Acta Neurol. Belg., 2011, **111**, 29-32

The impact of antiepileptic polytherapy on mood and cognitive function

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Abstract

This retrospective study was performed to reevaluate the effect of polytherapy on mood and cognitive function. 139 patients with refractory epilepsy were screened with a neuropsychological test battery and a depression score. Our regression model with age at admission, duration of the disorder and number of antiepileptic drugs as independent variables had a significant influence on 10 out of 11 neuropsychological parameters but not on depression. Looking at the significance of each predictor variable the number of antiepileptic drugs had a significant effect only on the estimation of the fluid intelligence. A significant effect on five neuropsychological parameters was found for the predictor variable duration of the disorder. Therefore our data do not support the commonly reported hypothesis that antiepileptic polytherapy itself is a substantial risk factor for cognitive deficits or depression in patients with refractory epilepsy. But there may be an influence of accumulative drug load during the course of the disorder as reflected by the effect of the duration of the disorder on five neuropsychological parameters.

Key words: Polytherapy; cognition; depression; intelligence.

Introduction

It is regarded as a well established fact that the risk of cognitive side effects of antiepileptic drugs is increased with polytherapy (1). Nevertheless, a comprehensive review published in 1995 (2) pointed to some facts, which make it difficult to draw sound conclusions from the polytherapy studies published so far. Therefore we decided to reevaluate the effect of polytherapy on mood and cognitive function with a cross sectional design and to separate it from the effect of a long refractory course of the disorder by a multiple regression model.

Patients and methods

For this retrospective study we took into account the data which were obtained as a routine procedure in a multi-modal therapy monitoring performed in a specialized epilepsy ward from January 2000 to December 2002. All patients without mental retardation were examined with a neuropsychological screening battery one day after admission. This neuropsychological battery included a vocabulary test (MWT-A) (3), a bedside test for general cognitive ability (KAI) (4), a selective reminding paradigma (5) for verbal memory, the Benton visual reproduction test (6) and a bedside test for mild cognitive impairment (c.I.-test) (7). After the neuropsychological screening the Self rating Depression Score (SDS) (8) was applied.

All data were stored and analyzed using the SPSS statistical package, version 15.0 (SPSS Inc. Chicago, Illinois, USA). The statistics included means and standard deviations for continuous variables, and frequencies and relative frequencies for categorical variables. Associations between several independent variables that best predict values of neuropsychological parameters were examined using multiple linear regression analysis. In all 11 regression analyses ascertainment if a linear model is appropriate for describing the relationship was realized. For each model regression coefficients, standard errors of the estimates and result of the *F*-test of the ANOVA were determined. A significant result of the *F*-test indicated that the simultaneous test that each regression coefficient is 0 is rejected. All *p*-values were derived from two-sided statistical tests and *p*-values less than 0.05 were assessed as significant.

Results

The data of 139 patients (73 male / 66 female) derived from the neuropsychological and psychometric

Table 1

Regression model influence of age, duration of disorder and number of antiepileptic drugs (number of AEDs) on neuropsychological parameters

Neuropsychological parameter	Equations Standard error of regression coefficients in brackets	Significance of the model p-value
Premorbid intelligence (IQ MWT-A)	IQ = 101 + 0.458 (0.132) × age – 0.515 (0.124) × duration – 1.564 (1.440) × number of AEDs	< 0.001
Time needed to process the letter reading task (KAI)	Sec. = 6.20 – 0.012 (0.036) × age + 0.095 (0.034) × duration + 0.253 (0.394) × number of AEDs	0.006
Digit span task (KAI), number of items	X = 5.45 + 0.007 (0.007) × age ± 0.024 (0.007) × duration – 0.077 (0.078) × number of AEDs	< 0.001
Fluid intelligence (IQ KAI)	IQ = 113 – 0.061 (0.104) × age – 0.421 (0.098) × duration – 2.74 (1.136) × number of AEDs	< 0.001
Verbal memory, immediate recall, number of items	X = 8.23 – 0.015 (0.009) × age – 0.0 19 (0.009) × duration – 0.096 (0.102) × number of AEDs	0.001
Verbal memory delayed recall, number of items	X = 8.59 – 0.034 (0.019) × age – 0.0 15 (0.018) × duration – 0.381 (0.205) × number of AEDs	0.004
Visual Memory, number of correct reproductions (Benton-test B)	X = 6.25 – 0.021 (0.015) × age – 0.029 (0.0 14) × duration – 0.204 (0.165) × number of AEDs	0.001
Visual Memory, number of mistakes (Benton-test B)	X = 4.94 + 0.078 (0.039) × age + 0.059 (0.036) × duration + 0.315 (0.424) × number of AEDs	0.001
Time needed to process the symbol counting task (c.I.-test)	Sec. = 16.3 + 0.062 (0.117) × age + 0.112 (0.109) × duration + 2.24 (1.271) × number of AEDs	0.051
Time needed to process the interference task (c.I.-test)	Sec. = 9.08 + 0.159 (0.225) × age + 0.358 (0.217) × duration + 4.63 (2.490) × number of AEDs	0.004
Depression score (SDS)	X = 47.2 + 0.177 (0.087) × age – 0.068 (0.081) duration – 0.381 (0.946) × number of AEDs	0.200

investigation and the information about the number of antiepileptic drugs and the age at the first seizure were available. On the average the patients were 38.8 years old (SD 13.4 years) and had experienced their first seizure at the age of 15.3 (SD 13.8 years). The duration of the disorder was 23.5 years (SD 15.8 years) on the average. The patients mainly had symptomatic or cryptogenic location-related epilepsy (ILAE 1.2 + 1.3). On the average the patients took 2.2 (SD 1.1, range 0-5) different antiepileptic drugs. Regression equations with different neuropsychological parameters as dependent variable and age, duration of disorder and number of antiepileptic drugs as predictor variables and the significance of the model are represented in table 1. The effect of the model on depression was not significant. When the significance of the effect of each predictor was concerned, there was a significant effect of the duration of the disorder on six neuropsychological parameters, a significant effect of age on two neuropsychological parameters and depression and only one significant effect of the number of antiepileptic drugs, namely on fluid intelligence (Table 2).

Discussion

According to our data the model of the three predictor variables age, duration of disorder and number of antiepileptic drugs has a significant effect on all neuropsychological parameters except the time needed to complete the symbol-counting task. But with the exception of the effect on the KAI the standard-errors of regression coefficients of the number of antiepileptic drugs are well about 50% of the regression coefficient itself. Therefore in these cases the regression coefficient is not significantly above zero and an influence of the predictor variable on the outcome variable i.e. the cognitive parameter cannot be established.

We got a significant influence of the age at admission to our ward and the duration of the disorder on the results of the of vocabulary test. In a previous study we found a negative correlation between the age at onset of disorder and score in a vocabulary test in patients with epilepsy (9). So the acquisition of vocabulary may be more disturbed by the age at the onset of a chronic neurological disorder than by

Table 2

Significance of the effect of age, duration of disorder and number of antiepileptic drugs (AEDs) on neuropsychological parameters

Neuropsychological parameter	Age	Duration of disorder	Number of AEDs
Premorbid intelligence (IQ MWT-A)	0.001	< 0.001	n.s.
Time needed to process the letter reading task (KAI)	n.s.	0.006	n.s.
Digit span task (KAI), number of items	n.s.	< 0.001	n.s.
Fluid intelligence (IQ KAI)	n.s.	< 0.001	0.017
Verbal memory, immediate recall, number of items	n.s.	0.034	n.s.
Verbal memory delayed recall, number of items	n.s.	n.s.	n.s.
Visual Memory, number of correct reproductions (Benton-test B)	n.s.	0.043	n.s.
Visual Memory, number of mistakes (Benton-test B)	0.046	n.s.	n.s.
Time needed to process the symbol counting task (c.I.-test)	n.s.	n.s.	n.s.
Time needed to process the interference, task (c.I.-test)	n.s.	n.s.	n.s.
Depression score (SDS)	0.043	n.s.	n.s.

the duration of the disorder. To test this hypothesis we performed another regression analysis with age at admission, age at first seizure and number of antiepileptic drugs as predictor variables. The equation was (standard error of regression coefficient in brackets): IQ-MWT-A = 101.107 – 0.058 (0.122) age at admission + 0.515 (0.124) age at first seizure – 1.564 (1.440) number of antiepileptic drugs. In this equation the significance for the regression coefficients was $p = 0.637$ (age at admission), $p < 0.001$ (age at first seizure), $p = 0.279$ (number of antiepileptic drugs). So we assume that age at first seizure is the only significant influence factor on crystallized intelligence as measured by the vocabulary test in our patients.

Our data do not support the commonly reported hypothesis that antiepileptic polytherapy itself is a substantial risk factor for cognitive deficits or depression in patients with refractory epilepsy (10). But there may be an influence of accumulative drug load during the course of the disorder as reflected by the effect of duration of the disorder on five neuropsychological parameters. This influence may be intensified by an accumulative drug load with polytherapy. However in a recent study by Canevini and coworkers (11) the findings were consistent with the hypothesis that adverse events in antiepileptic pharmacotherapy are determined more by individual susceptibility, type of antiepileptic drugs used, and physicians' skills, than number of coprescribed antiepileptic drugs.

Acknowledgements

During their work Dr. Rösche and Dr. Uhlmann were supported by a grant given by the Department of Social Affairs of the Land Baden-Württemberg, Germany. Some data of this paper were presented as a poster on the 4. Gemeinsame Jahrestagung der Deutschen, Österreichischen und Schweizer Sektion der Internationalen Liga gegen Epilepsie in Innsbruck 2005 and as a platform presentation on the 9th European Congress on Epileptology, Rhodos 2010. Abstracts were published in: Zeitschrift für Epileptologie 2005; 18: 131 and Epilepsia 2010; 51 (Suppl. 4): 8-9.

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