Analysis of epilepsy pharmacotherapy using request forms for therapeutic monitoring of antiepileptics

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Changes of epilepsy pharmacotherapy of in-patients treated in 1993–2001 at University Hospital in Ostrava were studied. Request forms for therapeutic drug monitoring (TDM) were used as the source of data. An analysis of 4 528 blood samples obtained from 1 695 patients was performed. Throughout the follow-up period, 48 % of patients were examined once only. Medication was changed in 50 % of repeatedly examined patients (i. e. 26 % of the whole cohort). 49 % of blood samples were taken from patients treated by monotherapy, 33 % from those with combination of two drugs, and 14 % with combination of three drugs. Combinations of more than three drugs were less frequent. Among applied drugs, carbamazepine and valproic acid prevailed, together with phenytoin in adults; 60 % of patterns prior to 2 000 involved carbamazepine, valproic acid and phenytoin in monotherapy, and combination of valproic acid or phenytoin with carbamazepine. The proportion of phenytoin was decreasing in favor of valproic acid. Children were treated with valproic acid more often than adult persons. Phenytoin was given more frequently to male patients. Female patients were more often treated with combination therapy. In the last year of the study, the utilization of the third generation epileptics increased: the combinations with lamotrigine, vigabatrin, gabapentin, tiagabine and topiramate. Different results – as compared with the utilization given in defined daily doses per 100 bed days – were caused by disproportion between the prescribed and the defined daily doses of antiepileptics, bringing about underevaluation of carbamazepine and valproic acid utilization.
Key words: antiepileptics, utilization, combination, prescription, in-patients.

ROZBOR FARMAKOTERAPIE EPILEPSIE S VYUŽITÍM ŽÁDANEK PRO TERAPEUTICKÉ MONITOROVÁNÍ ANTIEPILEPTIK

Byly sledovány změny medikace podávané epileptickým pacientům hospitalizovaným ve Fakultní nemocnici s poliklinikou Ostrava (FNsP) v letech 1993–2001. Zdrojem dat byly žádanky o vyšetření hladin antiepileptik, které doprovází vzorky zasílané k rutinnímu vyšetření na Ústav klinické farmakologie FNsP. Ve sledovaném období bylo vyšetřeno 4 528 vzorků odebraných od 1 695 pacientů. Za celé období bylo pouze 1 × vyšetřeno 48 % pacientů. Medikace byla změněna u 50 % z opakovaně vyšetřených pacientů (tj. u 26 % z celkového počtu). Při monoterapii bylo odebráno 49 % vzorků, 33 % při dvojkombinaci, 14 % při trojkombinaci, kombinace více látek byly méně časté. Z účinných látek převažuje karbamazepin a valproát, u dospělých také fenytoin. Šedesát procent medikací před rokem 2000 tvořil karbamazepin, valproát nebo fenytoin v monoterapii a kombinace valproátu nebo fenytoinu s karbamazepinem. Podíl fenytoinu dlouhodobě klesá ve prospěch valproátu. Děti užívají ve větší míře valproát v porovnání s dospělými, fenytoin byl podáván častěji u mužů, ženy užívaly častěji kombinovanou terapii. V posledním roce dochází k nárůstu antiepileptik 3. generace (lamotrigin, vigabatrin, gabapentin, tiagabin, topiramát) podávaných v kombinacích. Odlišné výsledky ve srovnání se spotřebou v definovaných denních dávkách na 100 ošetřovacích dnů, jsou způsobeny disproporcí mezi předepisovanou a definovanou denní dávkou antiepileptik, která způsobuje podhodnocení spotřeby karbamazepinu a valproátu.
Klíčová slova: antiepileptika, spotřeba, kombinace, preskripce, hospitalizovaní pacienti.

Indroduction

The utilization of drugs brings about information on the exposition of a given population to a drug in the course of a given time interval and in a given socioeconomic environment[1]. It is largely expressed in defined daily doses (DDD)[2] converted to 1 000 persons (insured individuals) and to one day, in hospitals, it is given in DDD for 100 days of treatment. These procedures register the utilization of drugs on various levels of the health-care system; however, they do not yield information on the number of patients receiving the drug and on drug dosage. For outpatients, their number and combinations applied can be obtained e. g. from the databases of health insurance companies.

To complete the data, the information on several drug groups can be obtained from the therapeutic drug monitoring. There, antiepileptic agents represent the most important group. It includes a relatively small number of drugs. Three of them are considered as basic ones – carbamazepine, valproic acid and phenytoin[3], however, the last one has been lately described as a second-choice drug[4, 5]. The contemporary trend in the pharmacotherapy of epilepsy is monotherapy[7, 8, 9, 10, 11]; in case it is not effective, combinations of two event. three agents are applied. Combinations of several drugs used to be considered as disadvantageous, but their utilization has been recently reevaluated. Under the conditions of good knowledge of pharmacokinetic properties and reciprocal effects of individual antiepileptics, the utilization of combined therapy should not be strictly refused[4, 5].

The aim of the present study was to determine drug combinations applied to in-patients and thus complete previously published results using the classical way of expressing the utilization in DDD per 100 days of treatment[12].

Method

The source of data was request forms for the evaluation of levels of antiepileptics coming with samples for routine examinations. The study involved all samples collected in 1993–2001 at the hospital divisions of the University Hospital in Ostrava. Total number of samples was 4 528 (2 948 from children, 692 from adult male, 888 from adult female) obtained from 1 008 children, 383 adult males, 386 adult females. Children who reached the age limit of 15 years during the study were considered according to the age as children, and later as adult persons. The mean age of patients was 15 ± 15 years (children 7 ± 4, adults 30 ± 17). The mean body weight of the cohort was 39.0 ± 24.1 kg (children 25.5 ± 15.2 kg, adults 64.5 ± 16.0 kg). The number of patients on monotherapy and the applied combinations were followed. In repeatedly examined patients, the frequency of medication changes was registered. The samples were used for the analysis of applied combinations.

Results

In the follow-up period, most patients were examined once a year only (Table 1), 820 (48 %) patients were examined only once throughout the whole period. In each year, 5–7 different monotherapies, approximately 20 combinations of two drugs, and a similar number of three-drug combinations were administered. Combinations of four drugs varied around 4–5 (in 1993, 1997–2000), in 1994–1996 and in 2001, their number increased up to 11–12 (Table 2). Combinations of five or six drugs were less frequent; none were registered in 1999 and 2000. Changes of applied combinations were performed in the course of the follow-up, therefore the total number of applied variants was higher, reaching the total number of 184 different medications.

Approximately one half of samples contained one drug, one third two antiepileptics; combinations of several antiepileptics in combination were less frequent (Table 3).

Table 1. Number of examinations in one patient during one year and whole period

examination/year	1993	1994	1995	1996	1997	1998	1999	2000	2001
1	120	182	152	184	151	164	150	170	143
2	59	59	61	47	66	75	74	47	37
3	27	20	39	31	26	27	20	16	21
4	12	5	13	12	13	12	12	7	15
5	4	3	13	5	8	14	5	2	4
6	5	1	7	3	3	2	4	1	3
7	1	1	5	2	2	2	3	1	1
8	4	1	3	2	1			1	
9			1	2			3		
10	1			2					
11–15	2	1	1		1			1	1
16–20	1	1	3						
more than 20			1						
number of patients	236	274	299	290	271	296	271	246	225

Table 2. Number of drug variants administered

No of drugs administered/year	1993	1994	1995	1996	1997	1998	1999	2000	2001
1	7	6	6	7	6	6	5	6	5
2	18	18	22	21	17	18	17	19	20
3	19	22	20	27	18	23	20	22	26
4	4	11	12	11	4	4	5	4	11
5	4	1	9	3	3	1			2
6					1				
total	52	58	69	69	49	52	47	51	64

Table 3. Number of samples related to number of administered drugs

No of drugs administered/year	1993	1994	1995	1996	1997	1998	1999	2000	2001
1	251	202	346	264	264	255	256	197	178
2	167	151	240	170	166	194	159	132	129
3	75	63	88	74	67	83	78	52	72
4	9	29	27	19	5	6	10	4	18
5	7	1	9	3	3	1			2
6					2				
total	509	446	710	530	507	539	503	385	399

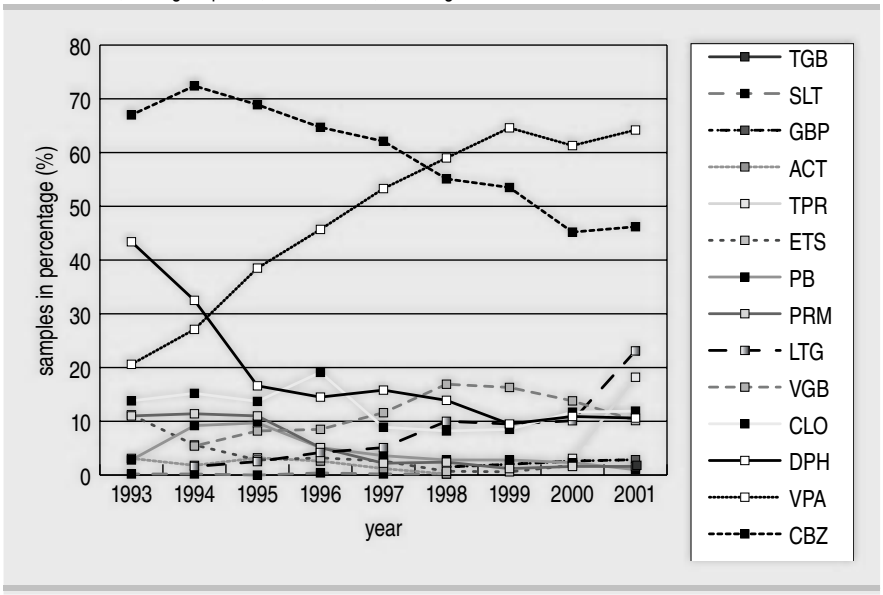
Table 4. Number of medication changes in repeatedly examined patients

No of changes/ year	1993	1994	1995	1996	1997	1998	1999	2000	2001
0	73	64	93	58	64	78	71	45	39
1	32	21	40	39	44	41	36	25	28
2	7	2	7	6	8	13	12	5	10
3	2	3	4	2	1		1	1	1
4		2	1		1		1		3
5			1		2				1
6	2		1	1					

Table 5. Number of variants (combinations + monotherapy) of individual antiepileptics

drug/year	1993	1994	1995	1996	1997	1998	1999	2000	2001
carbamazepine	29	35	39	43	33	29	26	23	29
valproic acid	21	23	29	25	24	28	25	29	34
phenytoin	25	26	18	20	13	14	15	12	16
clonazepam	16	17	21	21	15	13	12	10	19
lamotrigine		4	10	10	11	11	9	13	32
vigabatrin		6	15	17	11	12	14	12	17
primidon	11	14	16	16	5	8	5	5	3
phenobarbital	9	15	14	12	8	6	7	4	5
etosuximide	15	11	9	11	5	4	2	5	1
topiramat								7	24
acetazolamide	9	5	7	8	5	1			
gabapentin						5	4	6	10
sulthiam	1	1		1	1	1			
tiagabin									1
Number of variants	52	58	64	68	49	52	47	51	64

Fig. 1. Number of samples containing individual antiepileptic agents; the sum exceeds 100 % as some samples contained more than one drug; CBZ carbamazepine, VPA valproic acid, DPH phenytoin, CLO clonazepam, VGB vigabatrin, LTG lamotrigine, PRM primidone, PB phenobarbital, ETS etosuximide, TPR topiramate, ACT acetazolamide, GBP gabapentin, SLT sulthiam, TGB tiagabin



Therapy patterns were changed in 439 patients, i. e. in 26 % of the total number; in case of repeatedly examined patients in 50 % (Table 4).

The number of samples examined for individual antiepileptics is presented in the Fig. 1. The most frequent drug was carbamazepine (CBZ), followed by phenytoin (DPH) till 1994, since 1995 valproate (VPA) which was since 1998 the most frequently examined agent. Up to 1998, the representation of vigabatrin was increasing, lately, its utilization showed a mild decrease. The number of samples containing lamotrigine also increased, with the highest increase in 2001. Topiramate (TPR) also manifested an increase during the last year of the study.

The highest number of combinations contained carbamazepine, valproate and phenytoin (Table 5). The most frequent combinations are shown in the Fig. 2. Up to 1999, 60 % of samples contained one of five variants: monotherapy with CBZ, VPA and DPH, combination CBZ+DPH, combination CBZ+VPA. The proportion of monotherapy with phenytoin, event. its combination with carbamazepine, was gradually replaced by valproate monotherapy and by combination of valproate with carbamazepine, event. vigabatrin (VGB). Other combinations involved clonazepam with VPA or CBZ. Combinations of three drugs contained the most often CBZ+VPA+VGB. 174 combinations was examined less than sixty times, 137 out of them were examined ten times or less. The number of these combinations administered to one or few patients was

decreasing at first, with the onset of increase in 1999 up to 32 % in 2001.

In children, VPA was more frequently applied both in monotherapy and in combination with CBZ (Fig. 3). In adult males, DPH was relatively frequent – in monotherapy approximately as much as CBZ; the combination CBZ+DPH was frequent as well. One of five „major" medications was applied to 72 % of adult male patients. Adult female received more frequently combined therapy. The proportion of less frequent combinations, i. e. examined less than sixty times, represented 39 %. In comparison with children, adult female also received more frequently phenytoin in monotherapy as well as in combination with carbamazepine.

Fig. 2. Medication survey related to the years; CBZ carbamazepine, VPA valproic acid, DPH phenytoin, CLO clonazepam, VGB vigabatrin, LTG lamotrigin

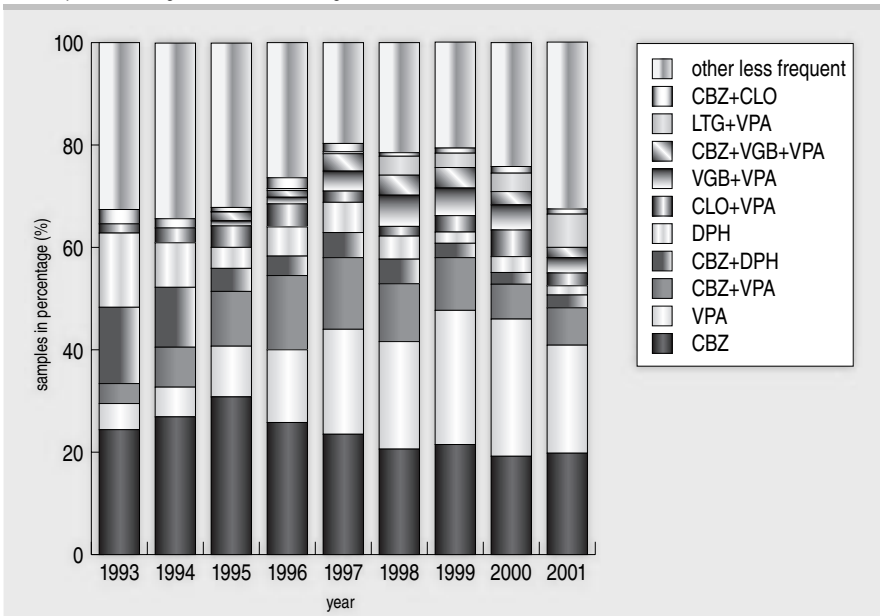
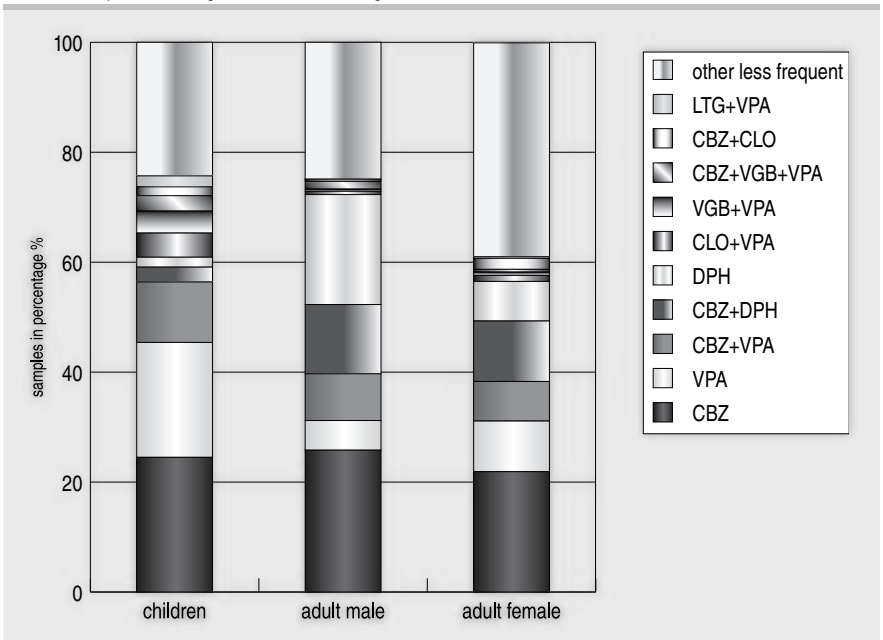


Fig. 3. Medication survey related to the age and gender; CBZ carbamazepine, VPA valproic acid, DPH phenytoin, CLO clonazepam, VGB vigabatrin, LTG lamotrigin



Discussion

The analysis of therapy was based on the evaluation of blood samples. Obtained results may be partially influenced by repeated examinations of the same patient, nevertheless most patients were examined only one in a year and 48 % of patients only once throughout the followed period. In 50 % of repeatedly examined patients, the medication pattern was changed which makes unable eventual interpolation to the patient. The percentage of patients treated with individual antiepileptics corresponds approximately to the percentage of samples examined for individual agents[12]. It can be thus supposed that other results will be also comparable.

The study involved only patients hospitalized in university hospital, i. e. examined during hospitalization. Changes of medication could occur during one stay in hospital or at visits in out-patients' department between hospitalizations. The real number of changes at one patient could be even higher. The choice of the examined group can be also reflected in the results – Lammers et al.[11] describe a higher proportion of monotherapy in outpatients in comparison with hospitalized ones.

A high proportion of monotherapy is in harmony with contemporary trends[4, 5, 6, 8, 9, 10, 11]. Administration of two-drug combinations is also frequent. Combinations of three and more drugs were registered in 4 % of examined samples only. Similar proportion was also described by Rochat et al.[8] and by Lammers et al.[11]. Müllerová et al.[7] also found monotherapy in 50 % of hospitalized adult patients, while three-drug combinations in 10 %, and four-drug combinations in 1 % of patients.

A high frequency of monotherapy with CBZ, VPA and DPH or with their combinations with CBZ corresponds to the fact that CBZ, VPA and DPH are considered as basic drugs[4]. Peytchev et al.[10] and Lammers et al.[11] reached similar results. In 1998 Rochat et al.[8] found the first five positions taken by monotherapy with CBZ, VPA, oxacarbazepin, phenobarbital and lamotrigine, while phenytoin monotherapy was as far as on the eighth position. A similar decrease in number of samples containing DPH, as well as the number of combinations with this drug, in the present

study is in harmony with the classification of phenytoin as the second choice drug[4, 6].

CBZ was the most frequently administered in 1994, the number of samples containing CBZ in monotherapy increased up to 1995, and the percentage of combinations with CBZ was increasing till 1997. It can be supposed that this trend was affected by the introduction of retarded drug forms of CBZ with better kinetic properties and lower occurrence of unwanted effects[13]. An increase of the number of examined samples was also observed at VPA, occurring up to 1999, with the highest increase (by 11 %) between 1994 and 1995, i. e. the time when first retarded form preparations were introduced into practice[14]. Since 1995, the number of patients treated by VPA monotherapy, event. by combination of VPA with CBZ, has been sharply increasing. A similar shift to the monotherapy with carbamazepine and valproate was described by Peytchev et al.[10] who also registered changed prescription at adults (the most often carbamazepine) and at children (the most often phenobarbital). On the contrary, Müllerová et al[7] presents phenytoin, carbamazepine, primidon and phenobarbital as the most frequent drugs administered to adult patients.

Introduction of antiepileptics of the third generation – lamotrigine and vigabatrin – in 1994 was followed by an increase of four-drug combinations in 1994–1997, both in the number of administered combinations and in the number of examined samples. A similar phenomenon occurred following the introduction of gabapentin in 1998 – an increase of samples with four-drug combinations in 1999; and that of topiramate and tiagabine – an increase in 2001.

The frequency of analyses of individual drugs according to the principles of TDM is in sharp contrast with the results obtained from the data on the drug utilization[12], presenting phenytoin as the most often used drug up to 1997 when it was replaced by CBZ. Since 1997, valproate is ranged as the third one, previously it held the fourth, in 1993 the fifth position. This disproportion is obviously due to the difference between DDD and the described daily dose that leads to the underevaluation of the utilization of carbamazepine and valproate[15]. The underevaluation of valproate utilization is further deepened by frequent administration of valproate to children who need lower doses. When interpreting results, it is therefore necessary to take into account that – despite the efforts to determine DDD for the drugs of the same ATC group as equally as possible – DDD of various drugs are not comparable. Also, mutual comparison of individual drugs using DDD does not have to correspond to their actual position in the pharmacotherapy.

Abbreviations

ACT acetazolamide
CBZ carbamazepine
CLO clonazepam
DDD defined daily dose
DPH phenytoin
ETS etosuximide
GBP gabapentin
LTG lamotrigine
PB phenobarbital
PRM primidone
SLT sulthiam
TGB tiagabine
TPR topiramate
VGB vigabatrin
VPA valproic acid

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