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

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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 < 0.5).

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: 1.1; reduction of the risk of nephrotoxicity in patients with TDM treated with amikacin HODD was 0.21 vs 0.40, ARR: 0.19; RRR: 0.48; 95% CI: 0.68-1.74; 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

So far in Poland there have been no pharmacoeconomic studies evaluating the efficiency of combined chemotherapy in serious infections, the frequency of side effects, TDM necessity and resulting costs.

Continuing our study (of Part I) the following problems were investigated:

What are the direct costs of treatment of serious bacterial infections in clinical unit in Lodz?

Will early identification of patients susceptible to NT and omitting TDM in those with no risk factors allow for the reduction in cost in clinical wards in Poland?

What can be financial consequences of the introduction of standard in bacterial infections treatment?

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Methods

Prospective, randomized 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].

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.

Study endpoints

1. Direct costs of treatment of serious bacterial infections with SAT versus OAT combined with amikacin.

2. Financial savings resulting from the introduction of a therapeutic standard increasing the effectiveness of therapy, decreasing the hospital stay from 13 days to 8 days and possibility of omitting TDM in selected patients.

The economic evaluation included the estimation of direct treatment costs in patients with complicated bacterial infections, hospitalized in our Clinical Unit [1-5].

Direct costs comprised:

1. Medical cost of the physician, nursing care, and specialist consultation.

2. Costs of the diagnostic and laboratory tests: Complete Blood Count (CBC), Comprehensive Metabolic Profile (CMP), microbial culture plus sensitivity, imaging techniques [X-rays, ultrasound, computed tomography [CT], magnetic resonance image [MRI] and electrocardiogram [ECG] including 24-hour Holter monitor and 24-hour blood pressure recording and TDM [5-6].

3. Costs of the antimicrobial drugs; antibiotics and fluoroquinolone [7].

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

Cost of the physician, specialist and nursing care were calculated from the equation:

\[ C = \frac{I}{Np \times Nph \times T} \]

where:

- \( C \) – costs of the physician [and nursing] care per patient during of hospitalization days
- \( I \) – income of physicians and/or nurses per annum [basic salary and on call, bonuses, additional rewards]
- \( Np \) – number of patients hospitalized per year in the Clinical Unit
- \( Nph \) -number of physicians (and nurses) working in the Clinical Unit
- \( T \) -number of hospitalization days.

In the study the following procedures, were also estimated: intravenous infusion [IV], intramuscular drug administration [IM], nursing procedures, blood pressure, temperature measure and oxygen therapy. Costs of the procedures included agents and materials and nursing working hours. The cost of drug preparation, storage, distribution and administration were also included in the calculation.

Health Care Fund established the total cost of therapy per day of hospitalization as EU 42.11 in the year 2000 [6].

The cost of hospitalisation given by the Health Care Fund included costs not related to the disease, number and type of procedures, diagnostic tests, specialist consultations and drug therapy, etc.

Cost of patient’s therapy using TDM was investigated in relation to the risk factors of adverse drug reaction. Mean drug concentration in each patients and costs of providing TDM were calculated.

The discounting was not performed because achieved benefits appeared to be parallel to cost, i.e. in the same calendar year.

Statistical analysis was performed using the STATISTICA -SNSP 8018048612 G51 computer program. In order to compare the cost, the following tests were done: Kolmogorow – Smirnow with Lillieforse probability, U-Mann-Whitney at the absence of normal distribution, and Kruskal-Wallis for comparison of more than two variables. 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

Cost estimation

The concentration of aminoglycoside was determined as 2.8 per patient, and the cost of one measurement 15.26 EU (immunoradiological test cost 8.2EU, personnel cost 7.07 EU). TDM application increased the direct cost by 42.73 EU per patient and in all patients the costs were 2734.72 EU.

Direct cost per patient without the risk of nephrotoxicity successfully treated during 13 days of hospitalization was 78.30 EU. Direct cost of therapy in patients over 60 years of age, with other dis-
In successfully treated patients resources used up on pharmacotherapy reached about 30%, on physician and nursing care plus speciality consultation only 23%, on diagnostic investigations 47% [Table 1].

In 2000 the Health Care Fund paid 42.11 EU per one hospitalisation day per patient; Total cost of hospitalisation = direct cost + hotel cost

Mean direct costs of treatment were 111.80 EU [without TDM 78.30 EU and in patients with risk factors 145.13 EU].

Hotel cost = 560.06 EU - 111.80 EU = 448.26 EU

The total cost of one patient with serious bacterial infection was about 560.00 EU including direct cost only 14% and hotel cost up to 86%.

Direct cost in patients with TDM services represented only 26% of hospitalization cost.

In patients with complicated bacterial infections and risk of NT, costs of antibiotic and symptomatic therapy were higher by 52.64 EU. than in patients without TDM.

In patients below 60 years of age direct cost reached 74.81 EU. It was calculated that in patients older than 70 years, in whom TDM was provided, direct cost of treatment was higher by 43.18 EU. The highest direct costs were noticed in patients between 60 and 70 years of age, who constituted 43% of the studied population.

**DISCUSSION**

Economic evaluation of selected medical procedures, diagnoses and treatments have been studied in some European countries and also in the United States of America [2, 3]. Information on the economic impact of antibacterial treatment and its impact on the Polish Health Care System is very limited [8-14].

In Poland combined antibiotic therapy with aminoglycoside has been routinely monitored by the level of drug in blood, thus increasing the direct cost of treatment. In our study we have attempted to answer whether application of cheap, safe drugs of confirmed efficacy in vitro (aminopenicillin SAT) or alternative OAT combined with amikacin is effective and safe and whether omitting TDM in patients without risk factors can reduce the cost.

These studies indicate where significant savings may be achieved in the future by implementation of new and modification of older therapeutic standards in the Clinical Unit of Internal Diseases, Department of Clinical Pharmacology, Medical University of Lodz, Poland.

Basing on the results of the other study it was confirmed that time of hospitalization has the greatest influence on the reduction of total costs. Shortened hospitalisation time in the Clinical Unit of Internal Diseases, Department of Clinical
Pharmacology, Medical University of Lodz, Poland, will generate significant savings in the future.

Calculation of savings with shorter hospitalization (5 days):

\[ C = D_c + H_c \]

where:

- \( C \) – total cost,
- \( D_c \) – mean direct costs,
- \( H_c \) – hotel cost,
- \( H_c = (\text{EU/patient/day} \times \text{number of hospitalization days}) \)

- \( D_c, H_c = (42.11 \text{ EU} \times 13.3) = 111.73 \text{ EU} \)
- \( H_c = 448.33 \text{ EU} \),
- \( H_c = 33.71 \text{ EU/day} \)

Savings per patient = \( 33.71 \text{ EU/day} \times 5 = 168.55 \text{ EU} \)

The saving of 168.55 EU will be achieved. With hospitalization of 1000 patients per year total savings would be 168550 EU. It should be emphasized, that savings can be achieved only when the Health Care Funds will pay for every hospitalized patient [9, 12, 14].

The saving of 168.55 EU per patient, due to shortening of hospitalization, can be achieved only if expected therapeutic success is 80% or greater.

Decreasing resources for diagnostics and laboratory tests may also achieve reduction of direct costs. However, it should be emphasized, that in Poland, spending on physician, nursing care and specialist consultations are drastically low and can not be the source for savings.

Drug prices and cost of pharmacotherapy may significantly influence direct costs only when the change in SAT guarantees higher effectiveness by more than 25% [15].

Economic aspects enforce shortening of time for antibiotic intravenous administration in hospital and continuation of treatment with oral antibiotics with follow-up on outpatient basis.

Many authors have reported, that shortening of hospitalization by one day may give significant economic profits per year [9, 10, 16, 17].

However, attention should be drawn to the fact, that outpatient treatment requires continuation of pharmacotherapy monitoring for 2 to 6 weeks after discharge from the hospital. Outpatient treatment phases the risk of recurrence of disease and readmission to hospital as well as adverse reactions of treatment. Cost of outpatient treatment, occurrence of late ADR and asymptomatic infections in patients with diabetes also needs to be taken into consideration.

Paretsch and Paladino observed that empiric therapy of patients with pneumonia and the change of intravenously administered ceftriaxone into oral cepfodin made economic difference. They calculated, that the change in antibiotic therapy from intravenous to oral allowed to save 46.05 USD per patient, shortened hospitalization time by one day and showed no recurrence of the infection for about 30 days [18].

Fligelman et al. reported that application of sequential therapy with ciprofloxacin gives savings of 1159.97 USD as compared to treatment with ciprofloxacin administered only intravenously. They demonstrated that it was cost justified and acceptable for savings of 293 USD per patient with serious bacterial infections [17].

Jensen and Paladino studied economic impact of treatment with ciprofloxacin and enoxacin with comparison to standard intravenous antibiotic therapy. They discovered, that time of antibiotic therapy in hospital or outpatient treatment has a crucial influence on the cost. The average treatment cost was 4818 USD [19].

Economic aspects of 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.

A priori a group of patients with potential risk factors was selected; in this group kidney damage was expected in even all 100% cases. 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 [20].

The objective of therapeutic drug monitoring with serum drug concentration is to achieve quick therapeutic success, decrease in the frequency of adverse drug reactions, decrease in cost associated with therapy of drug-induced complications and long time hospitalization.

Costs of TDM investigation are different and depend on the quality of service. "Low" quality of TDM determined only drug concentration in the blood. The average cost was 154 USD per patient at a mean number of measurements – 5.3. "High" quality of TDM service needs specialist laboratory, professionally trained medical personnel and computer software. The mean cost of such investigation was 302 USD per patient [from 175 to 386 USD] [21, 22].

In our study the mean cost of TDM services was 42.73 EU per patient and the mean number of measurements was 2.8.

The results were not statistically significant, however some authors question necessity of reaching statistical significance in pharmacoeconomic analyses [23].

Effective empiric antibiotic therapy combined with high once daily doses of amikacin, daily phys-
ical examination, laboratory tests (particularly creatinine level), selecting a group of patients with high risk of Adverse Drug Reaction (ADR), prognosis of pharmacodynamic and pharmacokinetic drug interactions, use of TDM, might decrease direct and hotel cost of treatment of complicated bacterial infections in Poland and reduce resources of Health Care Found in the future.

Bertino et al. worked out specific principles for aminoglycoside monitoring and suggested that TDM was not needed in all patients. It was revealed that therapy monitored with measurement of serum drug concentration is cost justified only if it is possible to decrease nephrotoxicity on average by 6% – 7% at mean nephrotoxicity of 14% – 15%. TDM is not cost justified at frequency of ADR of 9% – 10%, and monitoring therapy leads to decreases in renal injury signs only in 3% – 4% of patients [21].

Moreover, high once daily dose regimen increased the effectiveness of therapy and does not require intense monitoring with TDM, in contrast to conventional therapy. A single bolus of intravenous aminoglycoside caused the reduction of therapy costs by about 50%. The cost of therapy with single dose decreased from 199.43 CanD to 97.62 CanD [20].

In the Clinical Unit of Diabetology with Department of Clinical Pharmacology, resources directly associated with medical care, treatment and diagnosis of patients represent only 14% of money designated by the Health Care Funds for hospitalization per patient.

In Poland, direct costs of therapy with therapeutic drug monitoring are lower than in other countries because of low income of professional medical personnel. However, due to insufficient funds for hospital from the national budget, some savings can be achieved during the year by modifications of standards for therapy monitoring used only for selected patients.

The results of the study demonstrate that shortening hospitalization by only 5 days using SAT or OAT with amikacin treatment and limiting the number of patients requiring TDM service allows for a decrease in direct cost of about 235410 EU per 1000 patients/year.

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