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Evidence of renal function deterioration on once-daily administration of amikacin in an elderly patient: a warning case

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SUMMARY
Although some experience with single daily doses of amikacin in adults and children has been reported, to date there is no clear evidence whether the once-daily regime of aminoglycosides is safe to be administered to elderly patients. Despite the convenience and potential cost-effectiveness of once-daily administration of aminoglycoside antibiotics, there is concern over the potential cumulative toxicity associated with their use in elderly patients. This may be particularly relevant where there is concomitant use of other nephrotoxic agents. However, despite these concerns, the use of once-daily dosing of aminoglycosides is common in elderly patients and the consequences are unquantified. We present a case of 70 years old male patient, who developed extremely toxic levels of amikacin on a once-daily regime (1 g/day in 30 min. infusion) with clear evidence of renal function impairment.
Key words: amikacin, elderly, nephrotoxicity, therapeutic drug monitoring.

SOUHRN
Tesfaye H., Jedličková B., Průša R.: Zjištěné zhoršení renálních funkcí u staršího pacienta léčeného amikacinem podávaným jednou denně: varovný případ
Přestože jsou publikovány některé zkušenosti s podáváním amikacinu jednou denně u dospělých a dětí, není dosud doloženo, zda je podávání aminoglykosidů jednou denně bezpečné u starších pacientů.
Podávání aminoglykosidových antibiotik jednou denně je sice pohodlnější a pravděpodobně i nákladově efektivnější, avšak u starších pacientů je možné riziko kumulativní toxicity. Toto riziko může být zvýšeno obzvláště při současném užívání dalších nefrotoxických látek. Přes toto riziko je podávání aminoglykosidů jednou denně u starších pacientů běžné a jeho důsledky nejsou dosud známy. Uvádíme případ sedmdesátiletého muže, u kterého byly zjištěny extrémně toxické hladiny amikacinu při dávkování jednou denně (1 g/denně v 30minutové infuzi) spolu se zhoršením renálních funkcí.
Klíčová slova: amikacin, stáří, nefrotoxicita, terapeutické monitorování léků.

Introduction

Since their discovery, aminoglycosides have played an important role in the treatment of gram-negative bacteraemia in seriously ill patients [1]. Aminoglycosides are rapidly bactericidal and show concentration--dependent killing, a feature that favours regimens that achieve high peak serum concentrations [2, 3]. The advantages, both theoretical and practical, associated with once-daily administration of aminoglycosides are well known. Several clinical trials and animal model studies that have suggested that aminoglycosides can be given in this way, achieving high peak concentrations associated with maximal bacterial killing without an increase in toxicity [4] in comparison with more frequent administration [5, 6,7]. In one review [8] of once--daily amikacin, the half-life was approximately 3 hours in adult patients with infections but was greater than 4 hours in elderly patients, suggesting that new recommendations for therapeutic drug monitoring should be formulated. Vanhaeverbeek et al. [9] reported comparable clinical safety and efficacy of amikacin both during once or multi-daily regimen. However, there is no convincing evidence about safety of the once-daily amikacin dosing regimen in elderly patients, who may be more prone to drug toxicity due to the aging process accompanied by various physiological changes [10]. This is problem is illustrated in the following case presentation.

Case presentation

A 70 years old male with previous history of myocardial infarction and ischemic heart disease was admitted to ICU for septic fever. Objective findings at admission were as follows: body weight = 86 kg, height =178 cm, blood pressure = 108/79 mmHg, pulse rate = 80/minute, body temperature = 38.4 °C, conscious. The working diagnosis was urosepsis based on clinical manifestation and other routine laboratory findings such as urinalysis. Amikacin 1g/24 hours in combination with a betalactam antibiotic containing piperacillin with tazobactam, namely tazocin 4 g every 8 hourly was started as empiric treatment measure. Fever was controlled completely after initiation of combination antibiotic therapy. Urine culture revealed Proteus, which was proved to be sensitive to the prescribed

antibacterial drugs. There was no further deterioration of infection associated symptoms. However, gradual serum creatinine elevation compared to the baseline level of 93 μmol/l was evident during amikacin treatment (139 μmol/l, 160 μmol/l, 213 μmol/l), ending up with the level of 233 μmol/l (Fig. 1) i. e. an approximate 250 % increase 8 days after initiation of amikacin therapy. Blood urea was also abnormal (26.3 mmol/l). Peak and trough serum amikacin levels were measured as 138.5 mg/l (236.835 μmol/l) and 72.6 mg/l (124.146 μmol/l) respectively. After pharmacokinetic evaluation (Fig. 2), amikacin was temporarily discontinued up to the next level (5 days later), which revealed a concentration of 4.4 mg/l (7.524 μmol/l), still therapeutic level. There was evidence of renal function restoration after drug withdrawal based on the decline in serum creatinine (see Fig. 1). Despite the absence of audiometric assessment, we assume that exposure to toxic levels of amikacin for long time in this case (see Fig. 2) may also affect the auditory health of the patient.

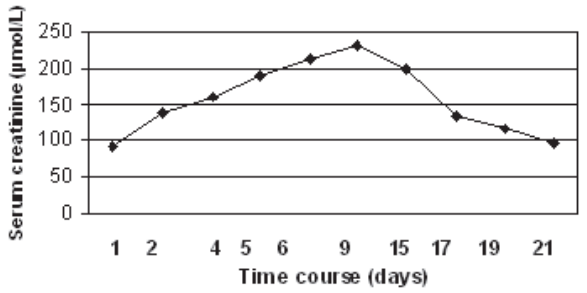

Fig. 1. Serum creatinine elevation during the course of amikacin treatment followed by declination after drug withdrawal (9th day)

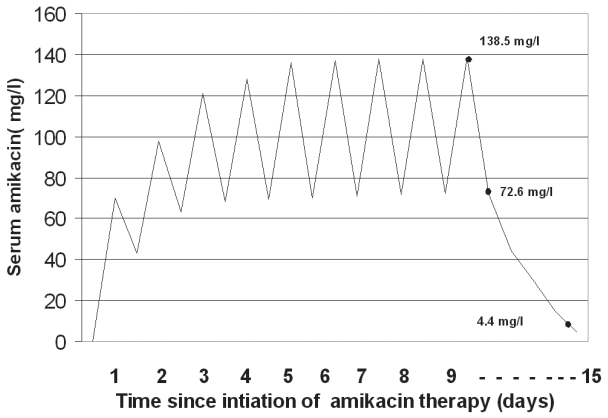

Fig. 2. Computer assisted simulation of amikacin concentration time curve and measured concentrations (•) illustrating toxic levels on once-daily regimen till withdrawal (- - -).

Discussion

Several decades after clinical experience with aminoglycoside antibiotics, there is continuing debate over the most appropriate administration regimen for these drugs. In recent years, once daily administration has been used increasingly, in the hope of both improving efficacy and reducing toxicity. Toxicity was generally determined using rather less-sensitive markers such as measurement of serum creatinine for nephrotoxicity and clinically detectable hearing loss for ototoxicity. Most meta-analyses found clinical efficacy to be significantly better with once daily administration, and some of them reported significantly less nephrotoxicity with once daily administration [11–13]. There is debate about how therapeutic drug monitoring should be performed, and whether it is still required with once daily administration. Previous experience with the aminoglycosides, especially in patients with impaired drug clearance caused by renal impairment, suggests that monitoring is still prudent. Advanced age has also been associated with an increased incidence of aminoglycoside nephrotoxicity, especially in rats [14, 15]. Subclinical evidence of impaired renal function was also demonstrated in humans [16]. Studies of risk factors for aminoglycoside nephrotoxicity in humans concluded that age was a risk factor, although statistical significance was found only in complex multivariate analyses [17, 18]. The correlation of increased risk of toxicity with age and/or pre-existing renal disease may be misleading, and it is unclear whether an increased risk exists when the dosing regimen is adjusted for pre-existing decrease in glomerular filtration rate.

In the present report, combination with another antibiotic which is partially eliminated by kidney possibly aggravated the renal function impairment in an elderly man. Both tazobactam and piperacillin are eliminated by the kidney via glomerular filtration and tubular secretion. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the dose as unchanged drug and the remainder as the single metabolite. Piperacillin is excreted rapidly as unchanged drug, with 68% of the dose in the urine. In subjects with renal impairment, the half-lives of tazobactam and piperacillin, after single doses, increase with decreasing creatinine clearance. At creatinine clearance below 20 ml/min, the increase in half-life is 4-fold for tazobactam and 2-fold for piperacillin compared to subjects with normal renal function. Streetman et al. [19] recently published that concurrent piperacillin administration may increase the risk of aminoglycoside-associated nephrotoxicity. Throughout the 9 days course of therapy in the present case, no measurement of amikacin concentration, amikacin or tazocin dose adjustment were carried out. This as a result might lead to serum creatinine elevations and extreme accumulation of amikacin many fold exceeding conventionally proposed therapeutic levels are trough below 5 mg/l and peak level up to 30 mg/l depending on the seriousness of the infection even being up to 60 mg/l in neutropenic patients [20]. Raveh et al. [21] showed that renal damage correlated with a high aminoglycoside trough level (>1.1 μg/ml) on a once-daily regimen in elderly patients. In contrast to previous studies, Koo et al. [22] found a correlation between high serum peak concentrations and incidence of nephrotoxicity in the once-daily dosing group of elderly patients, indicating that high serum peak con-

centrations that occur with once-daily aminoglycoside dosing may increase the risk of nephrotoxicity. Extremely high peak and trough levels after 9 days as we report here, clearly indicates that age is an additional risk factor, warranting timely therapeutic drug monitoring for once-daily aminoglycoside regimen as considered by Barclay et al. [23]. Bartal et al. [24] suggested that individualized pharmacokinetic dosing of aminoglycosides reduces the incidence of nephrotoxicity and may allow the use of higher doses of aminoglycosides. In a retrospective study Kirkpatrick et al. [25] reported that a drug clearance change occurred on average 3 days before the change in creatinine clearance indicating creatinine value was a delayed indicator of nephrotoxic effect of an aminoglycoside. The slow restoration of serum creatinine levels to baseline value as a result of amikacin discontinuation in the present case also indicates once-daily amikacin therapy related nephrotoxicity in elderly.

Conclusions

The case presented above indicates that elderly patients may produce unpredictable renal alterations during a once-daily course of amikacin. The fact that there is a longer exposure time to toxic levels may mean most toxic effect to the patient. Therefore clinicians should be very careful while applying the whole day dose administration of amikacin calculated on dosing weight basis once-daily regardless of initial normal serum creatinine. Based on our past experiences, whenever a once-daily regime of amikacin is a choice, obtaining serum amikacin levels immediately before the next dose is warranted in elderly patients, i. e. it is not rational to wait for days until the renal function deteriorates. Earlier therapeutic drug monitoring to adjust the dosage regime is simple and may ensure safer and effective therapy with a great deal of cost-savings and better overall health outcomes.

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Tematický plán kurzů Katedry klinické biochemie IPVZ pro období září – prosinec 2007 (část 3)

211007 Kurz – Neaterotrombotická poškození myokardu

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Místo konání: Praha 4, Budějovická 15

Termín: 17.–18. 10. 2007

Předpokládaná cena: 1000,- Kč

Vedoucí kurzu: prof. MUDr. M. Engliš, DrSc., doc. MUDr. Š. Alušík, CSc., prof. MUDr. K. Cvachovec, CSc., MBA, prof. MUDr. V. Staněk, CSc., prof. MUDr. J. Pirk, DrSc. (e-mail: englis@ftn.cz)

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