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ORIGINAL ARTICLE

Once versus individualized multiple daily dosing of aminoglycosides in critically ill patients

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Abstract *Background and objective:* The purpose of this study was to evaluate the once daily dosing (ODD) program in critically ill Egyptian patients compared to individualized multiple daily dosing (MDD) in terms of clinical and bacteriological efficacy. In addition, the incidence of nephrotoxicity associated with both regimens in this specific group of patients was assessed.
Methods: Fifty-two patients with suspected or confirmed bacterial infections admitted to the Critical Care Medicine Department, Kasr El-Aini-Cairo University Hospitals comprised the study population. The amikacin group (30 patients) was sub-divided into 14 patients receiving amikacin ODD (1 g i.v.) and 16 patients receiving amikacin in MDD (500 mg i.v./dose). The gentamicin group (22 patients) was sub-divided into 10 patients receiving the drug ODD (240 mg i.v.) and 12 patients receiving gentamicin MDD (80 mg i.v./dose). Amikacin or gentamicin serum levels were determined by the enzyme multiplied immunoassay technique using Emit 2000. MDD regimen was adjusted based on the individual pharmacokinetic parameters using the Sawchuk–Zaske method.
Results: There was no significant difference between the two dosing regimens with regard to clinical and antibacterial efficacy or incidence of nephrotoxicity of both gentamicin and amikacin

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groups. In the ODD regimen, duration of treatment had no effect on increasing incidence of nephrotoxicity unlike the individualized MDD regimen. No dose adjustments were needed in the once daily dosing regimen since trough concentrations have never been above toxic level.
Conclusions: The study showed that the ODD regimen is preferred in critically ill patients to individualized MDD as shown by comparable efficacy, nephrotoxicity and lesser need for therapeutic drug monitoring and frequent dose adjustments required in the individualized MDD regimen.

1. Introduction

Aminoglycosides are extremely active antimicrobial agents (Gilbert, 1991) and currently play a pivotal role in the management of serious infections (Durante-Mangoni et al., 2008; Trenika et al., 2005). They have been traditionally administered every 8–12 h. Although this dosing schedule has been shown to be effective in eradicating various strains of bacteria, it has been associated with dose limiting toxicities, mainly nephrotoxicity and ototoxicity (Maglio et al., 2002). However, the high efficacy and rare emergence of resistance to aminoglycosides made the attention to the correct use, monitoring of aminoglycosides and understanding of aminoglycosides' pharmacokinetics so as to ensure the achievement of therapeutic serum levels while avoiding toxic concentrations. Substantial inter- and intra-patient variations occur in the distribution volume and the elimination rate constant of aminoglycosides, which determine dosage requirements. Hence, the pharmacokinetic dosing method has been recommended as the most desirable dosing method (Zaske et al., 1982). In addition, the emergence of once daily aminoglycoside administration can be attributed to several pharmacodynamic characteristics of the drug class, including: concentration dependent killing, the post-antibiotic effect, a diminished propensity for adaptive resistance, and reduced toxicity (Freeman et al., 1997; Klastersky et al., 1974; Ward and Theiler, 2008).

2. Patients and methods

2.1. Patients' characteristics

Fifty-two patients (26 males and 26 females) with mean age (42.4 ± 18.4, range 21–80) with suspected or confirmed bacterial infections for which an aminoglycoside (amikacin or gentamicin) was indicated were included in the study. Apache II score was applied for all patients before and after stopping aminoglycoside therapy. The data with respect to infections for which treatment is indicated, coexistent disease, and concomitantly prescribed drugs were obtained. All patients were with creatinine clearance of 30 ml/min or more except one patient had creatinine clearance of 18.3 ml/min, they had no clinically apparent hearing loss or vestibular disease. Twenty-two patients received gentamicin (80 mg/ampoule) by intravenous route. They were divided into two subgroups, the first subgroup comprising 10 patients, received 240 mg gentamicin once daily and the second subgroup of 12 patients received 80 mg gentamicin every 8 h. Thirty patients received amikacin (500 mg/vial) by intravenous route. They were also divided into two subgroups, the first subgroup comprised 14 patients who received 1000 mg amikacin once daily and the second subgroup comprised 16 patients, 14 of them received 500 mg amikacin 12 hourly and 2 received 500 mg 8 hourly. All patients whether taking gentamicin or amikacin also received other antimicrobial agents as prescribed by their physicians. As some patients in the two treatment subgroups whether in amikacin group or gentamicin group, had multiple infections, some had single infections and few received amikacin or gentamicin for prevention of infections, this study dealt with each infection whether confirmed or suspected separately so that clinical and microbiological cure of each confirmed or suspected infection could be evaluated. The need for informed consent form was waived because all invasive procedures used were already undertaken for clinical purpose.

2.2. Serum aminoglycoside level determination

The decision to start aminoglycoside therapy either once or multiple daily dosing and the choice between gentamicin and amikacin were made by the attending physician according to clinical status independent of the study. Following clinical evaluation and routine laboratory tests all patients received the antibiotic chosen with periodic measurement of serum levels of either amikacin or gentamicin. The appropriate therapeutic serum levels for multiple daily dosing were 5–10 μg/ml for gentamicin peak, 0.5 to <2 μg/ml for gentamicin trough, and 15–35 μg/ml for amikacin peak, 5–10 μg/ml for amikacin trough (Schentagjj, 1980; Zaske, 1986). Serum aminoglycoside level determination was determined using enzyme multiplied immunoassay technique (EMIT) using the Vitalab VIVA analyzer (Syva Company, Dade Behring Inc., USA) (Mendu et al., 2007; Nishihara, 1995). The sampling intervals include; 30 min after end of infusion of the third dose, half of the dosing interval between the third and fourth dose, and 15–30 min just before the fourth dose (Dorman et al., 1998; Huber, 1996; Jikoo et al., 1996). These intervals were chosen to ensure that the drug had reached steady state concentration.

2.3. Pharmacokinetic parameters and dose individualization

Both drugs were given with 100 ml saline over 1 h, and aminoglycoside dosing was individualized for the conventional dosing group if trough concentration exceeded the toxic level. Datakinetics program (developed by MDK, Inc., Baldwin, MO, USA, and marketed by American Society of Health-System Pharmacists [ASHP]) was used to calculate the estimated pharmacokinetic parameters, calculated pharmacokinetic parameters according to serum drug concentrations, and for individualizing pharmacokinetic dosing (Erdman et al., 1991; Goldman and Fuller, 1993; Sawchuk and Zaske, 1976). No dose adjustments were needed in the once daily dosing regimen since trough concentrations have never been above toxic level in both aminoglycosides.