The study on the resistance of non incosomial bacterial strains “Alexander” demonstrated high susceptibility of bacterial strains responsible for lower respiratory tract infections (Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis), urinary tract infections (Escherichia coli, Proteus vulgaris) and other infections (Staphylococcus aureus) to standard cheap antibiotics (aminopenicillins) and pefloxacin, which are rarely used in everyday clinical practice in Poland [1].

In patients with severe bacterial infections and risk factors of side effects administration of chemotherapy combined with amikacin requires

GENERAL

ECONOMIC IMPACT OF STANDARD ANTIBIOTIC THERAPY COMBINED WITH AMIKACIN, IN CLINICAL UNIT, LODZ, POLAND – PART I∗

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Abstract: The study “Alexander” on bacterial resistance to antibiotics conducted in Poland revealed high sensitivity of bacterial strains to simple and cheap antibiotics. In Poland pharmacoeconomic studies on the safety, effectiveness and costs of treatment are rare. Development of therapeutic standards in bacterial infections on the basis of pharmacoeconomic analyses and clinical studies determining effectiveness and safety of therapy allows for more rational pharmacotherapy. The following problems were investigated: is the treatment of serious bacterial infections with cheap standard antibiotics [SAT] or other antibiotics therapy [OAT] combined with amikacin safe and effective? What are the direct costs? How can reduction in costs be achieved? Prospective, randomized, single-blind study was performed in the group of 152 patients, admitted from 1 January to 31 July 2000, treated with amikacin combined with aminopenicillin/amoxicillin [SAT] versus other antibiotic therapy [OAT]. The economic evaluation was done by estimation of direct cost of treatment in patients with risk factors of nephrotoxicity [NT] and therapeutic drug monitoring [TDM] versus without TDM. The statistical significance was evaluated. This study revealed that effectiveness of the SAT versus OAT combined with amikacin in serious infections is high, 80% vs. 87%, respectively.

Amikacin used in high once daily dose [HODD] in combined therapy with SAT or OAT was more safe in patients with risk of nephrotoxicity and TDM (21%) vs without TDM (10%) than used in conventional therapy [CT] 40% vs 19% [p<0.05]. Evaluation of the absolute risk of nephrotoxicity increase in patients with TDM was 0.16 vs 0.34 Absolute Risk Increase (ARI) 0.18, Relative Risk Reduction (RRR): 0.53; 95% Confidence Interval (CI): 0.87-2.82. The number needed to treat (NTT): 5.43; reduction of the risk of nephrotoxicity in patients without TDM treated with HODD was 0.19 vs 0.09, Absolute Risk Reduction (ARR): 0.09; RRR: 0.47; 95% CI: 0.74-1.34; NNT: 11.1; reduction of the risk of nephrotoxicity in patients with TDM treated with amikacin HODD was 0.21 vs 0.40, ARR: 0.48; RRR: 0.48; 95% CI: 0.68-1.14; NNT: 5.3;

Direct costs of the treatment with SAT vs OAT combined with amikacin are low [EU 78.30 vs EU 145.16] in the Clinical Unit of Lodz, compared with other countries. Out of EU 530 for the hospitalization of one patient, 86% constituted "hotel costs". Omitting TDM in patients without risk factors can significantly decrease costs by EU 66 860 per 1000 patients.

Introduction of safe and cheap standard in the treatment of bacterial infections in clinical unit, shortening hospitalization by 5 days and limiting the number of patients requiring TDM service allows for a decrease in direct cost of about EU 235410 per 1000 patients/year.

Keywords: pharmacoeconomics, amikacin, effectiveness, nephrotoxicity, therapeutic drugs monitoring

∗ Presented in part: Kusowska J, Analiza opłacalności TDM w zapobieganiu nefrotoksyczności po aminoglikozydach. (Cost justified TDM in prevention of nephrotoxicity during aminoglycoside therapy) [abstract 36]. In programme and abstract of the” VII Ogólnopolski Zjazd TTM” (Spa) Poland, DC: Problemy Terapii Monitorowanej 2001: 9

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increased pharmacovigilance, monitoring the treatment with clinical examinations, laboratory tests and TDM. TDM increases the cost of treatment. So far in Poland there have been no pharmacoeconomic studies evaluating the efficiency of combined chemotherapy in serious infections and nosocomial infections, the frequency of side effects, TDM necessity and resulting costs.

An objective of this study was to answer the questions whether administration of empirical standard cheap antibiotic therapy [SAT] with amikacin versus other antibiotics and [OAT] with amikacin is effective in patients with serious bacterial infections?

What is the frequency of nephrotoxicity [NT] in patients in severe clinical condition in whom SAT or OAT with amikacin in HODD or CT were used?

**METHODS**

Prospective, randomised single blind study was performed in 152 patients (160 patients were enrolled in the study, 8 died in the course of treatment because of stroke [5], sudden cardiac death [2], ketoacidosis with diabetic coma [1]).

**Inclusion criteria:** patients with serious bacterial infections, age >45 years, Caucasian race

**Exclusion criteria:** symptoms and signs of renal failure [creatinine over 1.5 mg/dL], dehydration, stroke, diabetes with ketoacidosis or hyperosmolar coma, hypotonia, neoplastic diseases, hypersensitivity to antibiotics and fluoroquinolones, severe dermatitis and bacteria resistance to the selected chemotherapeutics.

**Characteristic of population:** Patients with serious bacterial infections treated from the 1st January to the 30th June 2000 in the Clinical Unit of Internal Diseases, Department of Clinical Pharmacology, Medical University of Lodz, Poland (Table 1).

OAT was given to the remaining 74 patients, as follows:

- Cefuroxime + amikacin 30 patients
- Cefotaxime + amikacin 18 patients
- Cloxacillin + amikacin 14 patients
- Penicillin G + amikacin 1 patients
- Pefloxacine + cefuroxime + amikacin 11 patients

In 36 patients with severe clinical condition (congestive heart failure IV class pro NYHA and/or respiratory failure) clindamycin was used additionally at the same time against anaerobic bacteria. All patients with complicated and nosocomial infections were treated with SAT or OAT with amikacin given intravenously in divided daily dosage of 0.5 g CT or of 1.0 g HODD.

Antibiotics were administered using empirical sequential therapy and pharmacodynamic / pharmacokinetic properties of the drugs as well as microbial culture and sensitivity of strains. When clinical improvement was achieved, intravenous drugs were switched to oral forms [2-4]. All patients were treated for concomitant diseases at the same time.

Out of patients from both groups receiving SAT and OAT and amikacin, 64 patients with high risk of adverse drug reactions (ADR) were selected prior to the use of TDM services. Independent risk factors of amikacin nephrotoxicity were as follows: age over 60, concomitant diseases affecting pharmacodynamics and pharmacokinetics of the drug i.e; [heart failure – class III/IV pro NYHA], liver cirrhosis, e.g. with generalized oedema, ascites or hydrothorax, [hypo- and dysproteinæmia], administration of other drugs with potential nephrotoxic-

### Table 1. Baseline characteristic of the studied population (mean values for both study groups)

<table>
<thead>
<tr>
<th>Patients</th>
<th>SAT + amikacin</th>
<th>OAT + amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67±8</td>
<td>69±4</td>
</tr>
<tr>
<td>Male</td>
<td>68%</td>
<td>65%</td>
</tr>
<tr>
<td>Lower respiratory tract infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community acquired pneumonia</td>
<td>39%</td>
<td>15%</td>
</tr>
<tr>
<td>Bronchitis and chronic obstructive pulmonary diseases</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>28%</td>
<td>8%</td>
</tr>
<tr>
<td>Nosocomial infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital acquired pneumonia</td>
<td>24%</td>
<td>56%</td>
</tr>
<tr>
<td>Other resistant to SAT</td>
<td>20%</td>
<td></td>
</tr>
</tbody>
</table>
ty [furosemide, cephalosporins], or those affecting the metabolism of other drugs [inductors or inhibitors of isoenzymes of cytochrome P450 CYP3A4].

In patients in whom TDM was used and symptoms of NT after amikacin appeared, the dose of aminoglycoside was modified using a computer programme (17 patients) or amikacin was discontinued (26 patients).

Study endpoints
1. Therapeutic success – regression of all symptoms of bacterial infection
2. Progressive improvement – regression of all clinical symptoms and some laboratory symptoms
3. Signs of nephrotoxic effect of amikacin with HODD and CT (increase of creatinine level > 1.5 mg/dL) in patients without NT risk factors and in selected patients evaluated by TDM (increase of creatinine > 1.5 mg/dL and/or serum amikacin ≥ 2.0 µg/mL)
4. Identification of factors increasing NT > 15% in patients with bacterial infections and TDM

Therapeutic effectiveness was analyzed daily by monitoring of fever, dyspnoea, chest pain, productive cough, shortness of breath or wheezing, chills, dysuria and other reported complaints as well as daily physical examination. Laboratory tests; complete blood count [CBC], urinalysis, comprehensive metabolic profile [CMP], including fasting blood glucose, evaluation of acid-base balance, level of urea and creatinine, electrolytes, liver function tests [bilirubine, levels of alanine and aspartic transaminase] were monitored on the days: 1st, 4th, 7th, 14th of hospitalization or on day 3 following the regression of infection. Prior to drug administration, chest X-ray, microbial culture and sensitivity were analyzed. The full physical exam and laboratory tests were performed before and 30 days after discharge from hospital.

The effectiveness of pharmacotherapy and the frequency of ADR other than nephrotoxicity were recorded. In the study a standard definition of nephrotoxicity was defined as an absolute increase in serum creatinine level by 0.5 mg/dL [5, 6].

Therapeutic Drug Monitoring
TDM was also used in 64 patients treated with aminoglycoside. In order to determine amikacin concentration, blood samples were collected 10 minutes after iv drug injection and prior to the administration of the next dose. Aminoglycoside concentration in the blood was determined by using immunofluorescence method in polarized light, reagents and TDX [ABBOTT].

Symptomatic treatment included pharmacotherapy with theophylline, mucolytics, β-adrenomimetics, cholinolitics, glycocorticosteroids, cromolyn sodium and antihistamine medicines, NSAID [non-steroidal anti-inflammatory drugs], non-opioid analgetics, anxiolytics, hypnotics and antitussive drugs.

Statistical analysis was performed using the STATISTICA -SNSP 801804612 G51 computer program. Demographic data and differences of clinical effectiveness were analyzed by means of chi-square test with Yates modification for groups of small numbers. The statistical significance was evaluated at p value of less than 0.05.

The study was approved by the Health Research Ethics Board of the Medical University of Lodz, Poland.

RESULTS

The effectiveness of treatment in patients with serious bacterial infections was assessed as therapeutic success or failure. Therapeutic success was consistent with the regression of all clinical and laboratory signs of infection, and progressive improvement of health, based on physical examinations and tests.

As a result of SAT, therapeutic success was achieved in 80% patients versus OAT, combined with amikacin (87% patients). On physical examination and in laboratory tests regression of all bacterial infection symptoms or progressive health improvement were found in those patients. Failure of treatment was observed in patients with slight improvement after therapy and/or side effects (hipersensitivity, dyspepsia, headache, sleep disorders and insomnia) [Table 2].

Amikacin was mostly administered with ampicillin/amoxicillin (in 51% of patients). In 14% of patients during hospitalization health improvement was not achieved after 3 days of treatment with antibiotics such as imipenem, aztreonam, piperacillin with cephalosporins and metronidazole. The average time of hospitalization was 13.3±6.1 days, for patients additionally treated with aminoglycoside it did not exceed 7 days.

The evaluation of aminoglycoside nephrotoxicity was performed in all patients by determining the serum creatinine level. Sixty-four patients with risk of ADR, were monitored with TDM service.

In 50% of patients treated with the combination of drugs with amikacin nephrotoxicity of the drug was observed which required modification of the maintenance dose and subsided after the discontinuation of aminoglycoside. Among patients without TDM service, drug nephrotoxicity appeared in
24 patients (about 19% of patients following standard treatment) and in about 9% of patients, to whom amikacin was administered in a high once daily dose (p < 0.5).

In 52 patients with risk of nephrotoxicity, determination of amikacin concentration was performed. Symptoms of drug toxicity were observed in about 40% treated with conventional dose and in about 21% of patients receiving aminoglycoside in high dose once daily [Figure 1].

In the group of patients without TDM the prevalence of renal failure was 16%, and in the group of patients with risk factors and TDM services 34% (p < 0.5).

Evaluation of the absolute risk of nephrotoxicity in patients with TDM 0.34 vs 0.16, Absolute Risk Increase (ARI) 0.18; Relative Risk Reduction (RRR) 0.53; 95% Confident Interval (CI): 0.87-2.82; The number needed to treat (NNT): 5.43. The number of patients with risk factors was calculated. In those patients TDM should be employed in order to avoid nephrotoxic effect of amikacin NNT = 1/0.184 = 5.43.

Reduction risk of nephrotoxicity in patients without TDM treated with HODD was 0.19 vs 0.09, ARR: 0.09; RRR: 0.47; 95% CI: 0.74-1.34; NNT: 11.1.

In patients without TDM, in whom HODD was used, the reduction in risk of nephrotoxic effect was 0.47. In order to avoid symptoms of renal failure in a patient, amikacin in HODD should be administered to 11 patients.

Reduction of the risk of nephrotoxicity in patients with TDM treated with amikacin HODD 0.21 vs 0.40, ARR: 0.19; RRR: 0.48; 95% CI: 0.68-1.74.; NNT: 5.3.

The increase in creatinine concentration by more than 0.5 mg/dL was not observed in patients under the age of 70 with amikacin concentration less than 2.0 µg/mL or potentially toxic more than 2.0 µg/mL and simultaneously receiving other potential nephrotoxic drugs, i.e. furosemide, cefuroxime,
Aminoglycosides administered with ampicillin/amoxicillin in patients with complicated bacterial infections were effective in as many as 80% vs. 87% in OAT of treated patients.

Jensen and Paretsch reported that therapeutic success in 72% to 76% of treated patients indicated very good effectiveness of chemotherapy. Information from other publications showed, that most often intravenous antibiotics such as cefuroxime, gentamicin or ampicillin and oral cefuroxime and pefloxacin were administered more often than carbapenems or clindamycin [15,16].

The study “Alexander” in Poland on bacterial strains resistance has proved the highest in vitro effectiveness of aminopenicillins against pathogenic strains of Streptococcus pneumoniae (87%) and Haemophilus influenzae (88%) in infections of lower respiratory tract. The research also showed very good effectiveness of ampicillin and pefloxacin in urinary tract infections caused by Escherichia coli. [1, 17].

The present study of the empirical SAT or OAT combined with aminglcoside in complicated bacterial infections demonstrated that it is effective and cost justified due to quickly achieved therapeutic success. Statistical analysis has shown no significant differences between the effectiveness of SAT and OAT combined with amikacin therapy, p > 0.05.

### Nephrotoxicity in TDM

TDM increases the cost of antimicrobial therapy in hospital. In USA the cost of monitoring therapy with TDM in 100 patients receiving aminoglycosides was calculated as 30187 USD.

Since 1985-1990 the definition of nephrotoxicity was standardized as “an absolute increase in creatinine level of 0.5 mg/dL”’. During the last 10 years of observations it was estimated, that incidence of nephrotoxicity decreased from 38% to 8%. The meta-analysis performed in 1992-1997 demonstrated no significant difference in nephrotoxicity between the administration of high once daily

### Table 3. Patients with risk of nefrotoxicity in combined therapy with aminoglycoside

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of patients N=64 (%)</th>
<th>Number of days</th>
<th>C min (mg/mL)</th>
<th>Risk factors</th>
<th>Nephrotoxicity of drugs</th>
<th>Nephrotoxicity n &gt; 15%</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-50</td>
<td>9</td>
<td>5.0</td>
<td>&lt; 2.0</td>
<td>2</td>
<td>Furosemid</td>
<td>2</td>
</tr>
<tr>
<td>50-60</td>
<td>9</td>
<td>5.0</td>
<td>&gt; 2.0</td>
<td>2</td>
<td>Cephalosporin</td>
<td>0</td>
</tr>
<tr>
<td>60-70</td>
<td>16</td>
<td>5.8</td>
<td>4</td>
<td>4</td>
<td>Other</td>
<td>0</td>
</tr>
<tr>
<td>70-80</td>
<td>44</td>
<td>6.7</td>
<td>&lt; 2.0</td>
<td>6</td>
<td>Furosemid</td>
<td>2</td>
</tr>
<tr>
<td>80-95</td>
<td>22</td>
<td>4.15</td>
<td>4</td>
<td>2</td>
<td>Cephalosporin</td>
<td>4</td>
</tr>
</tbody>
</table>

* concomittant diseases – congestive heart failure, oedema, ascites, cachexia
* cephalosporin – at the same time therapy with cephradin, cefotaxime, cefuroxime
* other – at the same time therapy with other inhibitor/inducer of P450 CYP3A4
dosage and conventional dosage of aminoglycosides [18-20]. The decrease in nephrotoxicity after high once daily doses was statistically significant only in one of 18 studies [21].

In the study on intermittent renal damage (increase in creatinine level > 1.5 mg/dL) it was found in 24 patients without TDM and in 52 patients with risk factors in whom TDM was carried out. Administration of amikacin in combined treatment in high once daily dose increased the safety of treatment.

Amikacin administered in divided daily dosage was 40% using TDM, and 19% without TDM. Amikacin administered in a high once daily dose caused renal injury in a smaller number of patients 21% – 10% than in case of conventional treatment and the observed nephrotoxicity did not depend on TDM services.

A priori a group of patients with potential risk factors was selected; in this group kidney damage was expected in even all 100% cases. An increase in pharmacovigilance, monitoring of treatment with daily clinical examination and laboratory tests, TDM, quick modification of the dose of amikacin or discontinuation of amikacin increased the safety of pharmacotherapy in these patients [6].

It was discovered, that frequency of amikacin nephrotoxicity increased significantly and appeared in as many as 28% of patients, depending on the number of risk factors [Table 2]. Patients over the age of 70 receiving aminoglycosides were found in the highest risk group and signs of renal injury occurred more often in patients with chronic heart failure, ascites and hydrothorax or in those who were taking many other drugs [polypragmasis]. Amikacin and pefloxacin administered in patients over the age of 60 with chronic heart failure, who were receiving therapy with furosemide and cephalosporins, showed increased risk of renal failure. It has been assumed that pefloxacin as an inhibitor of isoenzymes of cytochrome P450 CYP3A4 inhibits the metabolism of other drugs and potentially increases the risk of ADR.

Acknowledgement

Sources of financial support: This study was supported by the Medical University of Lodz, Poland (502-11-760).

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Received: 14.04.2005