mg/L and seven observations at 0.9 mg/L. These data confirm that an MIC value of 1 mg/L of gentamicin for P. aeruginosa NCTC 10662 should be expected in a conventional agar MIC determination with doubling dilutions and is in agreement with the expected MIC value for P. aeruginosa NCTC 10662 published in the Guide to Sensitivity Testing.1 However, data from the same laboratory for daily MIC determinations between 1993 and 1999 show a reduction in the number of times P. aeruginosa NCTC 10662 was inhibited by ≤1 mg/L gentamicin, from 97.4% in 1993 to 51.5% in 1999 (Figure). Tests were also performed at Oxoid, using an Etest method to determine, retrospectively, the MICs of gentamicin for P. aeruginosa NCTC 10662 on representative batches of media produced between 1996 and 1999. Around 50% of these tests gave MICs > 1 mg/L although there was no indication of any temporal trend in the susceptibility results (Figure).

Differences between MIC values for P. aeruginosa NCTC 10662 on current batches of ISA and those published previously by the BSAC for other aminoglycosides have also been noted by St Thomas’ Hospital. Specifically the MICs were consistently higher than previous values for netilmicin (range 2–8 mg/L compared with an earlier value of 1 mg/L) and gentamicin (range 1–4 mg/L compared with 1 mg/L previously). However, for tobramycin the current results remain similar to the published MIC values (range 0.25–1 mg/L compared with 0.5 mg/L previously).

The Swedish Reference Group on Antibiotics have not tested MICs of aminoglycosides for P. aeruginosa, but have

Figure. Percentage of tests on Pseudomonas aeruginosa NCTC 10662 with gentamicin MICs >1 mg/L. ——, Birmingham; – – –, Oxoid.
observed that median zone diameters when testing netilmicin by disc diffusion were smaller after the introduction of a new batch of ISA medium in 1997 (median zone diameter was 27 mm between 1993 and 1996, and 24 mm in 1997 (Dr G. Kahlmeter, Swedish Reference Group of Antibiotics, personal communication).

From these data it would be reasonable to conclude that there has been a subtle alteration in the components of ISA since 1991, with the proportion of gentamicin MIC values >1 mg/L for P. aeruginosa NCTC 10662 rising from 2.6% in 1993 to a plateau of 23–50% between 1996 and 1999. The change has not been large, in that the actual MIC of P. aeruginosa NCTC 10662 was 0.8–0.9 mg/L in 1991, meaning that it would take only a small change to increase the MIC to >1 mg/L as determined with a standard two-fold dilution series. The change may also have been gradual though the two data sets shown in the figure are contradictory on this aspect. A gradual change may explain why the situation has not provoked more widespread comment. Nevertheless, some laboratories using breakpoint methods to determine sensitivity have increased the concentration of gentamicin in response to susceptible control strains appearing resistant to the breakpoint concentration tested (Dr T. Winstanley, Committee Member British Society for Microbial Technology, personal communication).

Until the reason for this change in performance of ISA can be elucidated the Working Party feels that it is necessary to raise the MIC breakpoint for gentamicin from 1 to 2 mg/L and is amending the zone diameter breakpoints to ≤14 mm = resistant, 15–19 mm = intermediate and ≥20 mm = sensitive, until the issue can be resolved. It is hoped that this measure will prevent gentamicin being unnecessarily withheld from therapeutic use. With the assistance of the media manufacturers the Working Party hopes to formalize a ‘standard’ for media performance for use with BSAC disc diffusion sensitivity testing methodology.

References