CLINICAL STUDY

Pharmacoeconomic aspects of patients treated by hemodialysis

Gazdikova K, Korecka P, Springer V, Gazdik F

*Clinic of Pharmacotherapy, Institute of Preventive and Clinical Medicine, Bratislava, Slovakia.***gazdikova@upkm.sk**

Abstract

Hemodialysis as a therapeutic procedure in patients being in the end-stage of renal failure has been used since the sixties of the 20th century.
Generally speaking, the conservative drug therapy in patients treated by hemodialysis is complex, and economically it consummes as great proportion of financial expenses.
The aim of the study was to perform an economic analysis of 101 patients, both sexes (37 females and 64 males, aged from 22 to 81 years) treated by hemodialysis, in respect of drug treatment costs. The total average cost of treatment medication represented 161,589 SKK/patient/year. Eighty one percent of total expenses were linked with the consumption on antianemic drugs (102,298.40 SKK/patient/year). The second most expensive drug group (9 % of the total cost) were medications used in coincidence with hemodialysis complications (14,981 SKK/patient/year). Diuretic – furosemid was the most frequently used drug out of the category of antihypertensive medications (68 % of patients), followed by beta-blockers (preparation Concor), calcium channel blockers (preparations Norvasc and Plendil) and angiotensin converting enzyme tritace inhibitors (ACEI, preparations Trirace, Enap, Prestarium), respectively. Only 27 % of patients were treated by hypolipidemic drugs mostly by the preparations of Gevilon and Innogen. In the majority of patients (93 %) preparations for the correction of calcium and phosphorus metabolisms such as Vitacalcin and Rocaltrol were administered, the latter being most expensive. Antianemic drugs have been used in all patients. In this category of preparations, those composing acid folate and erythropoetin were used most frequently. Alkaline supplementation of $NaHCO_3$ (bicarbonate) was used in 88 % of patients. In order to prevent the development of thrombosis and other vascular complications, the drugs with antiaggregative effects were used (Ibustrin, Curantyl, Anopyrin). To prevent the manifestation of gastrointestinal adverse reactions, the administration of H2-antagonists have been preferred (Famosan, Quamtel). The group of "Other drugs" was represented by vitamins and drugs with anti-uratic effects (ascorbic acid – preparation Celaskon, tocopherol – preparation E-vitamin and Milurit).
When summed together, the costs of therapy in patients treated by hemodialysis are three times higher compared with those in the pre-dialysis phase. In addition to the latter hemodialysis is associated with a large number of medical, psychic and social complications. In the presented pilot study the authors analysed the financial expenses coinciding with drug costs (direct loads) which are significant, but represent only a part of the pharmacoeconomic complexity. In the future it is necessary to perform a more complex pharmacoeconomic analysis in order to evaluate also other factors, such as the costs of hospitalization, dialysate solutions, technologys, salaries of the staff, etc. ***(Tab. 6, Ref. 37.)***
Key words: hemodialysis, pharmacoeconomy, antianemic drugs, antihypertensive therapy, hypolipidemic drugs.

Hemodialysis is a therapeutic procedure that has been used since the sixties of the 20th century in the treatment of subjects in the end-stage phase of kidney failure. Many patients, especially those at the age over sixty and patients with diabetes mellitus aged over 70 are included into the hemodialysis regime. The mentioned therapeutic procedure is associated with multifactorial medical, psychosocial and pharmacoeconomic problems.

Clinic of Pharmacotherapy, Institute of Preventive and Clinical Medicine, Bratislava, and Faculty of Pharmacy, Comenius University, Bratislava

Address for correspondence: K. Gazdikova, MD, PhD, Clinic of Pharmacotherapy, Institute of Preventive and Clinical Medicine, Limbova 14, SK-833 01 Bratislava 37, Slovakia.

In 1995, the total financial costs linked with hemodialysis and transplantations performed in USA represented 13.1 billions of USD, and the costs for one patient/year represented USD 45,000, respectively (Pastan and Bailey, 1999). In the same year in the Czech Republic, the total expenses represented CZK 1.5–2 billions and CZK 1.0 million CZK/patient/year (Lachmannová, 1999).

The aim of our pilot study was to evaluate the financial expenses associated with drugs, conservative medications of patients regularly treated by hemodialysis.

Patients and methods

The data used in our analysis were collected from medical records of patients of three out-patient nephrologic departments in the Slovak Republic (Bratislava, Nitra, Liptovský Mikuláš). Only the patients with the history of hemodialysis within the post three months and more were included into the evaluation.

A total number of 101 patients aged from 22 to 81 years of both sexes (37 females (36.6 %) and 64 males (63.4 %)) were analysed. The average age of patients was 56 years (average age of females and males 55.5 years and 56 years, respectively). The renal failure was caused by tubulointerstitial nephritis in 42 % of patients, glomerulonephritis in 28 % and diabetes mellitus in 14 %, respectively. Polycystic nephropathy (10 % of patients), analgetic nephropathy (4 % of patients), acute renal failure (1 %), hereditary nephropathy (1 %), and amyloidosis (1 %) were other etiologic entities leading to chronic renal failure. The frequency of hemodialysis procedure varied from 2–4 times weekly and the duration of each of them lasted from 3.5 to 5.0 hours (average 3 times weekly lasting 4 hours).

The cost of drugs used in the financial calculation were obtained from Prescription and Drug Delivery Guide of Drugs (Prescription and Drug Delivery Guide of Drugs, 2001). The following groups of drugs were calculated: antihypertensive drugs, hypolipidemic drugs, drugs for the correction of calcium and phosphorus metabolisms and acidosis disorders (drugs with alkaline effects). The other groups of drugs represented medications used in dialysis complications (antiaggregative drugs, antagonists of H2-receptors, drugs with hepatoprotective effects, prokinetics and cardiac glycosides) and the group of "Other drugs" (drugs with anti-uratic effects and vitamins).

Results

The average total of financial expenses for the treatment of one patient per one year anounted to SKK 161,589. The drug group of antianemic drugs was the most expensive (SKK 102,298/year/patient) and represented 81% of total expenses, followed by the drugs used in hemodialysis complications (SKK 33,202/patient/year). The third position was occupied by the group of antihypertensive drugs (SKK 14,981/patient/year) representing 9 % of the total cost.

Antihypertensive drugs were most frequently prescribed as a combination of diuretic drugs with beta-blockers and/or with calcium channel blockers (in 26 % of patients). The latter were followed by combinations of three antihypertensive drugs, diuretic drugs, beta-blockers and angiotensin-converting enzyme inhibitors (ACEI) prescribed in 24 % of patients. The diuretic drugs – furosemid was the most frequently administered drug (68 %). It was followed by beta-blockers (Concor 30 %) and calcium channel blockers – Norvasc (25 %), Plendil (17 %) and ACEI Prestarium (16 %). No therapy was administered in 8 % of patients. The list of financial costs for each/patient/year is shown in Table 1.

Only 27 % of the total number of analyzed patients were treated by hipolipidemic drugs. Fibrates such as Gevilon (18 %) and Innogen (3 %) and statins such as Lipostat (4 %) and Sortis (2 %) were used most frequently. The list of hypolipidemics with financial expenses are summarized in Table 2.

Tab. 1. Financial expenses of antihypertensive drugs.

Name of drug	No of patients	% of patients	SKK/patient/year
Furosemid	68	67.33	6591.90
Concor	30	29.70	1952.75
Norvasc	25	24.75	11136.15
Plendil	17	16.83	8011.75
Prestarium	16	15.84	4909.25
Ebrantil	15	14.85	8843.95
Enap	14	13.86	3737.60
Tritace	13	12.87	5796.20
Deprazolin	11	10.89	1620.60

Tab. 2. Financial expenses of hypolipidemic drugs.

Name of drug	No of patients	% of patients	SKK/patient/year
Lipostat	4	3.96	10358.70
Innogen	3	2.97	3241.20
Gevilon	18	17.82	4964.00
Sortis	2	1.98	13647.85

Tab. 3. Financial expenses of drugs using for disorder of calcium and phosphorus metabolisms.

Name of drug	No of patients	% of patients	SKK/patient/year
Vitacalcin	88	87.13	5482.30
Rocaltrol	44	43.56	8092.05
Calcium efferv	8	7.92	1963.70

Tab. 4. Financial expenses of antianemic drugs.

Name of drug	No of patients	% of patients	SKK/patient/year
Eprex	77	76.24	175192.70
Ac. folicum	89	88.12	233.60
Venofer	62	61.39	8964.40

Tab. 5. Financial expenses of drugs used for the treatment of hemodialysis complications.

Name of drug	No of patients	% of patients	SKK/patient/year
Famosan	22	21.78	1065.80
Ibustrin	20	19.80	6759.80
Anopyrin	60	59.40	211.70
Ascorutin	11	10.89	766.50
Quamatel	9	8.91	1693.60
Digoxin	7	6.93	142.35
Curantyl	5	4.95	1080.40
Pyridoxin	72	71.29	299.30
B-komplex	11	10.89	408.80
Thiamin	9	8.91	346.75

Tab. 6. Financial expenses of "Other" drugs.

Name of drug	No of patients	% of patients	SKK/patient/year
Vitamin E	33	32.67	923.45
Celaskon	62	61.39	105.85
Milurit	45	44.55	452.60

The majority of patients (93 %) were treated by drugs used for the correction of calcium and phosphorus metabolisms. Monotherapy was reported in 47 % of patients while a combination of two drugs in 38 %, respectively. Vitacalcin (87 %) and Rocaltrol (44 %) were the most frequently administered drugs. In respect to financial costs, Rocaltrol was the most expensive with the average cost of SKK 8,092/year/patient (Tab. 3).

Each patient in the analysed group was treated by antianemic drugs, and combinations of drugs have been preffered. In 33 % of patients, combinations of three preparations were used (Venofer – parenteral formula of iron, erythropoetin – Eprex and Acidum folicum – folic acid).

Preparations with folic acid were mostly preffered (89 %), followed by Erythropoetin (76 %) and Venofer (62 %). In respect of the financial evaluation, the preparation of Eprex represented the most expensive drug with its average cost of SKK 175,192/year/patient (Tab. 4).

The correction of metabolic acidosis is of importance in the therapeutic management in patients with renal failure. Natrium bicarbonate ($NaHCO_3$) in the dose of 1.5–12 g depending on the pH value of body fluids has been administered regularly in 88 % of patients.

In the prevention of vascular complications (including thrombosis), Ibustrin (20 %), Curantyl (5 %), Anopyrin (antiaggregans, 59 %) and Ascorutin (composed of rutin and ascorbic acid, 11 %) were also administered. H2-blockers (Famosan (22 %) and Quamatel (9 %)) were reserved for the management of gastrointestinal complications. Thirty seven per cent of patients were treated at least with one of the drug indicated in complications linked with hemodialysis and 14 % of patients with two preparations most frequently in combination of antiaggregation drugs (antithromotic drugs) and antagonists of H2-receptors. Fourty one per cent of patients treated by hemodialysis did not use any drugs indicated in hemodialysis complications. Renal diseases are associated also with neurologic symptoms, therefore vitamins such as Pyridoxin (72 % of patients), Thiamin (9 %) and B complex (11 %) were administered. When summed together, the preparations that were most frequently used to prevent complications in dialysis procedure were Pyridoxin (71 %), Anopyrin (60 %), Ibustrin (20 %) and Ascorutin (11 %). The list of this group of drugs together with their financial costs are shown in Table 5.

The group of "Other drugs" included vitamins (ascorbic acid – Celaskon, tocopherol – E-vitamin) and the antiuratic drug – Milurit, respectively. This group of medications was administered in 90 % of patients (Tab. 6).

Discussion

The total cost of the pharmacological treatment in the analysed group of patients on regularly treated by hemodialysis represented SKK 161,589/patient/year. These patients are characterized by a great number of medications used in their therapeutic managements. The number of combinations of the administered preparations varied from 6 to 17 daily in each patient.

Twelve preparations daily were used already by 19 % of patients followed by a combination of 13 (15 %) and 10 drugs daily (14 %), respectively. Only a minority of patients (1 %) used a combination of six drugs daily. This trend in the pharmacologic management in hemodialyzed patients has been reported also by Tozawa et al. He reported an increased number of drug usage in Japanese hemodialyzed patients in comparison with the common population (7.2 versus 2.7). In 850 hemodialysed subjects, the drugs used for the correction of metabolism of calcium and phosphorus were administered preferrentially (88 %), followed by antihypertensive drugs (71 %) and erythropoetin (60 %), respectively (Tozawa et al, 2002).

In our group of analysed patients, the choice of drug groups used for the therapy has been different. All patients were treated by antianemic drugs, followed by the drugs used for the correction of calcium and phosphorus metabolisms (93 %) and by antihypertensive drugs (92 %), respectively. The next position was occupied by the group of medications marked as „Other group" (90 %), followed by the group of drugs used for the correction of metabolic acidosis (87 %), group of drugs linked with hemodialysis complications (59 %), respectively. Only 27 % of patients were treated by hypolipidemic drugs.

Hypertension of essential or renal origins represents one of the key factor of renal failure progression and is of importance also in dialysed patients due to cardiovascular complications. The preparation Furosemid was used most frequently not only for its antihypertensive effects but also owing to its ability to reduce the level of potassium in plasma by increased renal excretion. Beta-blockers (Concor) and calcium channel blockers (Norvasc, Plendil) were the subsequent as to the frequency of their administration. The preparation Norvasc (second generation Ca-blocker of dihydropyridin type) was the most expensive

in respect of its financial calculation (SKK 11,136/patient/year). On the other hand this therapy is effective and fully indicated. The treatment with ACEI possesses not only antihypertensive effects but it has also antiproliferative and protective effects in terms of heart remodelation. In respect of the financial calculation, the therapy with Tritace was more expensive in comparison to Enap, but the dosage once daily increased the compliance of patients. Except for antihypertensive effects, some other benefits of ACEI such as the reduction of left ventricular hypertrophy and increased antioxidative defense were also observed (De Cavanagh et al, 1997, 1999; Efrati et al, 2002). In respect of its medical aspects, ACEI significantly reduced the mortality of hemodialysed patients (Hörl, 2002). In respect of pharmacoeconomic aspects the antihypertensive treatment by drugs produced in Slovakia is less expensive in comparison with drugs produced abroad.

Dyslipoproteinemia is often considered to be associated with renal diseases. Increased levels of triglycerides and decreased levels of HDL cholesterol represent the risk factors of calcification progression in vessels (Tamashiro et al, 2001). In the analysed group of patients, the usage of fibrates instead of statines has been preferred. In respect of financial expenses, the preparation Sortis was most expensive, but it was very effective in lowering the levels of total cholesterol, LDL- cholesterol and triglycerides. In addition, to the latter, Sortis decreased proteinuria (Bianchi et al, 2003). The tolerance and safety of this preparation in patients was good and in accord with other reports (Harris et al, 2002).

Decreased levels of calcium due to disorders in regulation of calcitriol and parathormone resulting in the development of secondary hyperparathyreoidism are a characteristic feature of renal failure. Therefore, the goals of the treatment of calcium and phosphorus metabolisms are as follows: the correction of calcium level in plasma (supplementation by calcium preparations), the correction of hyperphosphataemia (the binders of phosphate by $CaC0_3$, preparation Renagel) and the supplementation of the active form of D vitamin (calcitriol-preparation Rocaltrol) (Jehle et al, 1998; Castro et al, 2002; Bardin, 2003).

In the presented group the majority of patients (93 %) were treated by this group of drugs with the exception of the usage of the preparation Renagel with its properties to bind phosphates, to lower LDL-cholesterol level and to prevent the development of calcification of vessels (Bardin et al, 2003). In this group of drugs, the treatment with Rocaltrol (SKK 8,092/patient/year) was the most expensive.

Anemia is presented in 90 % of patients with renal failure. The lack of erythropoetin and decreased stores of iron increased the susceptibility and incidence of inflammation, infections and hyperparathyreoidism. The latter as well as access of aluminium are the most important factors responsible for the development of anemia (Rao et al, 1993; Muirhead et al, 1990; Macdougall et al, 1989). Other factors such as plasma uremic toxins inhibiting the synthesis of heme, and proliferation of stem cells contribute to the shortening of the time of erythrocyte survival (Gafter et al, 1989; Kushner et al, 1991; Niwa et al, 1990). The supplementation of iron by iron preparations is recommended in combination with human recombinant erythropoetin (Hörl et al, 1999; Silveberg et al, 1996). Some authors reported insufficient supplementation of iron by peroral administration and therefore parenteral supplementation is recommended (Fishbane et al, 1996; Silverberg et a_1, 1996).

Preparations with folic acid were mostly used in the group of antianemic drugs especially in patients with malnutrition (89 %). A majority of patients used erythropoetin – preparation Epprex (76 %), parenteral formula of iron – Venofer (62 %). The supplementation by means of antianemic drugs resulted in better tolerance of physical exercise, regression of left ventricular hypertrophy, corrections of anorexia, depressions and disorders of sexual libido, improved quality of life, cognitive functions, lowering of hospitalization days and mortality (Mocks et al, 1997; Wolcott et al, 1989). Normalization of hemoglobine levels significantly affects the quality of life of patients treated by dialysis (Furuland et al, 2003).

The maintenance of physiologic pH in human body seems to be the crucial factor in the reduction of uremic symptoms and mortality in hemodialyzed patients. Metabolic acidosis caused by an increased uptake of proteins is the leading factor in the alteration of aminoacid metabolism and malnutrition (Bray et al, 1996). The correction is achieved by peroral supplementation by means of drugs with alkalising effects and/or by higher concentrations of bicarbonate in dialysed solution. (Feriani et al, 1998).

The development of thrombosis in the site of fistula represents frequent complications associated with hemodialysis (Macdougall et al, 1991). In order to prevent vascular complications Ibustrin, Curantyl, Anopyrín and Ascorutin were administered.

Cardiovascular diseases frequently appearing in the dialysed patients are considered to be crucial factors of morbidity and mortality in this group of patients. Acceleration of atherogenesis is caused by hypertension, diabetes mellitus, hyperlipidemia, insulin resistance, oxidative stress, dysbalance of anti-oxidative defense in favour of prooxidants, smoking, uremic toxins, hyperhomocysteinaemia, hyperphosphataemia and chronic inflammation (Zoccali, 2000; Hörl, 2002).

Heart failure occurs frequently in hemodialysed patients and in a half of patients with systolic dysfuncion (Sulková et al, 2000). Therefore the therapy with Digoxin is indicated and this phenomenon has been observed also in our group of patients. The administration of high doses of drugs with folic acid and vitamins of group B reduces hyperhomocyteinemia which is also considered to be one of the risk factors of cardiovascular diseases (Ducloux et al, 2002; Sombolos et al, 2002).

Gastrointestinal disorders are frequently linked with hemodialysis resulting in the reduction of food intake, development of malnutrition and psychical disability of patients (Strid et al, 2002). The incidence of gastric ulcers is also frequent, therefore the administration of H2 antagonists were fully indicated (Famosan, Quamatel).

Neurologic complications are frequently associated with hemodialysis. The supplementation of pyridoxin in dialysed patients resulted in the improvement of peripheral polyneuropathy despite the reference of absence of pyridoxin insufficiency. In this analysis, pyridoxin was administered in 72 % of patients (Okada et al, 2000). Hung et al (2001) also reported that thiamin administration had a beneficial effect in patients with encephalopathy.

The conservative drug therapy in patients treated by hemodialysis is complex and brings about both physical and severe psycho-social problems. In addition, financial expenses exerted by patients in coincidence with hemodialysis (the cost of hemodialysis not calculated) is 3-times higher when compared with those coinciding with the pre-dialysis phase (Gazdíková et al, 2002). In the future it is necessary to perform a more complex analysis in order to evaluate more pharmacoeconomic factors together, such as the cost of hospitalization, medical staff, hemodialysis machine, solutions, etc. High financial costs of conservative drug therapy support the arguments for the development of kidney transplantation program not only from the pharmacoeconomic aspect but also due to the fact that kidney transplantation improves extremely the quality of life.

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