

CLINICAL REPORT

Pharmacoeconomy of adult asthmatics

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*Department of Clinical Immunology, Institute of Preventive and Clinical Medicine, Bratislava, Slovakia. gazdik@upkm.sk***Abstract**

Asthma bronchiale represents serious social and economic problems in all over the world. Financial expenses are elevated every year.

The aim of the presented study was to analyze the current therapeutic approach in the management of bronchial asthma and to evaluate pharmacoeconomic aspects of treatment in selected outdoor asthmatic patients in region of Košice (Eastern Slovakia).

Patients: The data of the total number 297 patients (183 females — 61.6 %, 114 males 38.4 %), aged from 18 to 78 (average age 38) were analyzed.

Results: The total expenses per day for all asthmatics represented 19 465 Sk (65.54 Sk/day/patient). Short-acting β_2 -agonists (β -A) (55.2 %) were administered most frequently, followed by inhaled corticosteroids (CS) (43.1 %), theophyllins (T) with slow released formulas (36.4 %), cromoglycates (C) (33 %), long-acting β -A (19.9 %), combined preparations β -A with anticholinergics (ATCH) (Berodual, Combivent) (12.12 %), depot CS (10.44 %), antileucotriens (ALT) (10.10 %), combined preparation β -A with C (Ditec, 8.75 %), short-acting T (6.73 %), systemic CS (5.72 %), ATCH (4.71 %). Additive therapy represented antihistamines (AH) (69.36 %), topic AH, nasal and eyes drops (38.8 %), specific immunotherapy (36.03 %), immunomodulatory therapy (23.23 %), expectorans and antitusive drugs (15.49 %), respectively. C (20.33 %) represented the highest financial cost from the total financial budget followed by inhaled CS (16.34 %), long-acting β -A (13.20 %) and ALT (8.9 %), short-acting T (0.39 %) and short-acting β -A (3.41 %), respectively. In the group of additive drugs AH dominated (15.85 %).

Conclusion: The optimal selection of antiasthmatic drugs should be kept in mind by physicians. Our study shows some reserves in respect of optimal selection of antiasthmatic (generic drugs should be preferred), therapeutic efficacy and compliance of patients. (*Tab. 11, Ref. 15.*)

Key words: asthma bronchiale, antiasthmatic drugs, pharmacoeconomy.

Asthma bronchiale represents serious social and economic problems in all over the world. The prevalence of asthma varies from 1 to 30 %, in USA 5 %, Switzerland 7 %, Great Britain 10 %, Australia 30 % (Brenner, 1999; Jankins, 1998; Chapel et al, 1999; Doan, 1996). The financial expenses exerted in coincidence with the treatment are growing. The working disability of population together with the absence at school lessons increase too. They are reasons why society focuses its interest on the economic aspect of therapy.

The increase in allergic diseases in general, including bronchial asthma (BA), leads the scientists to develop the educational programme for the needs of a broad population (Doan, 1996; Taitel, 1995). The aims of such programs are to affect the known risk factors supporting the development and progression of the

disease. In USA (year 1998) the total financial expenses represented 11.3 billions USD (direct costs 7.5 billions USD and non-direct costs 3.8 billions USD). Financial costs associated with hospitalisation represent 3.8 billion USD.

The aim of the study was to analyze the current therapeutic approach of BA and to evaluate the pharmacoeconomic aspects of treatment in the area of Kosice region (Eastern Slovakia).

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Material and methods

The data were recruited from health records of the patients with the diagnosis of BA after the last visit in the year 2000. Thirteen outdoors of allergology in the region of Kosice were included into the study.

The data of 297 asthmatics aged from 18 to 78 (the average age 38), both sexes (females 183, 61.6 %, males 114, 38.4 %) have been evaluated. 238 patients (80.1 %) have been suffering from allergic asthma (extrinsic BA) and 59 patients (19.9 %) from non-allergic asthma (intrinsic asthma), respectively. Fourty patients (13.5 %) have been classified with the diagnosis of „dry cough, equivalent of BA“, 4 patients (1.35 %) with aspirin BA, 2 patients (0.7 %) with occupational asthma, respectively. Distribution of asthmatics according to the criteria for clinical manifestations have been as follows: 143 asthmatics (48.2 %) with mild intermittent BA, 95 patients (32 %) with mild persistent BA, 40 (13.5 %) patients with middle severe persistent BA and 19 asthmatics (6.4 %) with severe persistent BA. The average duration of disease was 8.6 yrs (from 1 to 40 yrs).

The prices of drugs (daily defined dose, DDD) have been calculated from data published in Informant of Slovak Health Ministry, dated 14th February 2000, Prescription and Drug Delivery Guide of drugs, 2000 (Vestník MZ SR, 2000; Príručka na predpisovanie a výdaj liečiv, 2000).

Results

The total budget expended in treatment of all asthmatics per 1 day represented 19 465 Sk (65.54 Sk/day/patient).

Short acting beta 2 agonists (β -A) 55.2 % have been administered predominantly, followed by inhaled corticosteroids (CS, 43.10 %), theophyllins (T) with slow released formulas (36.4 %), cromoglycates (C, 33 %), long-acting β -A (19.9 %), combined preparations β -A with anticholinergics (ATCH, Berodual, Combivent, 12.1 %), depot CS (10.4 %), antileukotriens (ALT, 10.1 %), combined preparation β -A with C (Ditec 8.6 %), short-acting T (6.7 %), systemic CS (5.72 %) and ATCH 4.7 %, respectively (Tab. 1).

In the group of additive drugs antihistamines dominated (AH, 69.4 %, topical formulas nasal and eye drops represented 38.4 %), followed by specific immunotherapy (SIT, 36 %), immunomodulation (23.3 %) and antitussive drugs and expectorans (15.5 %), respectively (Tab. 1).

From the total budget the largest financial cost involved C (20.3 %), followed by inhaled CS (16.3 %), long-acting β -A (13.2 %) and ALT (8.9 %). The other antiasthmatics created only subtle part of total expenses, short acting T (0.4 %) and short-acting β -A (3.4 %).

In the group of additive therapy AH dominated (15.9 %). SIT and other immunomodulatory therapy have not been calculated, due to complicated calculation per day.

Tab. 1. Distribution of antiasthmatics and financial expenses.

Group of drug	No	%	Expenses/D (Sk)	Expenses (%)/D(Sk)	Expenses /pt/D (Sk)
Inhaled corticosteroids	128	43,10	3180,88	16,34	24,85
Systemic corticosteroids	17	5,72	100,26	0,52	5,90
Depot corticosteroids	31	10,44	87,32	0,45	2,82
Cromoglycates	98	33,00	3957,59	20,33	40,38
Antileucotriens	30	10,10	1732,05	8,90	57,74
Short-acting β -agonists	164	55,22	664,14	3,41	4,05
Long-acting β -agonists	59	19,87	2568,72	13,2	43,54
Systemic β -agonists	7	2,36	78,15	0,40	11,16
Anticholinergics	14	4,71	179,65	0,92	12,83
Ditec-combined drug	26	8,75	351,48	1,81	13,52
Berodual. Combivent-combined preparations	36	12,12	292,06	1,50	8,11
Short-acting theophyllins	20	6,73	75,17	0,39	3,76
Long-acting theophyllins	108	36,36	588,58	3,02	5,45
Antihistamines	206	69,36	3084,42	15,85	14,97
Topical therapy - nasal and eye drops	114	38,38	1940,75	9,97	17,02
Expectorans and antitussives	46	15,49	584,27	3,00	12,70
Allergen immunotherapy	107	36,03			
Immunomodulatory therapy	69	23,23			
Together			19465,48	100,00	

No — number of patients, D — day, pt — patient

Tab. 2. Inhaled corticosteroids.

Drug	No	%	Cost of DDD (Sk)
Aldecin	6	2,02	6,90
Becloforte	12	4,04	6,29
Beclomet forte á 250 mcg	10	3,37	5,44
Beclazone Inhaler á 100 mcg	1	0,34	6,84
Beclazone Inhaler á 250 mcg	14	4,71	4,92
Beclazone Easi-Breathe á 250 mcg	2	0,67	30,16
Becodisks á 100 mcg	2	0,67	28,60
Becodisks á 200 mcg	16	5,39	28,60
Bronilide	11	3,70	20,64
Pulmicort Turbuhaler á 200 mcg	27	9,09	32,00
Pulmicort Turbuhaler á 400 mcg	2	0,67	33,80
Flixotide Inhaler á 125 mcg	2	0,67	57,01
Flixotide Inhaler á 250 mcg	13	4,38	56,95
Flixotide Rotadisks á 250 mcg	1	0,34	60,78
Flixotide Rotadisks á 500 mcg	3	1,01	60,77
Flixotide Diskus á 250 mcg	3	1,01	56,49
Flixotide Diskus á 500 mcg	2	0,67	56,51

No — number of patients, DDD — daily defined dose

Tab. 3. Systemic corticosteroids.

Drug	No	%	Cost of DDD (Sk)
Medrol á 4 mg	3	1,01	7,5
Prednison	3	1,01	3,39
Triamcinolon	11	3,70	3,71
Diprophos	28	9,43	3,67
Kenalog	3	1,01	16,14

No — number of patients, DDD — daily defined dose

In the group of inhaled CS, high percentage of asthmatics used most expensive generics-fluticasone (8.1 %) preparations Flixotide and budesonide (9.8 %) preparation Pulmicort (Tab. 2). On the other hand these molecules of CS are clinically most effective and have good pharmacokinetic properties. Systemic CS is used by 5.7 % of asthmatics (Tab. 3). Depot CS are obsolete in the therapy of BA due to the inability to change promptly the dose regim according to the patient's clinical status and increased risks of adverse effects. Surprisingly, already 10.4 % of patients were treated with depot CS and in the cases of 4 patients it represented the part of administered therapy of the acute attack.

C have been administered in 33 % of patients, mostly the preparation Tilade in 16.2 % (Tab. 4). Twenty four (8.01 %) patients of the total number of subjects used combined therapy (inhaled CS with C, except Ditec).

In majority of patients ALT have been administered in combination with CS (10.1 %) (Tab. 4), monotherapy has been observed only in 6 subjects (2.0 %) from the total number of included patients.

Inhaled short-acting β -A have been prescribed in 55.2 %, mostly in the "on demand" dose regime (Tab. 5). Regular β -A

Tab. 4. Cromoglycates and antileucotrien.

Drug	No	%	Cost of DDD (Sk)
Cromogen	13	4,38	18,68
Cromolyn	4	1,35	24,06
Intal Inhaler	20	6,73	34,65
Intal tob.	5	1,68	26,84
Tilade	48	16,16	46,72
Tilade mint	8	2,69	79,86
Accolate á 20 mg tbl.	30	10,10	57,74

No — number of patients, DDD — daily defined dose, tob — tobales, tbl — tablets

Tab. 5. Bronchodilations: inhaled β 2-agonists, anticholinergics and combined preparations.

Drug	No	%	Cost of DDD (Sk)
Berotec	46	15,49	2,79
Bricanyl Inhaler	3	1,01	4,82
Salamol Inhaler	19	6,40	3,64
Salbutamol Inhaler	2	0,67	4,02
Ventolin Inhaler	77	25,93	4,34
Ventodisks 200	14	4,71	8,63
Ventodisks 400	3	1,01	8,06
Serevent Inhaler	57	19,19	49,99
Serevent Rotadisks	1	0,34	49,97
Serevent Diskus	1	0,34	47,08
Atrovent Inhaler	14	4,71	9,29
Berodual	34	11,45	6,19
Combivent	2	0,67	5,47
Ditec	26	8,75	36,35

No — number of patients, DDD — daily defined dose

administration took place only in 10 cases (3.4 % from total number). In the set of 51 patients (17.2 %) just one monotherapy with β -A has been observed. 8.8 % of patients inhaled the preparation Ditec, frequently in a regular dose regime.

In our analysis long-acting β -A (salmeterol, in all formulas) have been used in 19.9 % of patients mainly in combination with inhaled CS. Monotherapy has been observed only in 15 patients (5.1 % of total number). Systemic (peroral) β -A have been administered only in few cases (2.4 %) (Tab. 5). ATCH have been used more frequently in combined preparations, Berodual (11.5 %), Combivent (0.67 %), monotherapy has been prescribed only in 4.71 % of patients (Tab. 5).

T with slow released formulas have been used in a relatively high percentage of patients (36.4 %) in comparison with long-acting β -A (19.9 %). Frequently, T have been administered without inhaled CS (37 patients, 12.5 %). Spophyllin retard, the less expensive preparation, has been used most frequently (39 of patients, 13.1 % of total number). Short acting T have been used only in 6.7 % of patients (Tab. 6).

The most of AH have been prescribed in the group of additive therapy, namely dominated Claritine (22.6 %) (Tab. 7). To-

Tab. 6. Bronchodilatans: systemic β_2 -agonists and theophyllins.

Drug	No	%	Cost of DDD (Sk)
Spophyllin á 100 mg	2	0,67	1,92
Spophyllin á 250 mg	37	12,46	1,35
Afonilum á 125 mg	9	3,03	6,28
Afonilum á 250 mg	25	8,42	6,31
Uni-Dur á 400 mg	14	4,71	8,31
Euphyllin á 150 mg	2	0,67	14,59
Euphyllin á 250 mg	18	6,06	10,88
Aminophyllinum retard	1	0,34	4,02
Syntophyllin tbl	17	5,72	5,05
Pharophyllin	1	0,34	8,82
Oxyphyllin tbl	1	0,34	1,40
Lontermin tbl	3	1,01	5,20
Spiropent tbl	1	0,34	9,02
Volmax á 4 mg	3	1,01	31,52

No — number of patients, DDD — daily defined dose, tbl — tablets

Tab. 7. Antihistamines.

Drug	No	%	Cost of DDD (Sk)
Dithiaden	1	0,34	4,44
Fenistil retard	1	0,34	10,01
Hismanal	4	1,35	10,90
Loratadin	9	3,03	10,32
Flonidan	13	4,38	10,33
Claritine	67	22,56	14,69
Zyrtec	45	15,15	15,81
Kestine	29	9,76	16,82
Lotanax	3	1,01	11,42
Clarinase repetabs	5	1,68	25,96
Disophrol repetabs	1	0,34	27,50
Zaditen tbl	37	12,46	12,01
Zaditen SRO	7	2,36	12,02

No — number of patients, DDD — daily defined dose, tbl — tablets

pical nasal and eye preparations have been used in 38.4 % of asthmatics, most frequently Alergodil (10.4 %) (Tab. 8).

Antitussive drugs and expectorans have been used in 15.5 % of patients (Tab. 9).

High per cent of asthmatics have been treated with SIT (36 %) (Tab. 10). In the group of other immunomodulatory therapy (peroral bacterial lysates) have been prescribed in 16.2 % of patients (Tab. 11).

Discussion

The total evaluation of drug consumption according to pharmaco-economic groups, indicates that the health status in the population is stable. These data express the health status of the population. Immunopreparations, antiasthmatics and drugs with bronchodilating effects represent the 8th position

Tab. 8. Topical preparations: nasal and eye drops.

Drug	No	%	Cost of DDD (Sk)
Beclomet nasal 50	1	0,34	6,36
Beclomet nasal 100	5	1,68	7,14
Rhinocort	30	10,10	16,45
Flixonase	15	5,05	25,11
Cromobene nasal spray	5	1,68	25,70
Lomusol	2	0,67	26,18
Allergodil	31	10,44	17,41
Livostin nasal spray	20	6,73	43,76
Rhinaaxia	1	0,34	
Nasivin gtt 0,05 %	2	0,67	
Olynth 0,1 %	1	0,34	
Pinosol	1	0,34	
Vibrocil gtt	7	2,36	1,75
Cortison eye drops	1	0,34	31,60
Cromoglycate natrium (sodium)	1	0,34	5,91
Opticrom	2	0,67	28,87
Livostin gtt	13	4,38	91,25
Spersallerg	17	5,72	10,99

No — number of patients, DDD — daily defined dose, gtt — drops

Tab. 9. Expectorans and antitussive drugs.

Drug	No	%	Cost of DDD (Sk)
Ambrobene tbl	2	0,67	14,60
Ambrobene retard	1	0,34	7,86
Mucosolvan tbl	16	5,39	16,05
Bromhexin tbl	3	1,01	2,23
L-Cimexyl tbl á 200 mg	16	5,39	11,71
Codipront tbl	3	1,01	52,17
Diolan	2	0,67	
Kodynol	1	0,34	
Libexin	1	0,34	8,85
Stoptussin gtt	1	0,34	
Tussin	1	0,34	
Tussilen	1	0,34	

No — number of patients, DDD — daily defined dose, tbl — tablets, gtt — drops

and AH 11th position, respectively (consumption of antiasthmatics in 1999).

The drugs with antiinflammatory effects (C, CS, ALT, T) have a dominant position in the management of antiasthmatic therapy. Our analysis has confirmed this trend in therapeutic approach of BA.

Short-acting β -A (except combined preparation Ditec) have been administered only on demand in patients suffering from mild intermittent asthma. This observation is also in accordance with the contemporary trends in therapeutic management of BA.

In the group of inhaled CS, a high percentage of patients have used most expensive generics (fluticasone 8.1 %, and budesonid 9.8 %). On the other hand namely fluticasone in comparison with other inhaled CS is characterised by low bioavailability. That is the reason of low manifestations of systemic ad-

Tab. 10. Specific immunotherapy.

Drug	No	%
H-AL Sevac dep. pollen	23	7,74
H-AL Sevac dep. mites	42	14,14
H-AL Sevac per os pollen	3	1,01
H-AL Sevac per os mites	4	1,35
Phostal inj. pollen	4	1,35
Phostal inj. mites	9	3,03
Staloral sol. pollen	9	3,03
Staloral sol. mites	5	1,68
Alutard inj. pollen	1	0,34
Alutard inj. mites	1	0,34
Pollinex inj.	17	5,72

No — number of patients, DDD — daily defined dose, inj — injection, sol — solutio, dep — depot

verse effects. These pharmacokinetic properties prefer fluticasone against other molecules of CS. The administration of these preparations is recommended especially in patients needing high doses of inhaled CS, (with high risk of manifestations of adverse effects) or in the patients who have developed severe adverse effects (e.g. osteoporosis, hypertension, disorder of glucose metabolism and etc.) (Jenkins, 1998). The standard CS molecule beclomethasone belongs to the group of less expensive preparation and especially in cases of short duration treatment should be preferred in administration, to fulfill the pharmacoeconomic aspects (the sparing effects). It is important to notice the need of the inhaled chamber in administration of high doses of inhaled CS resulting improvement of the application route and decreasing the manifestation of adverse effects (Jenkins, 1998).

Systemic (peroral formulas) of CS should be reserved only for patients with the most severe type of BA, in cases when neither the combination with highest inhaled doses of CS, nor other antiinflammatory drugs lead to the control of the disease. After the controlling of the disease, the transfer to inhaled CS is recommended.

Thirty three % of patients have used C (most frequently Tilade, 16.6 %). When compared with the prices of generics in this group of C, we can notice that the preparation Cromogen is approximately twice cheaper than Intal Inhaler, and equally Tilade to Tilade mint, respectively. The preparation Tilade mint contains menthol composition which could induce cough. Beside it, menthol is listed in additives, probably risk factor for the development of aspirin asthma (The Joint Council of Allergy, 1999).

ALT represented the most expensive antiasthmatics. These drugs are reserved for patients do not respond to the conventional therapy (anti-leukotriens responders) and for patients with aspirin asthma (Graber, 1999). The combination with inhaled CS is preferred. If BA clinically does not improve after 1 month of ALT administration, it is recommended to exclude the medication (non anti-leukotrien responders). In our analysis 10.1 % of patients used ALT.

Short acting β -A are administered in monotherapy only in cases with mild intermittent BA, "on demand". If they are used

Tab. 11. Immunomodulatory therapy.

Drug	No	%
Bronchowaxom	26	8,75
Luivac	9	3,03
Biostim	4	1,35
Ribomunyl	8	2,69
Urowaxom	1	0,34
Imudon	1	0,34
IRS 19	7	2,36
Histaga	4	1,35
Norga	1	0,34
Immodin	2	0,67
Isoprinosine	5	1,68
Nalcrom	2	0,67
Polystafana	4	1,35
Autohaemoterapia	1	0,34

No — number of patients

more than two times weekly, combination with inhaled CS is recommended (Krištúfek et al, 1997; Gershmann, 2000). In our study the administration of β -A represented 55.2 %, mostly „on demand“. In majority of cases the inhaled preparations have been preferred. The DDD cost of fenoterol seems to be most convenient but the administration is less recommended due to frequent risk of adverse effects (the lowest selectivity, risk from overdosing). In combined preparation Ditec, the fenoterol content is lower. In our study, Ditec has been used in 8.8 % of patients. The cost of Ditec is relatively high (DDD/36.4 Sk) in comparison with other inhaled β -A and C. The cost of preparation Salamol Inhaler seems to be most feasible.

Long-acting β -A are frequently used in combination with inhaled CS. The combination of β -A is preferred in cases of absent therapeutic effects of inhaled CS in monotherapy used in standard doses (Hrubiško, 2000). Monotherapy of long-acting β -A is not recommended. The disadvantage of this group of drugs is the relatively high cost. In our analysis β -A have been used in 19.9 % of patients. The administration of preparations in many cases have been in monotherapy, without administration of inhaled CS (5.05 %). This phenomenon is not desirable because the addition of inhaled CS to therapy improves the control of the disease and leads to a decrease in β -A consumption.

The newly developed combined preparation Seretide (inhaled CS-fluticasone and salmeterol) seems to be more feasible due to its cost and patient's compliance. When the analysis was done, this preparation was not yet on the market.

ATCH represent additive drugs with bronchodilatating effect and are used regularly in cases of more severe types of BA. These groups of drugs have not any significant adverse effects and are preferred in administration to older patients and especially in cases of BA combined with chronic obstructive bronchopulmonary disease. The administration in a regular therapeutic regimen is preferred (Barnes, 1998). In our analysis, combined preparations Berodual (11.5 %) and Combivent (0.67 %) have been more used in the regimen "on demand".

T with slow released formulas, in combination with other antiinflammatory drugs, are reserved for patients suffering from the most severe type of BA (inhaled CS, inhaled β -A, ALT). In regular administration, T possesses CS sparing effects (decreases the consumption of CS). Monotherapy (without inhaled CS) is not recommended. Surprisingly, in our study a relatively high percentage of patients have used T (36.4 %) preparations and in monotherapy 12.5 % of patients (negative phenomenon). The less expensive Spophyllin retard, has been used most frequently (39 patients) (13.1 %).

Short-acting T have significant side effects. In our study a relative high percentage of patients have been treated with T (6.7 %).

AH (69.4 %) represents the most frequent group of additive therapy. In our analysis BA has been accompanied with pollinosis (55.9 %) and allergic perennial rhinitis (34 %). The improvement of clinical signs of upper respiratory airways also improves the BA symptoms. Claritine has been the most frequent preparation (22.6 %), the costs of other AH (Loratadin, Flonidan) seem to be more feasible.

SIT is recommended in cases either with positive skin tests of immediate hypersensitivity or with positive specific immunoglobulin E (IgE) against clinically relevant allergens (Theodoropoulos, 2000). Proper selection of patients and the choice of standard allergens according to WHO criteria are the terms determining the safety and therapeutic efficacy (Spertini, 1998). In our study SIT has been applied in 36 % of patients but standard preparations have been used only in 5.39 %.

Fundamental factor in pathogenesis of BA is the chronic inflammation. That is why the antiinflammatory therapy should be dominant in the therapeutic management. In general, our analysis has confirmed these trends, however in some cases the therapeutic approach was not optimal (monotherapy with long-acting β -A or with T, administration of depot CS).

The optimal selection of antiasthmatic drugs should be kept in mind by physicians. Our study shows some reserves in respect of the optimal selection of antiasthmatics (generic drugs should be preferred), therapeutic efficacy and compliance of patients.

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