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The effect of newer antiepileptic drugs in combination therapy

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ABSTRACT

Purpose: To assess the impact of the new AEDs on overall outcome for patients with epilepsy.
Methods: In 2004, the effect of combination therapy on seizure frequency in adult patients with focal epilepsy was evaluated in a cross-sectional study in our center. We repeated this analysis ten years and eight new antiepileptic drugs (AED) later.
Results: In 2014, a higher percentage of patients with polytherapy (117 out of 396; 30%) were seizure-free compared with the original analysis (22%) ($p = 0.042$). Eighty three out of 218 (38%) subjects on duo-therapy were seizure-free (27% in 2004) ($p = 0.040$); in the 151 receiving triple therapy there were 30 (20%) seizure-free subjects (10% in 2004). Four out of 27 subjects (15%) with four AEDs were seizure-free (0% in 2004). The most common pairing of 52 different combinations for duo-therapy was levetiracetam-oxcarbazepine. Eighty different AEDs regimens were being used in the patients administered three AEDs.
Conclusion: Our combined data from these two studies indicate that some patients with focal epilepsy might benefit from newer AEDs as an adjunctive therapy in the hope they could acquire seizure freedom.

1. Introduction

The target of all epilepsy treatment is seizure freedom for the patient with as few antiepileptic drug (AED) related adverse-events as possible. If the first or second monotherapy improves seizure control but does not achieve seizure-freedom, combination therapy should be considered (Brodie, 2005). Combination therapy has been shown to be successful in about 20–30% of patients (Mohanraj and Brodie, 2005; Peltola et al., 2008). If the patient has recurrent seizures, if the diagnosis of epilepsy is conclusively established and if epilepsy surgery will most likely not be beneficial, then it is recommended that further attempts at optimizing the medical therapy should be pursued (Ben-Menachem, 2014). The major issues are i) which AED to choose and ii) how to combine different AEDs in order to reach seizure freedom. The best human evidence for synergistic effect of two AEDs in combination therapy exists for pairing valproate with lamotrigine (Brodie and Yuen, 1997). Currently, the rational choice of AED combinations is based more on the avoidance of pharmacological adverse effects rather than on convincing evidence for synergistic anticonvulsant effects (French and Faught, 2009). On the other hand, it has been demonstrated that some individuals will respond even to their 4th or 5th treatment schedules (Brodie et al., 2009). The new wave of combination therapy has also raised concerns of irrational polytherapy or overtreatment of epilepsy causing tolerability problems, pharmacological interactions, reduced compliance and increased risk of mortality (Brigo et al., 2013; Canevini et al., 2010; Perucca and Kwan, 2005).

There is currently little evidence to guide the physician when and how to combine AEDs. Therefore current treatment recommendations remain largely empirical. Moreover, a wide range of modern AEDs are available, some claimed to have better tolerability profiles and fewer interactions than the older AEDs. In 2004, a cross-sectional evaluation of 193 subjects with focal epilepsy treated with polytherapy was undertaken in Tampere University Hospital (Peltola et al., 2008). During the past decade, a further eight new AEDs (eslicarbazepine acetate, lacosamide, perampanel, pregabalin, retigabine, rufinamide, stiripentol and zonisamide) have been introduced for the adjunctive treatment of epilepsy in Finland. Now 10 years later, we have repeated this analysis to assess the impact of the increasing range of newer drugs on the clinical outcome. The majority of refractory patients in the Tampere University Hospital district (population of 505 000) are monitored in our clinic. Only some elderly patients and those patients with mental retardation are treated elsewhere.

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2. Materials and methods

The study was carried out at the Outpatient Department of Neurology, Tampere University Hospital. Patients with focal epilepsy treated in our department 31.12.2014 were identified from the hospital patient registry using ICD-10 diagnostic codes for focal and unclassifiable focal epilepsy (G40.1X, G40.2X and G40.9). Only subjects with polytherapy were included in this study (n = 396). The information of patient characteristics was collected retrospectively from the medical records. Subjects were classified according to ILAE guidelines (Anon., 1989) for epilepsy type into temporal lobe epilepsy, frontal lobe epilepsy, parietal/occipital lobe epilepsy or multifocal epilepsy based on seizure characteristics, EEG and imaging findings, and in some patients on ictal video-EEG recordings. The etiologies were classified into either known (structural, metabolic, infectious) or unknown etiology (Scheffer et al., 2016); in the 2004 analysis, the etiologies had been classified similarly but with older terminology (remote symptomatic or cryptogenic). The seizure frequency was recorded for the previous year prior to the last visit date; seizure-free subjects had not experienced any seizures during the previous year. The AEDs currently used, information on doses, and duration of present regimen were registered. The study was approved by the Ethics Committee of the Tampere University Hospital.

According to local treatment guidelines, all adult (>16 years) patients with refractory epilepsy—except patients with moderate or severe mental retardation, those elderly patients with controlled epilepsy and patients with post-stroke epilepsy—in Pirkanmaa Hospital District (population of 505 000) are treated and followed-up in our institution. Our department also serves as a secondary referral center for refractory patients for a population of about 1 million including five central hospitals. The patients were monitored and regularly reviewed by three epileptologists in 2004 and 2014 analysis. Residents of neurology have monitored patients sporadically as a part of their degree. Patients with active epilepsy are reviewed between 1 and 3 months by epilepsy nurse or epileptologist. In addition, some of the patients had epilepsy surgery or other lesional surgery or were under presurgical or neuromodulative treatment evaluation, but none underwent operation during the follow up. No strict upper age limit was used. There has been participants in randomized controlled AED trials from our institution. However, these patients are treated and followed up in separate scientific clinic (Finn-Medi) and therefore not included in the current study.

Statistical significance was evaluated using a chi-square test when comparing the proportion of seizure-free subjects with different numbers of AEDs. Two-sample z-test was used to compare the proportions from studies in 2004 and 2014. Chi-square test was used for testing group differences for categorical variables. Independent *t*-test was used for comparing mean differences of changes between the two groups. An unadjusted and adjusted logistic regression models were used to analyze seizure freedom and the effect of year (2004 vs. 2014) on seizure freedom. The covariates considered were age, gender, etiology, duration of epilepsy and type of epilepsy. Confidence intervals (CI) are likelihood-based. The results were considered to be statistically significant if $p < 0.05$. All analyses were performed with Stata Statistical Software version 13.1.

3. Results

In the 2014 analysis, a total of 507 subjects with focal epilepsy were identified from a computerized patient database. One hundred and eleven subjects were excluded because they were receiving monotherapy, and thus 396 subjects on polytherapy were included in this study. There were significant differences between the groups in age and type of epilepsy (Table 1). Patients were significantly younger (41.6 vs. 48.2) on 2004 analysis than 2014. Further, temporal and frontal lobe epilepsies were more common in 2004 study.

Fifty-five percent of the subjects with combination therapy were being treated with two AEDs, 38% received three and 7% four AEDs. Eighty three out of 218 subjects (38%) were seizure-free on duotherapy and furthermore 30 out of 151 receiving three AEDs (20%) were seizure-free. Four out of 27 subjects (15%) administered four AEDs were seizure-free. The clinical characteristics of the seizure-free patients are presented in Table 2. Subjects with three or four AEDs were less likely to be seizure-free compared to those being treated with two AEDs (OR 2.7, 95% CI 1.6–4.4). Temporal lobe epilepsy was the most common type of epilepsy (N = 161, 41%) whereas 85 (21%) subjects had frontal lobe epilepsy, 37 (9%) had multifocal epilepsy and 24 (6%) suffered from parieto-occipital epilepsy.

The most common combinations with two AEDs included levetiracetam-oxcarbazepine (N = 29), carbamazepine-levetiracetam (N = 19), lacosamide-levetiracetam (N = 17), lamotrigine-levetiracetam (N = 13), lacosamide-topiramate (N = 11) and lamotrigine-valproate (N = 10). In all, 52 different combinations of two AEDs were being used (Table 3). The different combinations with the most seizure-free subjects were levetiracetam-oxcarbazepine (N = 15), carbamazepine-levetiracetam (N = 12), lamotrigine-levetiracetam (N = 7), lamotrigine-valproate (N = 7), levetiracetam-valproate (N = 4) and lamotrigine-topiramate (N = 4).

Subjects with three AEDs (N = 151) had 80 different combinations; the most common combinations included lamotrigine-topiramate-valproate (N = 7), levetiracetam-oxcarbazepine-topiramate (N = 5), levetiracetam-oxcarbazepine-pregabalin (N = 5), clobazam-lacosamide-topiramate (N = 5) and clobazam-lacosamide-zonisamide (N = 5). All of the subjects being treated with four AEDs had their own distinctive combinations. The mean and median doses of individual AEDs are summarized in Table 4. In this analysis, the most frequently used AEDs were levetiracetam (N = 100), lamotrigine (N = 49) and carbamazepine (N = 47) for two drug combinations and levetiracetam (N = 33), clobazam (N = 25) and lacosamide (N = 22) for three drug combinations. Table 5 presents comparisons with the results from 2004.

Table 6 shows unadjusted and adjusted odds ratios for covariates. Seizure freedom on duotherapy was found to be more frequent in 2014 compared to 2004 in unadjusted model and especially after adjusting for covariates. Instead, on those with 3 or 4 AEDs findings do not abundantly reach statistical significance. Compared to patients on duotherapy in 2004 analysis, patients with 2 AEDs on 2014 analysis had 2.00 times higher odds of being seizure free (odds ratio [OR] 2.00, 95% confidence interval [CI] (1.20–3.33); p = 0.008). Among those with 3 or 4 AEDs, patients on 2014 had 2.60 times higher odds of attaining seizure remission compared to patients in earlier study (OR 2.60, 95% CI 0.90–7.49; p = 0.076).

4. Discussion

The main finding of our study is that at least one year seizure-freedom with polytherapy had been achieved in 30% of the patients in the 2014 cohort, which is significantly higher than the value of 22% in the original analysis from 2004 (p = 0.042). The second significant finding is that in patients with duo-therapy, the rate of seizure-freedom increased from its 2004 value of 27%–38% in 2014 (p = 0.040). Furthermore, there is a trend towards improved possibilities for seizure-freedom in patients with three or four