

CLINICAL STUDY

Cost-effectiveness analysis of switching from intravenous to oral administration of antibiotics in elderly patients

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Abstract

Objective: The aim of the introduced work was to evaluate pharmacoeconomic advantages of timely switching from intravenous to oral administration of antibiotics (ATB).

Methods: The evaluated group was selected out of 2870 patients, who were hospitalised at the Clinic of Geriatric Medicine of the Faculty of Medicine of Comenius University in Bratislava from January 1st 1999 to December 31st 2001. In our retrospective study we analysed 96 patients with community-acquired pneumonia successfully treated by ATB. In 43 of them ATB were given intravenously and in 53 the therapy was switched, i.e. the intravenous administration was used at the beginning and oral administration when the condition improved. We applied a cost-effectiveness analysis to the pharmacoeconomic evaluation. The cost-effectiveness coefficient was calculated as the ratio of ATB price (Slovak Crowns) to the effectiveness criterion (number of asymptomatic days in month).

Results: According to the cost-effectiveness coefficient, the switch therapy was significantly less expensive in all evaluated ATB (except for pefloxacin) in comparison with intravenous administration: ampicillin-sulbactam 93.9 vs 168.1; cefuroxime 90.0 vs 123.3; amoxicillin-clavulanate 74.0 vs 116.3; ciprofloxacin 31.7 vs 54.1.

Conclusions: A timely switching from intravenous to oral administration of ATB in a suitable patient is an effective way to save financial resources. (Tab. 5, Ref. 21.)

Key words: cost-effectiveness analysis, antibiotics, pneumonia, switch therapy, intravenous administration.

The worldwide tendency of population aging is reflected also in Slovak demographic indicators. The proportion of people over 60 years of age increased from 16.5 % in December 1970 to 18.0 % in March 2001 (1). Pneumonia belongs among the most significant causes of morbidity and mortality. In Slovakia, the incidence of pneumonia reached the number of 319 per 100,000 inhabitants in 1997 and the mortality in this disease was 57.9 per 100,000 inhabitants (2). These facts point out the necessity to rationalize the pharmacotherapy of pneumonia in respect of the pharmacoeconomic point of view.

The choice of antibiotics (ATB) in pneumonia patients is in most cases empirical. In a patient with an easy clinical course of pneumonia, oral administration of ATB is advised. In risk patients with the presence of intercurrent diseases, it is advisable to administer ATB intravenously (i.v.) at least at the induction part of the treatment (2–3 days). This way of application is characterized by a prompt onset of effect. Its disadvantage is the

patient's discomfort, likelihood of complications such as skin abscess, thrombophlebitis or even sepsis. The most convenient way of application is the oral administration. Therefore in a patient capable of oral administration, it is suitable to change i.v. to

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Tab. 1. DDD and prices/DDD of ATB used in the group.

ATB	DDD (mg)	Price/DDD (SKK)
amp-sul i.v.	2000	268.5
cefuro i.v.	3000	427.4
amoxi-clav i.v.	1000	109.0
cipro i.v.	500	219.7
pef i.v.	800	88.9
amp-sul o.	1500	128.7
cefuro o.	500	78.8
amoxi-clav o.	1000	52.6
cipro o.	1000	54.9
pef o.	800	57.6

DDD — daily defined dose; SKK — Slovak Crowns; i.v. — intravenously administered drug; o. — orally administered drug, Amp-sul — ampicillin-sulbactam; cefuro — cefuroxime; amoxi-clav — amoxicillin-clavulanate; cipro — ciprofloxacin; pef — pefloxacin.

oral administration after the general clinical condition has improved, i.e. to apply the so-called switch therapy (3, 4, 5).

In addition to the favourable effect on patient's compliance, the switch therapy has also significant pharmacoeconomic consequences. These are given by shortening the duration of hospitalization as well as lower costs of oral administration. The price of i.v. application is increased by the costs associated with i.v. medicine manufacture, as well as the expenses associated with i.v. application (infusion set, medical personnel work) (6).

The aim of the introduced work is to affirm the favourable pharmacoeconomic impact of timely conversion of i.v. to oral administration of ATB.

Patients and methods

Group characteristics

Within the period from January 1st 1999 to December 31st 2001, 2870 patients were hospitalized at the Clinic of Geriatric Medicine of the Faculty of Medicine of Comenius University in Bratislava. Out of these patients we selected 96 patients with community-acquired pneumonia, in whom the first i.v. administration was effective or there was a switch in their therapy, i.e. the i.v. administration used at the beginning of treatment was switched to oral administration when the condition had improved.

We compared the effectiveness of costs between the group of 43 patients in which ATB were given during the whole i.v. treatment and the group of 53 patients in which the switch therapy was applied.

We also recorded the results of sputum microbiological examination. We drew all data for our study from the documentation of the Clinic of Geriatric Medicine of the Faculty of Medicine of Comenius University.

In pneumonia patients we required the diagnosis to be affirmed by X-ray examination. We considered the ATB treatment to be effective in patients, in whom a recession of clinical symptoms of pneumonia was observed (cough, expectoration, dyspnoea, painful breathing, present auscultatory finding, fever, shivers) and the recovery had to be affirmed by a control X-ray examination (7).

Tab. 2 Characteristics of the group (n=96).

Age (years)	77.6±7.3
Gender	
men	46 (48 %)
age (years)	75.4±7.4
women	50 (52 %)
age (years)	79.5±7.2

Age is provided as mean±standard deviation and the remaining data express the number of patients (% of n=96).

Cost-effectiveness analysis

For the evaluation of pharmacoeconomic consequences of timely conversion of i.v. to oral administration we used a cost-effectiveness analysis (8).

Out of direct costs we calculated the prices of used ATB. ATB prices were determined by the average price in Slovak Crowns (SKK) per daily defined dose (DDD) of ATB used from 1999 to 2001 (9). The information on ATB prices was obtained from the Pharmacy of the Academic L. Dérer's University Hospital, being the drug supplied or Clinic of Geriatric Medicine during the period from 1999 to 2001 (Tab. 1).

The therapy result was expressed by the effectiveness criterion (E). In our case, the criterion was given by the number of asymptomatic days in month. E was calculated by deducting the number of days during which the patient's documentation incorporated symptoms of pneumonia from the number of 30 (days in month). The main parameter of the analysis — the cost-effectiveness coefficient (price/E) was determined as the ratio of ATB price and effectiveness criterion (10, 11).

We evaluated the patients in whom ATB were administered i.v. during the entire treatment separately from those in whom the i.v. ATB administration at the beginning of treatment was followed by oral administration — so-called switch therapy.

Statistical methods

The pharmacoeconomic parameters (price, E, price/E) were characterized by median values and a 95 % confidence interval for median. To compare two continuous variables, of which at least one did not have a Gaussian distribution, we used the non-parametric Mann-Whitney test. The distribution normality was evaluated by skewness and kurtosis. All statistical tests were done at the significance level $p=0.05$. By specifying this level, we were willing to risk a 5 per cent chance of erroneously rejecting our null hypothesis when, in fact, the null hypothesis is true (12). We used the statistical program STATGRAPHICS plus Version 3.

Results

Table 2 shows basic characteristics of the evaluated group: age and gender.

In the evaluated group, the average duration of hospitalization was longer (average standard deviation: 14.1 ± 9.4 days) than

Tab. 3. Isolated pathogens in sputum (n=26).

Isolated respiratory pathogens	Number of isolants
<i>Klebsiella pneumoniae</i>	9
<i>Staphylococcus aureus</i>	5
<i>Haemophilus influenzae</i>	4
<i>Escherichia coli</i>	3
<i>Streptococcus pneumoniae</i>	3
<i>Proteus mirabilis</i>	2

the average period of ATB administration (average standard deviation: 8.5 ± 3.4 days).

Table 3 shows bacterial pathogens of pneumonia cultivated in patients' sputum. In 26 (27 %) of these 96 patients, the pathogenic agent of infection was successfully affirmed by cultivation. *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae* were most frequently isolated. All cultivated bacterial strains were sensitive to ATB currently given to the patient.

Table 4 describes the number of patients to whom the following ATB were given using the switch therapy or continual administration i.v.: ampicillin-sulbactam, cefuroxime, amoxicillin-clavulanate, ciprofloxacin and pefloxacin. The table also shows ATB costs in SKK and effectiveness criteria. In all cases except pefloxacin, the costs of ATB in switch therapy were statistically significantly lower in comparison to price of continual i.v. administration. We did not find out any significant difference when comparing the effectiveness criteria of ATB administered in switch therapy and continual i.v. patterns of administration.

The main parameter of analysis – cost-effectiveness coefficient of individual ATB is shown in Table 5. In terms of price per asymptomatic day, the switch therapy of evaluated ATB except pefloxacin was less expensive than continual i.v. administration.

Discussion

Timely application of ATBs is the determining factor in the treatment of pneumonia. In most cases ATBs are chosen empirically according to the regional recommendations for therapy of pneumonia. These take into consideration the state of regional sensitivity of most significant pathogenic agents of pneumonia, safety ATB profiles as well as the price aspect of the treatment (3, 13).

In a pneumonia patient it is necessary to review the patient's general condition and the presence of any factors aggravating the prognosis, e.g. age over 65 years, comorbid conditions (congestive heart failure, liver, renal, cerebrovascular and neoplastic diseases), respiratory rate >30 /min, heart rate >125 /min, systolic blood pressure <90 mmHg, body temperature ≥ 37.5 °C or <36 °C etc. (2, 14).

The success rate of identifying the bacterial pathogenic agent in sputum was low in our group (27 %). This fact is represented by age-relative uniqueness of patients in our group. In particular, the bad cooperation of elderly patients at sputum-taking is concerned, often the sputum production is reduced to absence (15). In Riquelme's study the respiratory infection pathogen was isolated in the sputum of 43 out of 101 elderly patients (16). Venkatesan et al described their successful identification of the causal bacterial agent in 43 % of patients in a group of 73 patients suffering from community acquired pneumonia (17).

ATB used in our group were indicated in compliance with regional recommendation for treatment of community-acquired pneumonia (3). All isolated bacteria were sensitive to ATB being currently applied ATB.

For our pharmacoeconomic study we chose the cost-effectiveness analysis. This method enables to compare the price of therapy in relation to the result expressed by natural units (e.g. number of asymptomatic days, number of years gained). The main parameter of the analysis – the cost-effectiveness coefficient is a

Tab. 4. Number of patients treated with ATB, prices of ATB and effectiveness criteria.

ATB	n		Price		p	E		p
	sw.	i.v.	sw.	i.v.		sw.	i.v.	
amp-sul	9	8	2533.9 (2201.2-2592.1)	4369.7 (3823.5-4515.9)	<0.001	26 (25-28)	26 (24-28)	NS
cefuro	12	9	2385.3 (2038.2-2671.6)	3205.3 (3142.3-3857.3)	<0.001	26 (24-27)	26 (24-28)	NS
amoxi-clav	13	11	1951.0 (1891.0-1997.8)	3139.0 (2616.0-3335.0)	<0.001	26 (24-28)	25 (24-27)	NS
cipro	9	7	824.2 (707.4-972.1)	1405.9 (1142.3-1657.4)	0.002	27 (25-29)	26 (25-28)	NS
pef	10	8	669.7 (656.1-715.0)	799.8 (624.4-803.5)	NS	27 (26-29)	27 (26-28)	NS

n — number of patients treated with mentioned ATB; sw. — switch therapy; i.v. — intravenous administration, Price in SKK; E — effectiveness criterion (number of asymptomatic days); Price, E are expressed by median of values (95 % confidence interval); p — statistical significance according to the Mann - Whitney test; NS — non-significant; amp-sul — ampicillin-sulbactam; cefuro — cefuroxime; amoxi-clav — amoxicillin-clavulanate; cipro — ciprofloxacin; pef — pefloxacin.

Tab. 5. Cost-effectiveness coefficient.

ATB	Price/E		p
	sw.	i.v.	
amp-sul	93.9 (85.4-99.5)	168.1 (147.1-189.1)	0.001
cefuro	90.0 (76.1-99.8)	123.3 (115.5-150.3)	0.001
amoxi-clav	74.0 (72.3-76.3)	116.3 (109.0-128.8)	0.001
cipro	31.7 (26.2-37.8)	54.1 (41.3-65.7)	0.007
pef	26.0 (24.8-27.0)	29.1 (20.8-33.3)	NS

sw. — switch therapy; i.v. — intravenous administration; Price/E — cost-effectiveness coefficient (SKK/asymptomatic day); Price/E is expressed by median of values (95 % confidence interval); p — statistical significance according to the Mann—Whitney test; NS — non-significant; amp-sul — ampicillin-sulbactam; cefuro — cefuroxime; amoxi-clav — amoxicillin-clavulanate; cipro — ciprofloxacin; pef — pefloxacin.

ratio of price to the effectiveness criterion. In our study this criterion was represented by the number of asymptomatic days in a 30-day month (8, 11).

We considered only the direct ATB costs, i.e. we did not calculate any additional direct costs, such as staff wages and hospital transport fees. These items were included in the sum of bed/day. In the period from 1999 to 2001, the hospital wards in the Slovak Republic were paid a certain amount of money per single bed with patient per day. The calculation of the above additional direct costs would misrepresent the dominant price impact of ATB on the entire pharmacoeconomic profile of the therapy.

Pharmacoeconomic studies also take into consideration the differences in the duration of hospitalization between various therapeutic alternatives (5). In most cases the hospitalization of geriatric patients in the introduced study was longer (average SD: 14.1±9.4 days) than the ATB treatment of pneumonia itself (average SD: 8.5±3.4 days). In most cases the patients underwent a complex examination and were treated for additional intercurrent diseases. Therefore in our study the hospitalization duration was not a suitable marker for the evaluation of therapy expensiveness.

Modern pharmacoeconomic analyses lay stress on the analysis of indirect costs in coincidence with the loss of patient's ability to work. In our groups this calculation was impossible because of the fact that the majority of patients had been old age pensioners (11).

We did not find any difference in the effectiveness of the treatment when comparing the effectiveness criterion in switch therapy and continual i.v. administration of ATB. The switch therapies by ampicillin-sulbactam, cefuroxime, amoxicillin-clavulanate and ciprofloxacin in terms of cost-effectiveness coefficient were statistically significantly less expensive than continual i.v. treatment by the above ATB. The continual i.v. administration of pefloxacin was more expensive than the switch therapy, but the difference was not statistically significant. This finding can be explained by a relatively minor difference in prices

of i.v. and oral forms of pefloxacin in comparison to other ATB (Tab. 1).

A patient, who in terms of prognostic factors is not at high risk and capable of oral administration is a suitable candidate for the conversion from i.v. to oral administration of ATB. This saves financial resources.

Bioavailability of orally administered ATBs used in our group reaches almost the level of ATB applied i.v. Such medicines are suitable for switch therapy (18).

The switch therapy was pharmacoeconomically favourable also according to the work of Ramirez et al (5). A timely change of i.v. to oral administration of ATB in 80 hospitalized pneumonia patients saved 114,080 US dollars. Simultaneously the risk of manifestation of i.v. administration complications decreased (skin abscess, thrombophlebitis, endocarditis, sepsis). Siegel et al came to similar conclusion, comparing the effectiveness and expensiveness of switch and i.v. administration of cefuroxime (19).

The pharmacoeconomic preference of oral administration in comparison with that of i.v. was pointed out by authors Chan et al (20). In their prospective study they compared i.v. with oral administration of amoxicillin-clavulanate and cephalosporins in the treatment of community-acquired infections of lower respiratory tract.

Halm et al found out, that the conversion of i.v. to oral administration was mainly preferred by pneumologists and infectologists (out of a group of 345 doctors of various specializations) (21).

According to the introduced cost-effectiveness analysis, timely conversion of i.v. to oral administration of ATB in a suitable patient capable of taking drugs orally is an advisable method of saving finances for ATB therapy. The effectiveness of both, intravenous administration and switch therapy evaluated by the effectiveness criterion was equivalent. The switch therapy has also a favourable influence on the patient's compliance.

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