

HIGH DOSES OF CARBAMAZEPINE FOR REFRACTORY PARTIAL EPILEPSY

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ABSTRACT - Forty-eight patients with partial seizures were analysed during treatment with 1200 mg/d or more of carbamazepine (CBZ). Thirty-three were on monotherapy and fifteen on polytherapy. The other drugs were kept unchanged in the patients on polytherapy. The dose of CBZ was increased if no control was observed and the patient had no side effects. The doses used ranged between 1200 and 1900 mg/day (1200 mg/day, n=18; 1300 mg/day, n=1; 1400 mg/day, n=7; 1600 mg/day, n=9; 1700 mg/day, n=4; 1800 mg/day, n=8; 1900 mg/day, n=1). Anticonvulsant plasma levels were taken to confirm patient compliance. The average plasma level was 9.6 ug/mL. The period of follow up varied from 3 to 96 months (M=25.6). Seizure's control was observed in 7 (14.48%) patients taking 1200 mg/day and in 2 (4.16%) patients taking 1400 mg/day of CBZ. Thirty-nine patients did not show any control (81.21%). Ten patients (20.81%) had signs of intoxication. When patients have no improvement with 1400 mg/day, it is difficult to obtain any control despite the use of higher doses of CBZ, which frequently expose the patient to significant side effects.

KEY-WORDS: epilepsy, carbamazepine, effectiveness, side effects.

Altas doses de carbamazepina para epilepsia parcial refratária

RESUMO - Foram analisados 48 pacientes epiléticos com crises parciais que faziam uso de carbamazepina (CBZ) em doses iguais ou superiores a 1200 mg por dia. Trinta e três estavam em monoterapia e 15 em politerapia. As outras medicações foram mantidas constantes durante a manipulação da dose de CBZ nos pacientes em politerapia. O critério utilizado para o aumento da dose de CBZ foi a falta de controle clínico e a ausência de efeitos colaterais (independente da dosagem sérica). A dose máxima variou de 1200 a 1900 mg/dia (1200 mg, n=18; 1300 mg/dia, n=1; 1400 mg/dia, n=7; 1600 mg/dia, n=9; 1700 mg/dia, n=4; 1800 mg/dia, n=8; 1900 mg/dia, n=1). Dosagens séricas de anticonvulsivantes eram utilizadas no sentido de confirmar a aderência ao tratamento. A média das dosagens disponíveis foi de 9,6 ug/mL. O tempo de seguimento variou de 3 a 96 meses (M=25,6). Houve controle das crises em 7 (14,48%) pacientes com 1200 mg/dia e em 2 (4,16%) pacientes com 1400 mg/dia. Trinta e nove pacientes não obtiveram controle (81,21%). Dez pacientes (20,81%) mostraram sinais de intoxicação. Quando doses de CBZ até 1400 mg não são eficazes, doses mais altas da droga são frequentemente incapazes de controlar as crises epiléticas. Nesta situação, a chance de intoxicação aumenta significativamente sem que haja benefícios para o paciente.

PALAVRAS-CHAVES: epilepsia, carbamazepina, efeitos colaterais, eficácia.

Carbamazepine (CBZ) was introduced in the clinical practice in 1963 and since then several studies demonstrated its efficacy in the treatment of epileptic patients with partial² and secondarily generalized tonic-clonic seizures^{3, 13, 17, 22, 23}. It is considered a first line drug in the treatment of such seizures with few side effects¹⁶. At least 50% reduction in the frequency of seizures is observed in 75% of the patients treated with CBZ⁷⁻¹³. Approximately 20-30% of the patients with focal epilepsy do not get any significant reduction of the seizure's frequency in spite of the adequate treatment with several antiepileptic drugs prescribed on mono or polytherapy, being therefore considered refractory⁶.

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11, 16, 18. Treatment is considered a failure when seizures remain severe or there is no reduction in its frequency, despite daily dosages that lead to unacceptable side effects¹⁷.

The minimum dose of CBZ used in adults is around 600 mg/day and the maximum dose is usually no higher than 1200 mg/day^{11,22,24}. In the present study, we analysed the response of refractory patients with partial epilepsy to high doses of CBZ.

METHODS

Forty-eight patients (men=28; women=20) were analysed retrospectively. The inclusion criteria were as follows:

- 1) simple or complex partial seizures secondarily generalized or not;
- 2) minimum dose of CBZ of 1200 mg/day;
- 3) lack of control with doses lower than 1200 mg/day;
- 4) good compliance.

These patients were selected from a pool of 1500 consecutive cases from the same outpatient clinic at our University Hospital. Age ranged from 18 to 51 years. Mean duration of the epilepsy syndrome was 4.7 years. None of them was diagnosed as having idiopathic epilepsy.

The patients had simple partial seizures (n=6), complex partial seizures (n=18), or simple partial followed by complex partial seizures (n=24). Forty-two patients had secondarily generalized tonic-clonic seizures. Thirty-three were on monotherapy and fifteen on polytherapy. The patients on polytherapy used phenobarbital (n=7), primidone (n=2), phenytoin (n=1), phenobarbital and phenytoin (n=2), primidone and phenytoin (n=2), and clonazepam (n=1). The doses of CBZ were progressively increased if there was no seizure control and the patient did not show side effects. Determination of anticonvulsant plasma levels was obtained in 25 patients.

RESULTS

The follow up time ranged from 3 to 96 months (average = 25.6 months). The maximum dose administered ranged from 1200 mg/day to 1900 mg/day (1200 mg/day, n=18; 1300 mg/day, n=1; 1400 mg/day, n=7; 1600 mg/day, n=9; 1700 mg/day, n=4; 1800 mg/day, n=8; 1900 mg/day, n=1) (Fig 1). Total control of seizures was observed in 7 patients (14.5%) using 1200 mg/day, and on 2 patients (4.2%) using 1400 mg/day (Fig 2). Three of these 9 patients were in polytherapy: one was

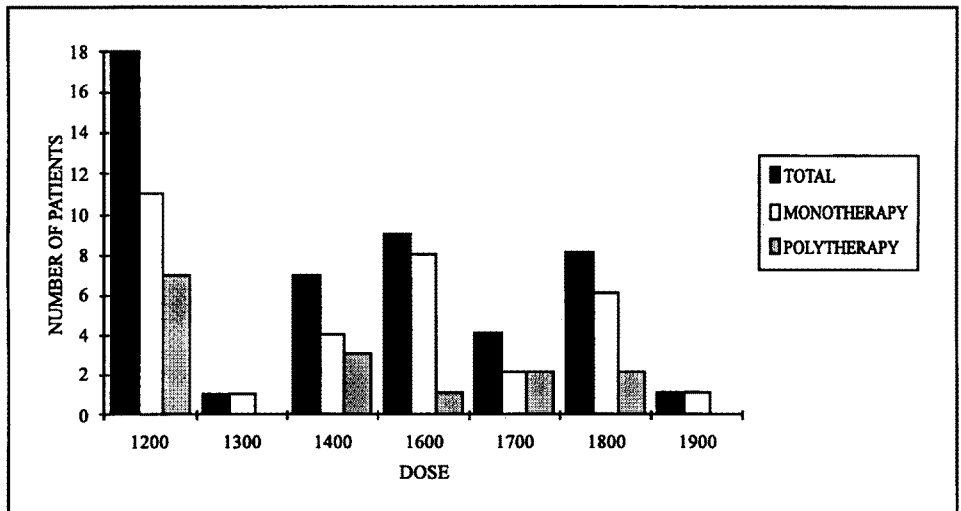


Fig 1. Distribution of the maximum dose of CBZ administered.

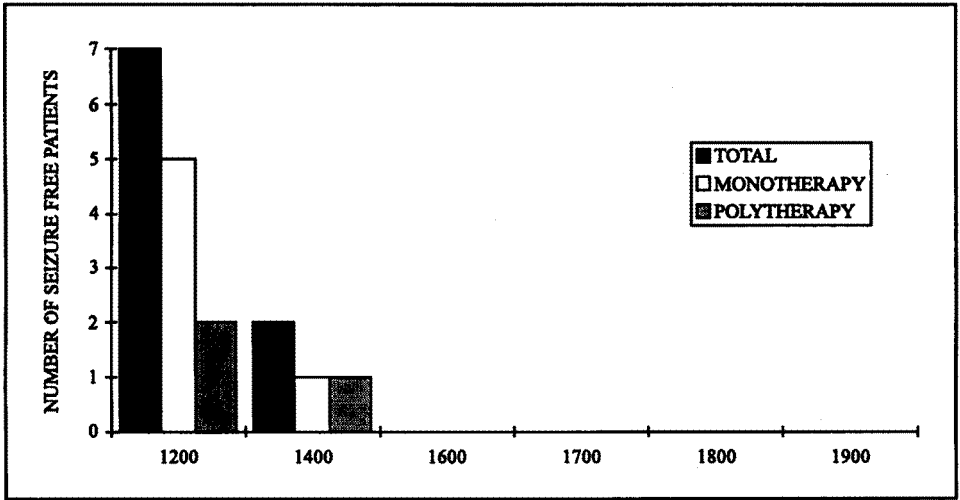


Fig 2. Distribution of seizure free patients in mono and polytherapy.

receiving phenobarbital 50 mg/day and phenytoin 600 mg/day, and two were under phenobarbital 100 mg/day. Thirty-nine patients (81.2%) had no clinical improvement regardless of the progressive increase on the dose of CBZ.

Antiepileptic drug monitoring showed plasma levels that varied from 6.0 to 17.0 microg/mL (mean: 9.6 microg/mL; therapeutic range: 4.0-10.0 microg/mL) (Fig 3). Ten patients showed signs of intoxication: diplopia (n=6), blurred vision (n=1), dizziness (n=1), tremor (n=1), diarrhea (n=1) and vomits (n=1). CBZ dosages were reduced after the appearance of side effects. In 3 cases another drug was introduced and in 3 cases surgery was carried out.

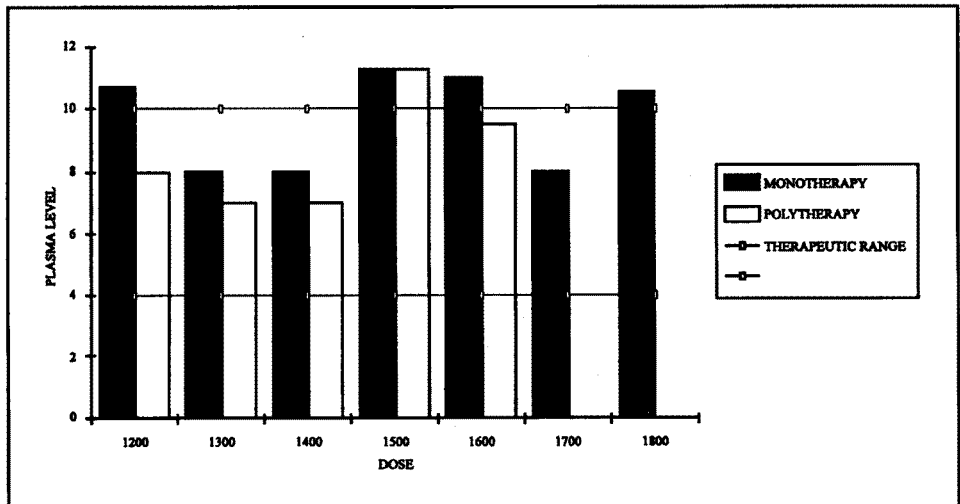


Fig 3. Average plasma levels of CBZ according to the prescribed dose.

DISCUSSION

The goal of this study was to analyse the clinical response to high doses of CBZ in refractory epileptic patients. It is known that 75% of the patients will have at least half of their seizures controlled, while approximately 25% of them will not show significant improvement^{1,7,11,13,16,17}. The number of seizure free patients tends to decline after 1 year, as seizures recur after being controlled for a period^{2,17}.

CBZ is the drug of choice for epileptic patients with partial seizures followed or not by secondarily generalized tonic-clonic seizures¹⁸, as has been demonstrated by several studies that compared different antiepileptic drugs^{2,16,17}. Monotherapy is the best regimen because it reduces antiepileptic drugs (AED) interactions and drug toxicity associated with polytherapy^{6,12,13,22}. A second drug improves seizure's control in 11% of patients and increases drug toxicity in 90%⁴. Aggressive monotherapy is the progressive increase of AED dose until seizure control is obtained or intolerable side effects are observed. The use of aggressive therapy without clinical improvement is considered a therapeutical failure^{4,10}. Nevertheless, some authors consider therapeutic failures when seizures occur associated with AED plasma levels in the superior limit of therapeutical range^{9,22}. However, there might be no correlation between clinical efficacy or side effects and AED plasma levels^{8,14,15,20,24,25}. Aggressive monotherapy, on the other hand, raises the cost of the treatment and may expose patients to unpleasant side effects, or lead to an increase in seizure frequency without any other signs of drug intoxication, which is known as paradoxical effect. Another disadvantage may be the delay on defining therapeutical failures, so that patients that eventually would get some benefit with new drugs or surgical treatment would had been unnecessarily exposed for prolonged and potentially harmful effects of epileptic seizures in the brain.

Forty-eight patients who used a minimum dose of CBZ of 1200 mg/day were analysed. Fifteen patients were on polytherapy with drugs that would potentially reduce the plasma level of CBZ¹³. CBZ was the only drug to have its dosage modified during the study.

The CBZ dose was progressively increased if no clinical improvement was observed and no side effects were noticed. However, an increased rate of remission with higher doses was not observed: only 19% of the patients showed seizure's control, while 81% had no significant reduction of the number of seizures. The patients that remained seizure-free used 1200 or 1400 mg/day, and no improvement was observed with doses higher than 1400 mg/day. Callaghan et al.³, in a study with 25 patients, have not obtained any control with doses of CBZ higher than 16 mg/kg/day.

Former studies demonstrated that long disease duration, high frequency of seizures^{2,9,22,24}, presence of more than one type of seizure and complex partial seizures are factors of bad prognosis^{1,5,7,9,21,24}. All patients analysed in this study had all these factors. The increase of the dose yielded more side effects such as diplopia, tremor, gastrointestinal symptoms and blurred vision, which were not tolerated by the patients and led to a reduction of the dose of CBZ. Potentially life-threatening side effects^{1,16,19} were not observed.

Although the limit for drug dosage increase in most studies is considered the presence of side effects, we observed no benefit with doses of CBZ higher than 1400 mg/day. Prospective studies may help to further define a therapeutic limit that would lead to actual benefits to patients using each one of the AED.

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