

Age-Related Pattern of the Antiepileptic Drug Utilization in Active Epilepsy: A Population-Based Survey

Ivan Bielen¹, Ana Sruk¹, Miljenka Planjar-Prvan¹, Ljerka Cvitanović-Šojat², Miljenko Košiček³, Biserka Bergman-Marković⁴, Ranka Baraba¹ and Silva Butković-Soldo⁵

¹ Department of Neurology, General Hospital »Sveti Duh«, Zagreb, Croatia

² Department of Paediatrics, University Hospital »Sestre milosrdnice«, Zagreb, Croatia

³ Pliva Croatia Ltd., Zagreb, Croatia

⁴ Health Care Centre »Tresnjevka«, Zagreb, Croatia

⁵ Department of Neurology, University Hospital Osijek, Osijek, Croatia

ABSTRACT

The aim of this study was to investigate the relationship between antiepileptic drug (AED) utilization and patient age in a population of patients treated by primary health care physicians. Data were collected by using questionnaires completed by family physicians and paediatricians working in primary health care. Only patients with active epilepsy confirmed previously by neurologists or neuropaediatricians were included. One hundred and twenty-three physicians provided the requested data for 966 patients (range 1–92 years). Most frequently prescribed AEDs were barbiturates (BARB) (37%) and carbamazepine (CBZ) (37%). Valproic acid derivatives (VPA) were prescribed in 28%, but the rate was higher (51%) in children. By calculating the correlation between age and the prescription of single AEDs across the whole sample, linear correlations were found for BARB ($r=0.94$; $p<0.01$), VPA ($r=-0.93$; $p<0.01$) and for topiramate (TPM) ($r=-0.90$; $p<0.01$). Since our results showed significant correlations between age and the use of the majority of AEDs, we concluded that the age may be considered a methodological bias in the presentation of data. Therefore we calculated AED utilization as the age-adjusted prevalence rates (per/1000 inhabitants). For the most commonly prescribed AEDs they were: BARB 1.8 (95% CI 1.6–2.0), CBZ 1.9 (95% CI 1.7–2.1), VPA 1.3 (95% CI 1.1–1.5), lamotrigine (LTG) 0.7 (CI 95% 0.6–0.8), TPM 0.6 (CI 95% 0.5–0.7). In conclusion, the age of patients has a significant impact on the prescription patterns not only between children and adults, but at every age. Therefore we suggest that reporting of AED utilization pattern should also include age-standardized prevalence rates of individual AED utilization.

Key words: active epilepsy, antiepileptic drugs, pharmacoepidemiology

Introduction

Information on antiepileptic drug (AED) utilization is an objective parameter that is useful in the evaluation of the standard of care of people with epilepsy (PwE) in different social environments^{1–4}. In developing countries the utilization pattern of AEDs is influenced by the absolute or relative unavailability of some AEDs. In other countries the differences may be the result of different clinical practices, but they may also be influenced by age-related differences in the studied populations. It is known that the age of the patient is one of the important factors influencing the choice of AED in an individual pa-

tient, but when the utilization structure in different populations is reported, it is usually reported for the whole population^{2,3,5–8}, for children only^{9–11} or for adults only^{1,12}. According to the studies published in the last twenty years valproic acid (VPA) was the predominant AED in therapy of children^{2,9–11,13}, whereas in adult populations the most frequently reported AEDs are carbamazepine (CBZ) and phenobarbital (PB), and somewhat less frequently VPA, oxcarbazepine (OXC) and phenytoin (PHT)^{1–3,6–8,12}. From these data it may be concluded that AED utilization is different in children and adult populations, but in

the available literature we did not find any population-based surveys focused on studying the influence of age on the pattern of AED utilization.

The purpose of this study was to investigate the relationship between AED utilization and patient age in a population of patients with active epilepsy treated by primary health care physicians.

Methods

The patient data were collected by using questionnaires, which were completed by primary health care physicians (PHPs). The choice of the surveyed physicians from all the main regions in Croatia was an unselective one; the sole criteria for inclusion into the survey were having a computerized patient database that enables quick and reliable access to the required information, and knowing the age-structure of the patients. Details concerning the procedures of PHP selection and the communication with them have been recently described¹⁴. The diagnosis of epilepsy in all patients was previously verified by neurologists or neuropediatricians. The PHPs ascertained whether their patients fulfilled the criteria of active epilepsy¹⁵ and included only those who had had at least one seizure in the previous five years. Only data about the therapy of patients with active epilepsy were registered.

In Croatia all inhabitants are provided with basic health insurance and the costs of AED therapy are reimbursed by the Croatian Institute for Health Insurance. At the time of data collection (between May and July 2005), according to the Anatomical Therapeutic Chemical (ATC) classification the following drugs coded by N03A were registered in Croatia: group of barbiturates (BARB – phenobarbital, methylphenobarbital, primidone), phenytoin (PHT), carbamazepine (CBZ), valproate (VPA – sodium valproate, valpromide), ethosuximide (ESX), lamotrigine (LTG), topiramate (TPM), gabapentin (GBP), vigabatrin (VGB), clonazepam (CZP). The PHPs are authorized to prescribe all the mentioned drugs, but for

some use is restricted: LTG, TPM, GBP and VGB are allowed only for refractory epilepsy confirmed by specialists.

Statistics: Statistical evaluation was performed using the program STATISTICA ver. 6.1. StatSoft Inc. Correlations between prescription of the used AEDs and the age have been tested by linear regression analysis. Correlations were calculated using the raw data. Pearson *r* correlation coefficient was defined by the level of significance of 99 % ($p \leq 0,01$). Age-adjusted prevalence rates were computed by the direct method using the European standard population.

Results

A total of 123 PHPs provided the required data about pharmacotherapy of 966 patients. The surveyed physicians were providing health care to a population of 201 466 people. Mean age was 34.5 (SD 23.2) years, range 1–92 years, and 54.3% were male. To present the prescription-rates of individual AEDs, we stratified our sample into age-groups (0–14, 15–24, 25–34, 35–44, 45–54, 55–64, ≥ 65); this is shown in Table 1. It can be seen that in the entire sample the predominant AEDs in adults are BARBs and CBZ, whereas VPA was most frequently prescribed in children. In the BARB group prescription rates were: phenobarbital (11.1%), methylphenobarbital (25.6%) and primidone (0.2%). The comparison of the presented prescription rates in different age-groups indicates that prescription rate of BARB rises with increasing age, whereas prescription of VPA, TPM and LTG decreases. To test statistically this finding, we made the linear regression analysis.

Correlations between the prescription of the most commonly used AEDs and the age of the patients were calculated across the whole group ($N=966$); the individual patients' data (age in years; prescription of single AEDs) were used for that calculation. Significant linear correlations between age and AED utilization, positive or negative, were found for BARB ($r=0.94$; $p<0.01$), VPA ($r=-0.93$; $p<0.01$) and TPM ($r=-0.90$; $p<0.01$), drugs

TABLE 1
PRESCRIPTION RATES OF AED USE IN DIFFERENT AGE-GROUPS

Years	Patients	Number (%)						
		BARB	CBZ	VPA	LTG	TPM	BZP	Other AED
0–14	258	44 (17.1)	44 (17.1)	131 (50.8)	34 (13.2)	56 (21.7)	7 (2.7)	18 (7.0)
15–24	129	15 (11.6)	57 (44.2)	48 (37.2)	30 (23.3)	22 (17.1)	11 (8.5)	9 (7.0)
25–34	139	51 (36.7)	67 (48.2)	34 (24.5)	25 (18.0)	20 (14.4)	18 (12.9)	11 (7.9)
35–44	103	41 (39.8)	57 (55.3)	20 (19.4)	12 (11.7)	5 (4.9)	13 (12.6)	3 (2.9)
45–54	99	52 (52.5)	40 (40.4)	13 (13.1)	12 (12.1)	12 (12.1)	5 (5.1)	2 (2.0)
55–64	103	65 (63.1)	45 (43.7)	12 (11.7)	17 (16.5)	6 (5.8)	5 (4.9)	7 (6.8)
≥ 65	135	88 (65.2)	45 (33.3)	9 (6.7)	6 (4.4)	2 (1.5)	5 (3.7)	6 (4.4)
Total	966	356 (36.9)	355 (36.7)	267 (27.6)	136 (14.1)	123 (12.7)	64 (6.6)	56 (5.8)

BARB – barbiturates: phenobarbital, methylphenobarbital, primidone, VPA – sodium valproate, valpromide, BZP – benzodiazepines: clonazepam, diazepam, clobazepam, CBZ – carbamazepine, LTG – lamotrigine, TPM – topiramate

that are used in our sample by 77.2% of patients with active epilepsy. No statistically significant correlations were found for CBZ or LTG.

Since our results showed significant correlation between age and utilization of many AEDs, we also showed AED utilization as the age-adjusted prevalence rates of AED users with active epilepsy. The prevalence rates were calculated using the direct method of standardization in relation to the European standard population. The results are shown in Table 2. It can be seen that in our sample BARB were most frequently prescribed, but as our results were presented as age-adjusted prevalences CBZ was slightly more prevalent.

Prescription rates of monotherapy and polytherapy (two or more AEDs) are shown in Figure 1. Monotherapy was prescribed in slightly more than 2/3 of all patients. Monotherapy was more frequent in patients ≥ 65 years of age and in children, whereas in the other age-groups the differences were smaller.

Discussion and Conclusion

The results show that BARB, CBZ and VPA are the most commonly prescribed AEDs in Croatia. This is in keeping with the findings from other European countries^{1–3, 6–12,16}. Although the trend of increasing utilization of VPA and the newer AEDs in Croatia has been recognized¹⁷, the newer AEDs are still prescribed considerably less frequently than the older AEDs, at least partly because prescription of new AEDs is restricted to pharmaco-resistant epilepsy. PHT, the cheapest AED available in Croatia, is, however, rarely prescribed. We believe that this is attributable to marketing neglect and to the perception of PHT as a drug with a narrow therapeutic range related to possible adverse side-effects.

The data about use of polytherapy in nearly 1/3 of patients corresponds roughly to the published literature. Although in comparable population-based studies the use of combination therapy was as high as 45%⁵, in the more recent literature polytherapy was prescribed in the range of 17–26%^{1–3,7–8}. In our survey polytherapy was

TABLE 2
AGE-ADJUSTED PREVALENCE RATES OF AED USERS WITH ACTIVE EPILEPSY OF THE MOST COMMONLY PRESCRIBED AEDs

AED	Users: Number (%)	Standardized prevalence: Users number/1000 inhabitants	95% CI
BARB	356 (36.9)	1.8	1.6–2.0
CBZ	355 (36.7)	1.9	1.7–2.1
VPA	267 (27.6)	1.3	1.1–1.5
LTG	136 (14.1)	0.7	0.6–0.8
TPM	123 (12.7)	0.6	0.5–0.7

BARB – barbiturates: phenobarbital, methylphenobarbital, primidone, VPA – sodium valproate, valpromide, BZP – benzodiazepines: clonazepam, diazepam, clobazepam, CBZ – carbamazepine, LTG – lamotrigine, TPM – topiramate

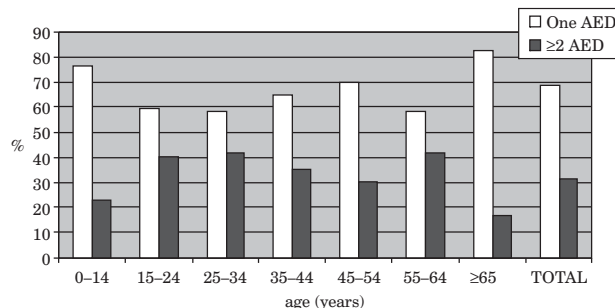


Fig. 1. Prescription rates of monotherapy and polytherapy.

less frequent in children and in older persons, which could be related to the higher prevalence of newly diagnosed epilepsy in those ages and consecutive initial monotherapy.

Based on the literature review and the results of our investigation, it seems that the age-related differences in AED utilization between children and adults are most evident. In our study, and in the vast majority of the published surveys, VPA is the main AED used in children with epilepsy^{2,9–11,13}. This might be a reflection of childhood epilepsy which is characterized by generalized seizure types requiring broad-spectrum AEDs such as VPA. In our study the prescription rate of VPA showed a constant gradual decrease correlating with increasing age. The BARB were considerably less frequently used in children than in adults. However, as recently reported¹⁸, in Croatia they are still rather frequently prescribed in preschool children (25% in the age-group 0–7 years). In part, high proportion of BARB in this age-group may be related to the attitude that BARB can be considered as first-line treatment for seizures in neonatal period^{19–20}.

We found a high utilization rate of BARBs and a high correlation between the BARB prescription rate and increasing age. We are aware that high prescription rates of BARBs in the older age group found here is not in harmony with contemporary attitudes. For epilepsy in the elderly, which is characterized by high incidence and prevalence^{21–23}, LTG and GBP are commonly recommended^{24–25}, but even in the most developed countries these recommendations have not been fully implemented in clinical practice²⁶. However, the information about suboptimal therapy and previously reported inadequate diagnosis¹⁴ might indicate that older PwE in Croatia are still a neglected population. It is possible that a considerable proportion of aged people with epilepsy are not under regular specialist review. These patients are treated by the primary health physicians who may be not adequately informed about the current recommendations for epilepsy treatment.

Our results have confirmed differences in the prescription pattern of antiepileptic therapy between children and adults, but they have also shown a significant correlation between the age and the use of some commonly used AEDs within the adult population.

When our sample is taken as an integral group, without subdivision into age-groups, it has been found that

many of AEDs are in positive or negative correlation with the age of patients. Although in other communities a different type of correlation for individual AEDs could be expected, this does not change the conclusion that the patients' age has a great impact on the prescription pattern of AEDs over all ages.

Our data indicating prevalence rates of AED use (number of AED users with active epilepsy/1000 inhabitants) are very similar to the corresponding data in Italy (prevalence of people using AEDs prescribed for epilepsy – 6/1000; standard AEDs – 4.6/1000; new AEDs 1.4/1000)¹⁶. However, since our results showed correlation between age and the use of AEDs, we concluded that the age may be considered a methodological bias in the presentation of data. Age standardization is the dominant method currently in use to remove the effects of variation in age structure and to facilitate comparisons of sets of age-specific epidemiological and demographic rates across populations with different age composition²⁷. Therefore we

found it appropriate to adjust the prevalence rates to the standard European population. Such a procedure diminishes methodological bias related to the differences in the age structure of the studied populations and facilitates comparisons between the data derived from different countries or communities. The AED prevalences in our sample and in the European standard population showed only slight differences, but if the studied population had an imbalanced age structure the obtained differences could be expected to be significantly greater. Therefore we suggest that reporting of AED utilization pattern should also include age-standardized prevalence rates of individual AED utilization.

Acknowledgements

We thank Prof. Ley Sander (UCL Institute of Neurology, Queen Square, London) for advice and reviewing the manuscript.

REFERENCES

1. OUN A, HALDRE S, MÄGI M, Eur J Neurol, 13 (2006) 465. — 2. ROCHAT P, HALLAS J, GAIST D, FRIIS ML, Acta Neurol Scand, 104 (2001) 6. — 3. MUIR TM, BRADELY A, WOOD SF, MURRAY GD, BRODIE MJ on behalf of the west of Scotland Epilepsy Research Group, Seizure, 5 (1996) 41. — 4. WILBY J, KAINTH A, HAWKINS N, EPSTEIN D, MCINTOSH H, MCDAID C, MASON A, GOLDER S, O'MEARA S, SCULPHER M, DRUMMOND M, FORBES C, Health Technol Assess, 9 (2005) 1. — 5. MCCLUGGAGE JR, RAMSEY HC, IRWIN WG, DOWDS MF, J R Coll Gen Pract, 34 (1984) 24. — 6. LANDMARK CJ, RYTTER E, JOHANNESEN SI, Seizure, 16 (2007) 356. — 7. MORGAN CL, BUCHAN S, KERR MP, Br J Gen Pract, 54 (2004) 781. — 8. OLAFSSON E, HAUSER WA, Epilepsia, 40 (1999) 1529. — 9. LARSSON K, EEG-OLAFSSON O, Eur J Paediatr Neurol, 10 (2006) 107. — 10. WHELLES JW, CLARKE DF, CARPENTER D, J Child Neurol, 20 (2005) S1. — 11. ACKERS R, MURRAY ML, BESAG FMC, WONG ICK, Br J Clin Pharmacol, 63 (2007) 689. — 12. FORSGREN L, Epilepsia, 33 (1992) 450. — 13. GUERRINI R, Paediatr Drugs, 8 (2006) 113. — 14. BIELEN I, CVITANOVIC-SOJAT L, BERGMAN-MARKOVIC B, KOSICEK M, PLANJAR-PRVAN M, VUKSIC L, MIKETEK G, MATEK P and the »Collaborative Group for Study of Epilepsy Epidemiology in Croatia«, Acta Neurol Scand, 116 (2007) 361. — 15. COMMISSION ON EPIDEMIOLOGY AND PROGNOSIS, INTERNATIONAL LEAGUE AGAINST EPILEPSY, Epilepsy, 34 (1993) 592. — 16. SAVICA R, BEGHI E, MAZZAGLIA G, INNOCENTI F, BRIGNOLI O, CRICELLI C, CAPUTTI AP, MUSOLINO R, SPINA E, TRIFIRO G, Eur J

Neurol, 14 (2007) 1317. — 17. BIELEN I, CVITANOVIC-SOJAT LJ, MATEK P, PLANJAR-PRVAN M, Coll Antropol, 27 (2003) 617. — 18. CVITANOVIC-SOJAT L, BIELEN I, SRUK A, KOSICEK M, PLANJAR-PRVAN M, BARABA R, BERGMAN-MARKOVIC B, BUTKOVIC-SOLDO S, Eur J Paediatr Neurol, (2009 Feb 2)[Epub ahead of print]. — 19. BARISIC N, Cerebralni napadaji i epilepsije/epileptički sindromi. In: BARISIC N (Eds) Pedijatrijska neurologija (Medicinska naklada, Zagreb, 2009). — 20. WHELLES JW, CLARKE DF, ARZIMANOGLU A, CARPENTER D, Epileptic Disord, 9 (2007) 353. — 21. SANDER JW, SHORVON SD, J Neurol Neurosurg Psychiatry, 61 (1996) 433. — 22. SANDER JW, Curr Opin Neurol, 16 (2003) 165. — 23. MACDONALD BK, COCKERELL OC, SANDER JW, SHORVON SD, Brain, 123 (2000) 665. — 24. ROWAN AJ, RAMSAY RE, COLLINS JF, PRYOR F, BOARDMAN KD, UTHMAN BM, SPITZ M, FREDERICK T, TOWNE A, CARTER GS, MARKS W, FELLICETA J, TOMYANOVICH ML, VA Cooperative Study 428 Group, Neurology, 64 (2005) 1868. — 25. TALLIS R, BOON P, PERUCCA E, STEPHEN L, Epileptic Disord, 4 (2002) S33. — 26. PUGH MJ, CRAMER J, KNOEFEL J, CHARBONNEAU A, MANDELL A, KAZIS L, BERLOWITZ D, J Am Geriatr Soc, 52 (2004) 417. — 27. AHMAD OB, BOSCHI-PINTO C, LOPEZ AD, MURRAY CJL, LOZANO R, INOUE M, Age standardization of rates: A new WHO standard. GPE Discussion Paper Series: No. 31. EIP/GPE/EBD. World Health Organization, 2003, Geneva, accessed 30.03.2008. Available from: www.who.int/entity/healthinfo/paper31.pdf.

I. Bielen

General Hospital »Sveti Duh«, Sveti Duh 64, 10000 Zagreb, Croatia
e-mail: ivan.bielen@zg.htnet.hr

POTROŠNJA ANTIEPILEPTIČKIH LIJEKOVA KOD AKTIVNE EPILEPSIJE U OVISNOSTI O DOBI: POPULACIJSKO ISTRAŽIVANJE

SAŽETAK

Namjera ovog istraživanja bila je da se unutar populacije osoba s aktivnom epilepsijom istraži struktura potrošnje antiepileptičkih lijekova (AEL) u odnosu na dob pacijenata liječenih u primarnoj zdravstvenoj zaštiti. Podaci su prikupljeni pomoću upitnika koje su ispunili liječnici obiteljske medicine i pedijatri u primarnoj zdravstvenoj zaštiti iz svih

glavnih regija Hrvatske. U istraživanje su uključeni samo pacijenti s dijagnozom aktivne epilepsije potvrđene sa strane neurologa ili neuropedijatra. Stotinu dvadeset i tri liječnika je dalo podatke o 966 pacijenata (raspon dobi 1–92 godine). Najčešće propisivani lijekovi bili su barbiturati (BARB) (37%) i karbamazepin (CBZ) (37%). Derivati valproične kiseline (VPA) su bili propisivani u 28%, no s višom stopom u djece (51%). Računajući korelaciju između dobi i stopa propisivanja svakog pojedinačnog AEL unutar cijelog uzorka, nađene su linearne korelacije za BARB ($r=0,94$; $p<0,01$), VPA ($r=-0,93$; $p<0,01$) i topiramat (TPM) ($r=-0,90$; $p<0,01$). Budući da su naši rezultati pokazali značajne korelacije između dobi i potrošnje većine AEL, zaključili smo da utjecaj dobi može dovesti do metodološke pogreške. Zbog toga smo izračunali potrošnju AEL kao dobno standardizirane stope prevalencije propisivanja (na/1000 stanovnika). Za najčešće propisivane AEL one su iznosile: BARB 1,8 (95% CI 1,6–2,0), CBZ 1,9 (95% CI 1,7–2,1), VPA 1,3 (95% CI 1,1–1,5), lamotrigin (LTG 0,7) (CI 95% 0,6–0,8), TPM 0,6 (CI 95% 0,5–0,7). Zaključno, dob pacijenta ima značajan utjecaj na izbor propisivanog AEL u svakoj dobi, a ne samo između djece i odraslih. Zbog toga predlažemo da se u prikazivanju strukture potrošnje AEL uključi i dobno standardizirana stopa prevalencije propisivanja za svaki pojedinačni AEL.