AGED PATIENTS WITH CONCOMITANT CARDIAC DISEASE ARE CERTAINLY PRONE TO TOXICITY WITH POTENTIALLY NEPHROTOXIC ANTIBIOTICS COMMONLY USED:

CASE SERIES BASED EVIDENCE.

Tesfaye H., Jedlickova B., Prusa R. Semansky M., Palivoda M., Pavelkova V., Skala P.

Department of Medical Chemistry and Biochemistry, Division of Clinical Pharmacology, Faculty Hospital Motol, 2nd Faculty of Medicine, Charles University, Prague, Czech Republic, ynlab czech, Prague, Czech Republic, Intensive Care Unit, Mediterra-Hospital, Sedlcany, Czech Republic, Masaryk Hospital, Division of Infectious Diseases, Usti nad Labem, Czech Republic, Masaryk Hospital, Division of Urology, Usti nad Labem, Czech Republic.

E-mail: hundie.tesfaye@fnmotol.cz

Abstract: - BACKGROUND: Elderly patients are prone to drug toxicity in general due to age determined physiologic deterioration of organ function. Furthermore, many of elderly patients are polymorbid and as a result are on concomitant drugs use. Under such conditions, any drug dosing error or inappropriate combination may be fatal particularly in this patient’s population. Aminoglycosides and glycopeptides antibiotics are known nephrotoxins in particular for these elderly patients. AIM: To describe case sires of elderly patients with underlying cardiac diseases, who developed renal function impairment following amikacin and vancomycin treatment and consequences related to toxic drug levels. METHODS: Data of 10 patients (66-85 years old) 4 males and 6 females treated with glycopeptides antibiotic (vancomycin) or amnoglycoside (amikacin) and suspected for associated toxicity were included in case series reviewed. Serum drugs’ levels determined by fluorescent polarization immunoassay (FPIA) method have been evaluated in clinical context to aid in dose adjustment using computer assisted simulation curves. RESULTS: Elderly patients on both amikacin and vancomycin therapy demonstrated evident renal function impairment manifested by 250-800 % serum creatinine increase. In one case of amikacin overdose, haemodialysis was required. Trough levels of the drugs were 2 -15 fold above the recommended range. History of ischemic heart disease, sepsis and other factors leading to or associated with cardiovascular disease were characteristic for these patients, where intervention was needed to rescue the patients from further renal function deterioration. CONCLUSIONS: These case series illustrate that elderly patients with pre-existing risk may be exposed to unpredictable renal function deterioration during aminoglycosides or glycopeptides antibiotics treatments unless monitored without delay regardless of initially so called “normal serum creatinine”. Therefore, in cases aminoglycosides or glycopetides antibiotics are of choice in particular in elderly cardiac patients, obtaining serum levels immediately before the second dose and accordingly dosing regimen adjustment is warranted. Timely therapeutic drug monitoring (TDM) as part of multi-disciplinary care may ensure safer and effective therapy with cost-savings and favourable treatment outcomes.

Key-Words: - NEPHROTOXICITY, AMINOGLYCODSE ANTIBIOTICS, VANKOMYCN, ELDERLY CARDIAC PATIENTS
1 INTRODUCTION

Elderly patients are prone to drug toxicity due to existing physiologic organ function deterioration. Furthermore, many of elderly patients are multimorbid and as a result are on concomitant drugs use. [1] Rodgers et al. [2] reviewed data of two hundred and forty-six patients over the age of 65 years treated for acute renal failure (ARF) during almost three decades published that the fatality has apparently not changed over the duration of the study. This particularly applies to patients with an underlying medical illness or with urological problems including ARF following surgery with perioperative sepsis, which continues to carry a poor prognosis. Underlying diseases: Pneumonia, S. aureus sepsis, other septicemia, ischemic heart disease, renal disease, multi-drugs use, mismatched transfusion, the use of invasive techniques with contrast media within pre-existing risk factors and concomitantly using nephrotoxic drugs may add to the risk due fact that renal reserve declines with advancing age and that elderly patients are among high risk groups already. Under such conditions, any drug dosing error may be fatal in this patient population. Aminoglycoside and glycopeptide antibiotics are known nephrotoxins in particular for these elderly patients. Studies of risk factors for aminoglycoside nephrotoxicity in humans concluded that age is a risk factor. Therapeutic drug monitoring may help to minimize risk of toxicity or therapeutic failure, if timely provided. Renal changes that occur with aging mainly consist of impairment in the ability to concentrate urine and to conserve sodium and water. These physiological changes increase the risk of volume depletion and the prerenal type of acute renal failure (ARF) in elderly people. Bladder outlet obstruction caused by benign prostatic hypertrophy is a common cause of ARF in elderly men. Another frequent cause of ARF in the elderly is drug-induced nephropathy. More likely, in patients with congestive heart failure, chronic renal disease (including diabetic nephropathy) or chronic liver disease than in otherwise healthy individuals. Renal vascular damage caused by arterial hypertension participates in the alterations to systemic vascular function and structure. Nephrosclerosis seems to run in parallel with systemic atherosclerosis, which accounts for the increased cardiovascular morbidity and mortality seen in hypertensive patients. Parameters indicating the existence of an alteration in renal function (increased serum creatinine, proteinuria and microalbuminuria) are independent predictors for an increased cardiovascular morbidity and mortality. Hence, parameters of renal function have to be considered in any stratification of cardiovascular risk in hypertensive patients. [3] It is of utmost importance to establish whether ARF is of prerenal or postrenal type, both of which are potentially fully reversible. In contrast, patients with ATN or rapidly progressive glomerulonephritis may not recover, or may only partially recover, their renal function. [4] The principal objectives of the present paper is to describe clinical case series of elderly patients on amikain and vancomycin therapy, who developed renal function impairment in association with toxic drug levels revealed after delayed monitoring and its consequences.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Initially prescribed nephrotoxic antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>M</td>
<td>Urosepsis, Post MI, IHD</td>
<td>Amikacin 1000mg/24hrs</td>
</tr>
<tr>
<td>2</td>
<td>76</td>
<td>F</td>
<td>Urosepsis, Diabetes type 2</td>
<td>Amikacin 1000mg/24hrs</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>F</td>
<td>MRSA, Sepsis</td>
<td>Vancomycin 1000mg/12hrs</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>F</td>
<td>Endocarditis, IHD</td>
<td>Amikacin 1000mg/24hrs</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>F</td>
<td>Sepsis, Fluidothorax</td>
<td>Vancomycin 1000mg/12hrs</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>F</td>
<td>MRSA, Sepsis, IHD</td>
<td>Vancomycin 1000mg/12hrs</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>F</td>
<td>MRSA, Sepsis</td>
<td>Vancomycin 1000mg/12hrs</td>
</tr>
<tr>
<td>8</td>
<td>85</td>
<td>M</td>
<td>Urosepsis, IHD</td>
<td>Amikacin 1000 mg/24hrs</td>
</tr>
<tr>
<td>9</td>
<td>76</td>
<td>M</td>
<td>Urosepsis IHD, Diabetes Type 2</td>
<td>Amikacin 1000 mg/24hrs</td>
</tr>
<tr>
<td>10</td>
<td>73</td>
<td>M</td>
<td>Sepses, IHD</td>
<td>Amikacin 500 mg/24hrs</td>
</tr>
</tbody>
</table>
Table 1. Patient characteristics in cases of nephrotoxic drug accumulations events including, age, gender, basic diagnosis and initial dosage regimens in elderly patients. M= male, F= female, MI= myocardial infarction, IHD, Ischemic heart disease, MRSA= meticillin resistant staphylococcus aureus

2 CASE SERIES AND OVERALL SUMMARY

Overall summary of the results show that the patients in the case series demonstrated evident renal function impairment manifested by 2.5-10 fold serum creatinine elevation. Trough levels of the drugs were 2 -15 fold above the recommended ranges. In one case of amikacin overdose, haemodialysis was required. Underlying ischemic heart disease and sepsis were characteristic for these patients with abnormal drug levels higher than the acceptable therapeutic limits.

**Case 1.** Fig 1. (upper part) Serum creatinine elevation compared to baseline level of 93 µmol/L to approximately 250 % was evident during amikacin treatment till the drug discontinuation, due to evident cumulation (Fig1. bottom part).

**Case 2.** Fig. 2. Rapid elevation of serum creatinine(Fig.3) compared to initial 102 µmol/L was significant to indicate renal function deterioration Associated with amikacin therapy. Serum amikacin level determined randomly before the next dose revealed concentration of 37.2 mg/L, thereafter four hours intensive dialysis Amikacin level has been eliminated to 8.24 mg/L.

**Case 3.** Fig. 3. Vancomycin levels only slightly declines in elderly patient with sepsis after the clinician reduced the daily dose by half. Trough level determined 48 hours after drug withdrawal, demonstrated significantly high potential toxicity.
monitoring demonstrating possible danger of long time exposure to high peak amikacin level in an elderly with ischemic heart diseases.

**Case 5.** Fig. 5. Vancomycin trough concentration exceeding the recommended range has been measured 16 days later since vancomycin administration started. Serum creatine in this case is also elevated to 170 µmol/L form initial 80 µmol/L. Computer assisted simulation shows dose adjustment from intial 1 g mg /12 hours to 500 mg twice a day.

**Case 7.** Fig.7a. Rapid elevation of serum creatinine (right Fig., table below) compared to initial 35 µmol/L was significant to indicate renal function deterioration associated With vancomycin therapy. Serum Vancomycin trough level determined just before the 5th dose and thereafter drug discontinuation, the randomly determined level was yet higher than the recommended trough concentration as illustrated on Fig 7. b below

**Case 7.Fig 7b** Demonstrating cumulative Vancomycin level and slow elimination even after withdrawal to come to acceptable target concentration as shown by computer assisted simulation of curves by fitting observed concentrations (white circles) and predictions post dose adjustment (right green line oscillations).

**Case 6.** Fig. 6. Computer assisted simulation of accumulating vancomycin level on 1g twice daily dosing regimen, where the random sample concentration (27 mg/L) after withdrawal indicates still toxic concentration under impaired renal function in an elderly woman with underlying ischemic heart disease.

**Case 8.** Fig. 8. Serum creatinine increased rapidly (by half the initial value) in elderly cardiac patient with urosepsis, just after first dose of an aminoglycoside (amikacin), which required dose
reduction by half of the initial dose as illustrated on computer assisted simulation.

**Case 9.** Fig. 9. Serum creatinine increased rapidly to 380 umol/L (compared to the initial value 103umol/L) in elderly cardiac patient with urosepsis, just after first dose of an aminoglycoside (amikacin 1g loading dose, thereafter 0.5 g/day). The trough level on 4th day was 22.6 mg/L, indicating poor elimination leading to further renal function elimination needing temporary withdrawal and dose adjustment by extending the dosing interval up to 72 hours on .5g dosing.

**Case 10.** Fig. 10. Serum creatinine level 192 just on 500 mg of amikacin doses per day for five days led to random therapeutic drug monitoring in this patient. The serum level of amikacin18 hours post last dose was reported to be 24.4 mg/L demonstrating slow down of drug elimination in this case. Based on these observed facto, the dosing regiment has been adjusted on 500 mg/72 hours by using computer assisted simulation for dose prediction.

### 3. DISCUSSION

Among glycopeptide antibiotics Vancomycin is currently a drug of choice in meticillin-resistant *Staphylococcus aureus* or *Staphylococcus epidermidis*. Aminoglycosides including amikacin are also of important clinical use, despite existing toxicity risk. The toxicity of these drugs has been generally determined using rather less- sensitive markers such as measurement of serum creatinine for nephrotoxicity and clinically detectable hearing loss as a result of ototoxic effect. However, reality shows that it is too late, when these toxicity signs manifest. The main approach for better estimation of the initial dose is the considering physiologic renal function decline after certain gain in age illustrated in the figure below.

Lash and Gardner [5], who reviewed the structural and functional changes that occur with aging and salient features of acute renal failure in the elderly population stated that the aging kidney is associated with a number of structural and functional changes and as a result of these changes the aging kidney is more susceptible to nephrotoxic and ischemic injury. Therefore, considering naturally existing age related renal function deterioration is an important point of view while treating elderly patients with nephrotoxic and renally cleared drugs in particular and in geriatric pharmacotherapy in general. There is debate about how therapeutic drug monitoring should be performed, and whether it is still required with once daily administration in normal renal function, although experience with aminoglycosides, especially in patients with impaired drug clearance, suggests that monitoring is still prudent. There is controversy on therapeutic concentration monitoring of Vancomycin too, despite evidences existing of its advantage especially in unpredictable renal fiction patients.
Advanced age has been reported in association with an increased incidence of aminoglycoside nephrotoxicity in both animal studies, whereas studies of risk factors for aminoglycoside nephrotoxicity in humans also concluded that age was a risk factor. In the present cases combination with other medicines, whose renal clearance is important were assessed. In one case, tazobactam and piperacillin, which are partially eliminated by kidney via glomerular filtration and tubular secretion, were documented. In another case with vancomycin therapy furosemide was concomitantly used. In all other cases both amikacin and Vancomycin were used either with penicillin or as a monotherapy. Therefore, considering age and age-related polymorbidity as a risk factor should guide monitoring of this patient population without delay independently of the initial serum creatinine to predict the right dosage regimen Cosgrove et al. [9] published that independent predictors of a clinically significant decrease in creatinine clearance were age > or =65 years and receipt of any initial low-dose gentamicin and concluded that initial low-dose gentamicin as part of therapy for S. aureus bacteraemia and native valve infective endocarditis is nephrotoxic and should not be used routinely, given the minimal existing data supporting its benefit. According to Hemmsen et al. [10] clinical outcomes did not differ significantly between high and low trough groups for deep-seated MRSA infections, but nephrotoxicity was consistently higher in the high trough group, regardless of the definition used. In a retrospective study by Jeffres et al. [11] also the overall mean change in CrCl for the study population was -13.5 (-16.0) mL/min (range, 0.0 to -62.6 mL/min), where, patients with maximum measured vancomycin serum trough concentrations > or =15 g/mL had significantly greater absolute changes in CrCl compared with patients with maximum measured vancomycin serum trough concentrations <15 g/mL respectively, suggest that aggressive vancomycin dosing and prolonged vancomycin administration may be associated with greater risk for renal toxicity. It is common to see that many older adults have decreased kidney function. It is of vital importance that practitioners should be informed that no single clinical assessment method is validated in predicting their kidney function. In a review based primary literature identified through MEDLINE/PubMed (1950-2010) and EMBASE (1980-2010) databases within search limited to English language, human subjects, and individuals 65 years of age and older, Nguyen et al. concluded that there is no proven valid method for eGFR in older adults; however, the CG and MDRD equations are routinely applied in clinical practice, although kidney function assessment in older adults remains a challenge.[12] In a study aimed to estimate the prevalence of decreased kidney function in an elderly population and to evaluate the impact of using alternative markers of glomerular filtration rate (GFR), focusing on serum cystatin C (Cys C) and the Modification of Diet in Renal Disease (MDRD) Study prediction equation, Wåsen et al. [13] published that the prevalence of moderately or severely decreased renal function, estimated by the MDRD Study equation, was 35.7%; the CG formula yielded 58.6%, whereas, the profile of Cys C performance, including variation across age groups and level of health status, showed greater similarity to GFR estimated using the MDRD Study equation than to SCreat alone, or GFR estimated using the CG formula. However, discordance between high Cys C levels and only mildly decreased GFR estimates was observed in subjects with functional limitations. Thus, prevalence estimates of decreased renal function amongst the elderly vary considerably depending on prediction formula used. Variation in creatinine metabolism amongst elderly comorbid patients and the critical dependence on the serum creatinine assay and exact calibration, make the use of creatinine-based formulae to predict GFR questionable in geriatric clinical practice.[13] Whatever is the formula used to estimated GFR with estimated creatinine clearance (CrCl) in the dosing of drugs requiring adjustments in elderly patients with declining renal function, none of the...
equations in the elderly was found to be better for estimating renal drug elimination.[14] Vancomycin is the drug of choice in the treatment of methicillin-resistant Staphylococcus aureus (MRSA) infection. However, the presence of certain clinical complications like renal failure alters vancomycin pharmacokinetics, leading to drug accumulation and toxicity highlighting the need to identify an effective substitute for treating MRSA infections when vancomycin cannot be used.[15] Vancomycin is used for the treatment of resistant staphylococcal and enterococcal infections as well as streptococcus pneumonia, but is associated with nephrotoxicity especially in elderly patients with underlying ischemic heart disease and endocarditis, despite initially apparent normal serum creatinine level, to deteriorate shortly after vancomycin treatment.[16] Beyond serum creatinine levels, there were several biomarkers proposed to monitor insults to kidney including neutrophil gelatinase-associated lipocalin (NGAL), which was recently identified as a sensitive biomarker for acute kidney injury. Park et al. [17] who, investigated the usefulness of serum NGAL in monitoring patients undergoing vancomycin therapy and observed significant positive relationship between NGAL level and creatinine level in patients with normal basal leukocyte levels but not in those with higher leukocytes indicating that the clinical usefulness of serum NGAL should be interpreted carefully when evaluating renal impairment in patients undergoing vancomycin treatment. Indoxyl sulfate, a protein-bound uremic toxin, was also found to be accumulated in kidney tissues with a reduction in renal function. In this regard serum indoxyl sulfate concentration was significantly increased in patients with dialysis and cardiovascular event (p<0.01, p<0.01, respectively) suggesting that serum indoxyl sulfate level may be a valuable marker in predicting cardiovascular disease and renal function decline in patients with advanced chronic kidney disease.[18] Nevertheless, the struggle to find out early marker of nephrotoxicity during the therapy with potentially nephrotoxic drugs continues. However, the best tool we have indisposition today to achieve better patient safety is early therapeutic drug monitoring and accordingly dose adjustment. [19]

4 Conclusion

Elderly patients are prone to drug toxicity for physiologic deterioration of organ function and have no reserve to compensate that any drug dosing error may be fatal. Furthermore, many of elderly patients are polymorbid and as a result are on concomitant drugs use to add to the risk. Our case series illustrate that elderly patients with pre-existing risk may be exposed to unpredictable renal function deterioration on long term aminoglycoside or glycopeptide antibiotics doses unless monitored without delay regardless of initially normal serum creatinine. We suggest that timely provided TDM may ensure safer and effective therapy with cost-savings and favourable outcomes.

References:

[1] Tesfaye H., Paluch Z., Jedlickova B., Skokanova J. Significant number of elderly patients live with potentially toxic levels of digoxin most probably overlooked for long enough. In: Recent Researches in Medicine and Medical Chemistry (Proceedings of the 3rd WSEAS International Conference on Cardiology (part of Summer WORLD MED) July 14-17, 2012 Kos Island, Greece (pp 213-219)


