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Short communication

Streptococcus pneumoniae bacteraemia: pharmacodynamic correlations with outcome and macrolide resistance—a controlled study☆

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Abstract

There are few data on macrolide pharmacodynamics in pneumococcal infections. We evaluated pneumococcal area under the inhibitory concentration–time curve (AUIC) values at the point of hospital admission in 59 bacteraemic patients failing in the community and in 98 bacteraemic controls without macrolide exposure. The area under the 24-h concentration–time curve (AUC_{24}) was calculated for each patient using age, weight and daily dose; using minimum inhibitory concentrations (MICs), the values of AUIC (i.e. AUC_{24}/MIC) were then computed. Clinical and outcome information was also collected in hospital. Five of six patients who died of pneumococcal bacteraemia in hospital received azithromycin, with a mean AUIC of 8.1 prior to hospital admission. Resistant isolates were recovered in 35 (59%) macrolide failures and in only 28 (29%) controls ($P = 0.001$). Azithromycin AUICs averaged 10 in failure patients and 17 in controls. For clarithromycin and erythromycin, the mean AUIC values in failures were 31 and 53, respectively, and the AUIC in controls was >100. Low AUIC values against *Streptococcus pneumoniae* precede macrolide failures in the community. Patient factors do not predict these outcomes and thus the most likely explanation for macrolide failure in the community is inadequate macrolide activity in patients who receive these antibiotics for treatment of organisms that are not sufficiently susceptible.

Keywords: Pharmacodynamics; CAP; Macrolides; *Streptococcus pneumoniae*; Treatment failures

1. Introduction

Macrolide-resistant *Streptococcus pneumoniae* are more common than penicillin-resistant *S. pneumoniae* in many parts of the world. With the widespread use of macrolides for treatment of community respiratory tract infections (RTIs), clinical failures related to therapy with macrolides are being increasingly reported [1–5]. Hospitalised patients have typically been the subject of reports of macrolide-associated breakthrough bacteraemia [6,7] and there is at least one case report of resistance development following intravenous macrolide therapy that preceded the death of the hospitalised patient [8]. There are a number of recent epidemiological studies describing resistance and failure of macrolides when *S. pneumoniae* is found during surveillance of blood cultures. In a recent series, macrolide failure was associated with 3.5% of bacteraemic pneumococcal

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infections. Of the 60 cases of macrolide failure reported, 64% presented with a macrolide-resistant organism in blood cultures [6]. Grant et al., from the Centers for Disease Control and Prevention, also found a 1.7% incidence of macrolide failure (26/1543) in bacteraemic patients. In failures, they found 81% with a macrolide-resistant isolate [7].

Patients with macrolide resistance frequently have a history of prior exposure to macrolides, even if they are not taking macrolides immediately upon presentation to hospital [7,9,10]. Surveys have confirmed the association between increasing macrolide use and increases in pneumococcal resistance to macrolides worldwide [11].

We collected a case series of bacteraemic macrolide failure patients and comparably ill bacteraemic patients not exposed to macrolides prior to hospitalisation. The objectives were to characterise the clinical, microbiological and pharmacokinetic/pharmacodynamic (PK/PD) outcomes of outpatients who are hospitalised with community-acquired pneumonia (CAP) caused by *S. pneumoniae*. In these cases and controls, calculations of the area under the 24-h concentration–time curve/minimum inhibitory concentration ratios (AUC_{24}/MIC) (defined as the area under the inhibitory concentration–time curve (AUIC)) were used to evaluate the meaning of in vitro susceptibility and variations in dosing. Since the MIC varies more than 10-fold even for organisms below the susceptibility breakpoint, it is necessary to evaluate cases using PK/PD indices. Furthermore, doses actually given to patients vary considerably, further necessitating the use of pharmacokinetics in relation to MIC variability. Animal models have previously defined AUIC values for the macrolides [12], but the threshold values arising from these models have not been tested on humans. Therefore, we sought to identify target AUICs associated with macrolide success and failure.

2. Patients and methods

This was a multicentre, retrospective, observational, descriptive study of patients hospitalised with bacteraemic CAP. Macrolide therapy was defined as a failure if the outpatient had received ≥2 days of macrolide therapy on admission to hospital with bacteraemia-defined CAP caused by *S. pneumoniae*. Controls were patients with bacteraemia-confirmed CAP caused by *S. pneumoniae* not receiving antibiotics at the time of hospital admission. Demographics and underlying diseases were similar between macrolide failures and controls. All sites had approval for data collection by their local Institutional Review Board, and proceeded to collect data on those cases approved for enrolment. Additional control cases ($N = 61$) were obtained from US patients enrolled prospectively in a previous study of pneumococcal bacteraemia conducted by some of the authors [13]. Each of these cases met the definitions of the study.

2.1. Inclusion and exclusion criteria

All patients included in the analysis must have been hospitalised for CAP defined in the usual manner and complicated by bacteraemia with *S. pneumoniae*. Macrolide failures had received at least 2 days of treatment with macrolides within 7 days of hospital admission, whilst controls had not been given macrolides within 30 days of admission.

2.2. Susceptibility testing and breakpoints

Each site investigator provided susceptibility testing results on the blood isolate collected from each patient. All local laboratories tested *S. pneumoniae* and reported penicillin and erythromycin susceptibilities as MICs or breakpoints based on Clinical and Laboratory Standards Institute guidelines. Where MICs were reported, erythromycin and clarithromycin were reported as susceptible at MIC ≤ 0.25 μg/mL, intermediate at MIC = 0.5 μg/mL and resistant at MIC > 1.0 μg/mL. For azithromycin, susceptible was defined as MIC ≤ 0.5 μg/mL, intermediate as MIC = 1.0 μg/mL and resistant as MIC ≥ 2.0 μg/mL.

2.3. Pharmacokinetics/pharmacodynamics

Patient age, height, weight, sex, serum creatinine, and daily antibiotic dose and interval were used to calculate AUC_{24} for the macrolide given to each patient, and the ratio of this value to the MIC was used to express the macrolide AUIC. For control patients who had not received a macrolide prior to hospitalisation, AUIC calculations were made for each macrolide based on patient weight, population pharmacokinetics and the available MIC. The AUIC calculation for clarithromycin in controls was based on dosing of 500 mg twice a day, erythromycin calculations were based on dosing of 400 mg every 6 h and azithromycin calculations were based on dosing of 500 mg daily. Both for macrolide failures and controls, AUIC calculations were made at three points in the outpatient phase of treatment (Day −5, Day −3 and day of admission) and then daily during hospitalisation where all antibiotics given to the patient were considered in the AUIC calculation. Antibiotic clearance was calculated by using the general formula: slope × CCr + y intercept (where CCr is creatinine clearance). Coefficient slope and intercept values used for all the antibiotics have been published previously [14].

2.4. Statistical analysis

Between-group contrasts were tested using χ^2, with Fisher exact test for categorical variables and a two-sample t-test for continuous variables. Minitab (Minitab Inc., State College, PA) was used to generate descriptive statistics. In addition to demographic and clinical variables in the macrolide failure versus control groups, the specific variables tested for differences between groups were the percent susceptible