SUMMARY

The aim of the thesis was to analyze the pharmacotherapy of epilepsy in the Czech Republic and quality of life (QOL) of patients with epilepsy as well as identification of factors with main influence on QOL. Each specific issue has been described and discussed in three chapters and published in five original papers.

1. Pharmacoepidemiology of antiepileptic drugs

1a. Pharmacoepidemiological study of a group of patients with epilepsy

Aim

Aim of the study was to analyze epilepsy treatment in patients from two specialized neurology departments in the Czech Republic, describe seizure type and seizure frequency, duration of the disease, antiepileptic drug (AED) treatment and employability of the patients.

Methods and results

Epileptic outpatients aged over 16 years with confirmed diagnosis of epilepsy attending the Centre for epileptology and epileptosurgery (CEE) Thomayer's Teaching Hospital in Prague or the Neurology department of University Hospital in Hradec Králové (FN HK) were included (n = 427). In the period April 2005 – June 2006, age, gender, type and frequency of epileptic seizures, prescribed AEDs and employability were retrieved from medical records. According to the seizure frequency, patients were classified into four groups. Seizures were classified according to the International League against Epilepsy. The majority of patients had partial seizures (71 %); a quarter of patients had more than 12 seizures per year. Higher seizure frequency had significant impact on employability of the patients. More than half of the patients were treated with combination of two or more AEDs. Seventeen patients were treated with combination of four AEDs; however, none of them was well-compensated on this treatment. VPA, CBZ and LTG were the most frequently prescribed AEDs. Age, gender and comorbidits were analyzed as potential factors influencing the choice of AEDs. Phenytoin, primidone and phenobarbital were prescribed to a low number of patients and more frequently to older patients. These AEDs are not recommended in the elderly and lamotrigine and gabapentin would be more appropriate because of their better tolerability. Lamotrigine with its lower risk of malformations was more frequently prescribed in women. Valproate with higher risk of malformations was used more frequently by men.

There were differences between the two neurology departments in the AEDs used and diagnostic procedures. In CEE the MRI was performed nearly in all patients with epilepsy,

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while in FN HK this diagnostic procedure underwent mainly patients with difficult-to-treat epilepsy and higher frequency of seizures. In CEE in Prague some new AEDs were prescribed to a higher extent.

Approximately a third of the patients were on disability pension. In CEE in Prague there was a higher number of employed patients, although there was also a higher number of patients with frequent seizures.

Conclusion

In conclusion, AED therapy was in accordance with recent reccomendations for therapy of epileptic seizures. The proportion of partial and primarily generalized seizures was comparable with other studies. Relatively high proportion of patients with polytherapy (60 %) seems to be inconsistent with previously described effectiveness of AED monotherapy.

Participating neurology departments are specialized centres presenting secondary and tertiary care units in epilepsy and thus higher proportion of patients with difficult-to-treat seizures and polytherapy regiments can be expected there. However, a patient's benefit should be highly considered when using combination of three or more AEs. Polytherapy is connected with increased risk of adverse drug reactions and interactions. High number of patients on disability pension can be explained by difficult-to-treat epilepsy but also by problems with employment. Further analyses focusing mainly on social problems in epilepsy are necessary.

The two neurology departments present specialized centres for epilepsy treatment. Some differences in AEDs prescribed, diagnostic procedures, employability of patients between these centres were desribed in our study. Comparison with primary care units would be interesting and provide a better insight into quality of care of patients with epilepsy in the Czech Republic.

1b. Clinical relevance of patients with epilepsy included in clinical trials

Aim

We aimed to assess how many patients with epilepsy in clinical practice would qualify for a standard efficacy AED trial after application of common exclusion criteria.

Methods and results

We examined all efficacy studies with AEDs published in the period from 2002 to May 2007 and made a list of the most frequently used exclusion/inclusion criteria. A total of 432 adult patients with epilepsy attending two neurology clinics in the Czech Republic represented the clinical practice cohort. Information was retrieved from medical records. Exclusion criteria that most frequently led to disqualification were the presence of neurologic, systemic or psychiatric comorbidity (n = 220, 51 %). After application of all 90

exclusion criteria, 9 % of patients would be eligible for entering a clinical trial. In patients with one or more seizures per month (n = 106), 36 % met eligibility criteria.

Conclusion

Since selected patients with specific clinical profiles are studied in AED trials, generalizability of clinical trial results to patients in clinical practice may therefore be limited.

2. Antiepileptic drug consumption analysis

Aim

To analyze consumption of old and new antiepileptic drugs in the period 1999 – 2004 using database of Health Insurance Company.

Methods and results

The data from extramurally prescribed AEDs (ATC code N03A) were obtained from one Czech Health Insurance Company (HIC) Škoda Mlada Boleslav covering approximately 130 000 (1,25 %) insured people in the CR. The AED utilization was assessed according to ATC/DDD methodology and expressed as the number of defined daily doses per 1000 insured per day (DDD/TID). The AED costs were expressed as total costs paid by HIC for AEDs in this period.

During the study period, the AED consumption increased from 4,5 DDD/TID to 5,8 DDD/TID. The most frequently prescribed AEDs were carbamazepine and valproate. The utilization of barbiturates and hydantoines was decreasing, while in clonazepam increasing. Low prescription of ethosuximide and sulthiam correlates with narrow spectrum of

indications of these drugs. New AEDs accounted for 76 % of increase of AED consumption. Gabapentin, lamotrigine and topiramate were the most frequently prescribed new AEDs. The total costs of AEDs increased three times in the period 1999 – 2004, 84,5 % of this increase accounted for new AEDs. In 1999, new AEDs accounted for 33,6 % of the total AED costs, while in 2004 it was 68 % of total costs. AED consumption in our study was a bit lower in comparison with other studies. Similar trend has been described in other groups of drugs. However, the source of data used in particular studies should be considered. AED utilization analyzed using the database of HIC is similar to data from the Institute of Health Information and Statistics, while the AED utilization counted using database of the State Institute for Drug Control is higher.

Conclusion

The results showed increase in AED consumption, 76 % of which consisted of new AEDs. Threefold increase in AED costs was described in our study, with major

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contribution of new AEDs. The most frequently prescribed AEDs in the whole period were carbamazepine and valproate. HIC database doesn't cover the information about the indication for which AED was prescribed. Some AEDs were probably used in other indications than epileptic seizures. In comparison with other studies assessing AED utilization, the AED consumption in our study was lower. However, differences in the sources of data used in these studies should be considered. The database of the State Institute of Drug Control is based on the reports of distributors and covers also drugs dispensed in hospitals or drugs that remain in pharmacies and are not dispensed to patients. The utilization assessed using this database is then higher.

Financial sources of health care are limited and rational using and prescribing of drugs is necessary. Drug utilization studies provide simple and useful tool to assess exposition to drugs, drug costs or to search for regions with inadequate (high/low) drug utilization or risk behavior related to drugs, and contribute to rational pharmacotherapy.

3. Health Related Quality of Life and Epilepsy

3a. Psychometric properties of the Czech version of the Quality of Life in Epilepsy Inventory (QOLIE-31)

Aim

To assess the psychometric properties of the Czech version of the epilepsy specific questionnaire QOLIE-31.

Methods and results

Patients with epilepsy older than 16 years attending the Neurology Clinic of the University Hospital Hradec Králové were asked to complete the questionnaire QOLIE-31. Two hundred and twenty one questionnaires were used in analysis. The QOLIE-31 is epilepsy specific questionnaire for assessing health related QOL. It comprises seven multiitem scales (Seizure Worry, Emotional Well-being, Energy/Fatigue, Cognitive Functioning, Medication Effects, Social Functioning, and Overall QOL) and one single item on overall health. Overall score and subscales scores are calculated according to the QOLIE-31 Scoring Manual. The raw values are converted to 0 – 100 scores, with higher values reflecting better QOL.

Internal consistency (Cronbach's alpha) and factor analysis were tested to assess the psychometric properties of the Czech QOLIE-31. Analysis of variance (ANOVA) was performed to investigate the effect of seizure frequency on QOLIE-31 subscale scores and

overall score.

Cronbach's alpha of each subscale was above the accepted standard of 0,7, except for that of Overall QOL and fulfilled the criteria for internal consistency. Factor analysis
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similarly to the original English version yielded seven factors. The first factor was more heterogeneous, containing high loadings from two subscales. The assignment of the items of the Social Functioning scale was not satisfactory. The Social Functioning scale had high loadings from the third and the sixth factor. The item "driving" constituted the seventh single factor. We recommended adding "problems with traveling or transport" to this item. Then it covers patients without a driver's license and those who cannot drive a car, whose answer to this item was frequently missing. ANOVA indicated large effect of seizure frequency on QOLIE-31 scores. The lowest QOLIE-31 scores had patients with the highest frequency of seizures.

Conclusion

It has been demonstrated that the Czech version of QOLIE-31 meets established criteria for validity and reliability. The QOLIE-31 questionnaire can be recommended as an appropriate and useful tool for assessing QOL in patients with epilepsy. Its usefulness has been demonstrated in studies from other countries where the QOLIE-31 was used. The QOLIE-31, due to its reasonable extent and composition, allows us to assess the effect of the disease on particular areas that influence QOL of patients. It can be simply used in an ambulatory sphere and completed by patients independently and repeatedly.

3b. Clinical and demographic characteristics predicting QOL in patients with epilepsy

Aim

The aim of this study was to assess the QOL and different clinical and demographic variables which can influence QOL in patients with epilepsy attending two neurology departments in the CR.

Methods and results

The QOLIE-31 questionnaire was administered between March 2005 and June 2006 during regular visits of patients in the Centre for Epileptology and Epileptosurgery of the Thomayer's Teaching Hospital in Prague and the Department of Neurology of the University Hospital Hradec Králové. Epileptic outpatients older 16 years with confirmed diagnosis of epilepsy were included in the study (n = 268). Clinical and demographic characteristics were retrieved from medical records. Age, gender, duration of epilepsy, age at onset of seizures, seizure type and frequency, the number of AEDs taken, the presence of comorbidities, and employement status/emplyoability were tested as potential predictors in the univariate analysis. Variables with significant influence ($p < 0,05$) on QOLIE-31 scores in univariate analysis were then included in a stepwise multivariate analysis.
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Seizure frequency, employability and psychiatric comorbidity were found to be important predictors acounting for 33 % of the variability of the QOLIE-31 overall score. Seizure frequency was the strongest factor predicting 20 % of the variability of the QOLIE-31 overall score and had significant influence on all seven subscales. Employability was strong predictor for all subscales except Seizure Worry and remained the strongest predictor for Overall QOL, Emotional Well-being, Energy/Fatigue and Cognitive Functioning. Psychiatric comorbidity was found to be important predictor for all

domains except Seizure Worry and Social Functioning.

Conclusion

Seizure frequency, employability and psychiatric comorbidity were found to be the strongest predictors for QOLIE-31 overall and subscales scores. Gender, seizure type, age at onset of seizures and presence of systemic comorbidity had no significant association in our study. Seizure remission remains crucial for maintenance or improvement of patients' QOL. Higher seizure frequency was related to lower QOLIE-31 scores and was the strongest predictor for four out of the seven domains. Employability of patients was another important predictor. Approximately 30 % of patients in our study were on disability pension and these patients had low QOLIE-31 scores corresponding to worse QOL of these patients. Disability is probably connected with insufficient compensation of epilepsy and/or with presence of other diseases or conditions, that contribute to lower QOL of these patients. However, employability or employement are probably influenced by other factors than seizure frequency and severity. Felt stigma, psychosocial characteristics of patients and other factors have been demonstrated to be important predictors influencing employability of patients. Training programs focusing on psychosocial problems of patients with epilepsy could help patients to cope with their disease and to achieve better employment positions. Special care should be provided to people with comorbid psychiatric conditions. Psychiatric diseases occur more frequently in patients with epilepsy and the psychiatric comorbidity was the third most important factor predicting QOL in our study.