Efficacy of Valproate in Partial Epilepsy and Patient Compliance and Satisfaction with Long Acting Valproate Form

Valproate'ın Parsiyel Epilepsiye Etkisi ve Uzun Etkili Valproate Formuna Hasta Uyumu ve Memnuniyeti

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Özet

Amaç: Çok merkezli, çapraz geçişli çalışmanın amacı parsiyel epilepsili hastalarda valproate etkinliğini ve kontrollü salınım formülasyonuyla (valproate-CR) uyumunun değerlendirilmesidir. **Hastalar ve Yöntemler:** On merkezden 94 hasta çalışmaya katılmış ve %81,9'u çalışmayı tamamlamıştır. Klinik ve demografik özellikler başlangıçta belirtilmiştir, tedavi uyumu ve memnuniyeti, etkinlik ve advers olaylar dört vizitte değerlendirilmiştir. Nöbet sıklığı, advers olayların insidansı, tedavi uyumu ve hasta memnuniyeti, valproate-CR'a geçişi takiben tüm ölçümlerdeki anlamlı iyileşme ile iki tedavi süresi arasında anlamlı olarak fark mevcuttu. **Bulgular:** İlk vizitte hastaların %30,5'inde ve beşinci vizitte %62,5'inde ya nöbet olmadı ya da nöbetler seyrekleşti ($p<0.001$). Advers olaylar ikinci vizitte 35 (37.6%) iken, beşinci vizitte 19 (25%) hastada gözlenmiştir. Tedavi uyumu ikinci vizitte %82,2 idi ve beşinci vizitte uzun etkili valproat forma geçişten sonra oran %97,4'e yükselmiştir ($p=0.001$). Çalışmanın sonunda hastaların %84,9'u tedaviden memnundu ve hastaların %74,4'ü iyileşmişti. **Sonuç:** Sonuç olarak valproate-CR kullanımı yan etkilerin insidansının düşüklüğü, hasta uyumu ve memnuniyetindeki iyileşme ile ilişkilidir.

Summary

Objective: The aims of this multi-centre cross-over study were to evaluate the efficacy of valproate in patients with partial epilepsy and compliance with the controlled-release formulation (valproate-CR). **Patients and Methods:** Ninety-four patients were included in ten centres and 81.9% completed the study. Clinical and demographic features were assessed at baseline, treatment compliance and satisfaction, efficacy and adverse events were evaluated at four visits. Seizure frequency, incidence of adverse events, treatment compliance and patient satisfaction differed significantly between the two treatment periods, with significant improvements in all measures following the switch to valproate-CR. **Results:** At first visit, 30.5% of patients were either seizure free or experienced rare seizures and were 62.5% at the fifth visit ($p<0.001$). Adverse events were observed in 35 (37.6%) at the second visit, while this number was 19 patients (25%) at the fifth visit. Treatment compliance was 82.2% at the second visit and this ratio increased to 97.4% at the fifth visit after the transition to long acting valproate form ($p=0.001$). At study-end, 84.9% of patients were satisfied with the treatment and 74.4% of patients were highly improved. **Conclusion:** In conclusion, use of valproate-CR was associated with a lower incidence of side-effects and improved patient compliance and satisfaction.

Anahtar kelimeler: Valproate, epilepsi, miyokloni, uzun etkili

Keywords: Valproate, epilepsy, myclonus, controlled release

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Introduction

Valproate has been widely used in epilepsy for more than 30 years because of its broad spectrum of antiepileptic activity. It is indicated both in partial and generalised epilepsies. The efficacy of valproate in the treatment of epilepsy has been demonstrated in several studies.[1-3] Given its broad antiepileptic spectrum, its acceptable tolerability and the absence of paradoxical seizure exacerbation, valproate has become the first-line treatment choice in a variety of epilepsy syndromes in adults and children.[4,5]

Although the mechanism of action of valproate is not fully elucidated, the anticonvulsant effect of this drug is believed to be related principally to an increase in the concentration of gamma-aminobutyric acid (GABA) in the brain through activation of the GABA-synthetic enzyme glutamic acid decarboxylase.[6,7] In addition, a decrease in glutamate-dependent synaptic excitation and a reduction in neuronal excitability through an action on voltage dependent sodium channels may also contribute to its mechanism of action.[8,9]

Valproate is rapidly absorbed following oral administration, with peak serum concentrations being reached within 1-4 hours after a single oral dose. Its serum elimination half-life is between 6-16 hours. Valproate is distributed rapidly and extensively in the body and is highly bound to plasma proteins (90%). It is metabolized primarily by glucuronide conjugation in the liver.[10,11]

Valproate is available in different dosage forms for oral and parenteral use. All available oral formulations are completely bioavailable, but their distribution and absorption rates differ.[12,13] In particular, the controlled release formulation (valproate-CR) has a particularly favourable pharmacokinetic profile. Fluctuations in serum concentrations of valproate are less marked with valproate-CR than with the standard formulation and this may be associated with a lower incidence of side effects related to peak plasma concentrations. In addition, drug intervals can be extended with valproate-CR, allowing once or twice daily administration. This in turn may be associated with higher patient compliance and satisfaction. A reduced frequency of drug administration may be particularly relevant in patients with refractory epilepsy who are characterised by low drug compliance).[14]

The primary objective of the present study was to assess compliance and satisfaction in patients with partial epilepsy following a switch from standard enteric-coated tablets of valproate to valproate-CR. Secondary objectives were to collect data on the safety and efficacy of valproate-CR compared to standard valproate.

Methods

This was a prospective, multicentre, study conducted in eleven centres in Turkey. Patients with partial epilepsy who were either treatment-naïve or were inadequately treated were included. A cross-over design was used to compare valproate-CR with standard valproate. The study aimed to test the hypothesis that treatment compliance, satisfaction and efficacy would be higher and the incidence of adverse events lower following the switch from standard enteric coated valproate to valproate-CR.

Patients

The study included patients with partial epilepsy aged between 18 and 65 years fulfilling one of the following two criteria: either treatment-naïve patients who were considered suitable for initiating valproate monotherapy or treated patients failing to respond to current therapy who were candidates for switching to valproate monotherapy. Patients were required to be able to read and write and to provide a signed informed consent form. Exclusion criteria included other epilepsy syndromes, liver disease, kidney disease, dementia, psychiatric disorders, progressive neurological disease and pregnancy.

Study procedures

During a screening visit, inclusion criteria were checked and informed consent provided. Standard biochemical and haematological tests were performed.

During the first study visit, patients were included in the study and treatment with enteric coated valproate tablets was initiated. The inclusion date for each patient was considered to be the first day on which valproate monotherapy was administered. Data were collected on demographic (age, gender, marital status, address, educational status, vocational status and important incidences occurring during the last month), clinical (medical history, laboratory data, age at first seizure and seizure type, frequency and aetiology) treatment (nature and duration of previous antiepileptic drug treatment,

concomitant medication) variables. The patient was provided with a treatment diary in which to report medication use and side-effects.

A second visit was made four weeks later when clinical state was evaluated and the valproate dose adjusted if necessary. At the third visit carried out eight weeks later, treatment was switched to valproate-CR. Biochemical and haematological tests were repeated during this visit. A fourth visit, four weeks later allowed the dose of valproate-CR to be adjusted according of the clinical state of each patient. Treatment was continued for a further eight weeks when the fifth and final study visit was made. The entire study duration was thus six months.

Outcome data was collected by the investigator at the second, third, fourth and fifth study visit and the patient completed a compliance questionnaire at the third and fifth visits. The patient provided additional information at the final study visit on specific adherence issues with the valproate-CR formulation. The investigator completed the Clinical General Impression rating scale at the end of the study.

Treatment

Standard enteric-coated tablets of valproate (Depakine® 500 mg) were administered during the first three months of the study. If patients were being switched from another antiepileptic drug, the previous drug was tapered and stopped in an appropriate fashion and valproate initiated concomitantly to cover the taper period. In accordance with national prescribing recommendations, the initial daily dose was 20-30 mg/kg. This dose could be adjusted if necessary at the second study visit. At the third study visit, patients were switched to an identical dose of valproate-CR (Depakine Chrono® 500 mg tablets) over a transition period of three days. Again, the dose could be adjusted four weeks later if necessary.

Outcome determination

Outcome data was collected on two questionnaires, one completed by the investigator and the other by the patients. The investigator-completed questionnaire (completed on Visits 2 – 5) recorded data on seizure control, drug treatments and adverse events. The patient questionnaire (completed on Visits 3 and 5) recorded data on drug compliance, satisfaction and side effects. Compliance was also evaluated by the investigator by determining the amount of unused medication, and by inspection of the patients' treatment diaries.

The questions used in the questionnaires were the Turkish translations of questions used in previous studies.[15] Examples of questions on drug compliance and satisfaction are given below:

- What is your contentment level with the present frequency of your antiepileptic drug?
- Are you bothered with taking your antiepileptic drug more than one in a day?
- How do you evaluate your antiepileptic drug from the point of seizure control?
- What can you say about the regularity of your antiepileptic drug use?
- Do you take your drug more often than recommended by your physician?

The patient was asked the following questions at the fifth visit only with the aim of evaluating adherence to the valproate-CR formulation:

- How frequently did you use your antiepileptic drug in the last three months?
- How easy is it for you to use your drug like this?
- At what frequency would you prefer to use your drug?
- Why would you prefer at this frequency?
- In your opinion what were the advantages to take your medicine only once a day?

Tolerability was evaluated from the Adverse Event Forms filled in by the investigator, by side-effects reported on the patient questionnaire, and by the proportion of patients completing the study.

Efficacy criteria evaluated were the proportion of patients responding to treatment, the proportion of seizure-free patients at each visit and the proportion of patients who completed the study (retention rate). Treatment response was defined as a decrease of at least 50% in seizure frequency compared to the four weeks preceding initiation of treatment with the study medication.

Data handling and statistical analysis

Following the termination of the study, data from all participating centres was collated in a master file. Demographic data, clinical properties, seizure status, side effects, compliance and questionnaire data were evaluated using percentage

ratios, arithmetic means, and standard deviations as appropriate. Variables were compared between the two treatment periods (standard valproate and valproate-CR) using the chi-square test, Wilcoxon test, Fisher's exact test and Mantel-Haentzel test as appropriate. Variables affecting compliance were evaluated using multivariate analysis. The statistical analysis was performed using SPSS software (version 2.0).

Results

Study participants

One hundred patients were included in ten centres. The distribution of the patients by study centre is presented in Table 1. One of the eleven planned centres did not participate in the study. Six of the 100 patients who were originally included in the study were subsequently excluded, since they did not return for follow up after the inclusion visit. For this reason, data are presented for the remaining 94 patients were evaluated.

Table 1. Inclusion of patients in the ten participating centres.

Center	Number of patients
Cukurova University Medical Faculty Neurology Dept.	20
BRSHH Education and Research Hospital II. Neurology Clinic	15
Gazi University Medical Faculty, Neurology Dept.	15
Istanbul University, Istanbul Medical Faculty, Neurology Dept.	10
Ege University Medical Faculty, Neurology Dept.	9
Istanbul University Cerrahpasa Medical Faculty, Neurology Dept.	8
Adnan Menderes University Medical Faculty, Neurology Dept.	7
Sisli Etfal Education and Research Hospital Neurology Clinic	6
Ankara University Medical Faculty, Neurology Dept.	5
Kırıkkale University Medical Faculty, Neurology Dept.	5

Sociodemographic characteristics

The age of the patients included ranged from 18-65 years, with a mean age of 30 ± 11.9 years. The majority of patients (64.9%) were in the 18-30 age group, 28.7% were in the 31-50 age group and 6.4% in the 51-65 age group. Forty-nine of the patients were male (52%) and 45 female (48%).

With respect to marital status, single and married patients were equally represented (46/45) and 3.2% of patients were divorced. Most of the patients (86.2%) lived in localities with a population higher than 50 000 people. Concerning educational level, 39.1% of patients graduated from primary school, 13% from secondary school, 34.8% from high school and 13% had received a higher education. Concerning employment status, 35.2% of patients were in active employment and 64.9% were unemployed, housewives, students or retired.

Seventeen patients reported social incidents in the previous month, of which six were familial, six vocational and five related to private life. These incidents included family disputes, moving house, leaving education, financial difficulties, unemployment and changes in marital status.

Clinical features at inclusion

The mean age at onset of epilepsy in the study population was 24.2 ± 13.2 years (range 0.5-64 years). For 94 patients, the duration of epilepsy varied between 0.03 and 33.2 years (mean 5.9 ± 7.4 years).

Seizure frequency of during the month preceding inclusion into the study was less than one seizure per month in 28% of 93 patients, between one and five seizures per month in 53% and more than five seizure per month in the remaining 19%.

Twenty eight percent of 93 patients, reported having only partial seizures (simple or complex), 72% of patients reported secondary generalized seizures which were seen alone or concomitantly with partial seizures. Seizure aetiology was unknown in 79.8% of 89 patients and symptomatic in the remaining 20.2% of patients.

At inclusion, 48 patients (51.1%) were treatment-naïve and 46 (48.9%) were treatment non-responders. In the group who had previously received antiepileptic drugs, these were used in monotherapy by 87% of patients. For the 45 patients

in this group for whom the duration of previous antiepileptic drug treatment was known, 21 (46.7%) received treatment for more than 36 months and five (11%) for between one and three months (Table 2).

In the medical records of 93 patients, antecedents of psychiatric disturbances were identified in 6.5% and medical and surgical antecedents in 17.2%.

Table 2. Duration of prior antiepileptic drug therapy

	Number of patients	Percentage (%)
1-3 months	5	11.1
4-12 months	10	22.2
13-36 months	9	20.0
Longer than 36 months	21	46.7
Total	45	100

Valproate treatment

At the third visit (end of standard valproate treatment phase), the maintenance dose of valproate was between 500-2000 mg/day in 97.6% of patients, with a mean dose of 1092 ± 342 mg/day. At the fifth visit (end of valproate-CR treatment phase), the mean dose was 1128 ± 371 mg/day, 96% of patients receiving between 500-2000 mg/day. Two patients at the third visit and three patients at the fifth visit required doses of over 2000 mg/day of the drug in order to control seizures.

Concomitant medication

Over the study period, 25 patients received concomitant drugs. Long-term treatment was used by four patients for depression, one patient for anxiety, one patient for Familial Mediterranean Fever (FMF), one patient for Diabetes Mellitus (DM), one patient for Hashimoto disease and one patient for Behcet disease. The reasons for short term drug use were gastritis, anaemia, candidiasis, tinnitus, upper respiratory tract infection, headache and dysentery.

Seizure control

The proportion of patients who were seizure-free or who had experienced less than one seizure per month was 30.5% at the first visit, 56.9 at the third visit and 62.5% at the fifth visit (Table 3). The difference between the first and third visits was more significant ($p<0.007$) than the difference between the third and fifth visits ($p<0.025$). There was no change of the seizure type between the first and fifth visits.

Table 3. Seizure frequency over the study duration.

Visit	Rare seizures (None or less than once a month)	Frequent seizures (more than once a month)	p value
1st visit	30.5%	69.5%	1-3 visit: <0.007
3rd visit	56.9%	43.1%	3-5 visit: <0.023
5th visit	62.5%	37.6%	1-5 visit: <0.001

Adverse events

Over the entire course of the study, 189 adverse events were reported in 46 out of 94 patients. At the second, third, fourth and fifth study visits, these were reported in 35, 25, 25 and 19 patients respectively. At the second study visit, nausea was the most frequent adverse event reported (n = 10; 10.6%), followed by hair loss, weight gain, vomiting and somnolence. At the following visits (3rd, 4th and 5th) hair loss was the most frequently reported adverse event (n = 10 at Visit 5; 13.2%), followed by tremor, weight gain, trembling, nervousness and nausea. The perceived causal relationship between the adverse events and valproate treatment is presented in Table 4. No significant difference in the severity of these adverse events was observed between the third (end of the standard valproate treatment period) and the fifth (end of the valproate-CR treatment period) study visit ($p=0.083$). Four patients discontinued the study prematurely due to the occurrence of an adverse event and the dose of valproate was reduced in 28 patients.

Table 4. Adverse events.

Relation to the drug	Number of patients	Percentage (%)
None	10	5.3
Possible	17	9
Probable	58	30.7
Present	60	31.7
Not mentioned	44	23.3
Total	189	100

Laboratory tests

Haematological parameters (haemoglobin, haematocrit, leukocyte counts and platelet counts) remained stable between

the first and third study visits, with the exception of one patient, in whom the platelet count decreased from 256 000 elements/mm3 to 116 000 elements/mm3. However, platelet count was only determined in 33 patients. Hepatic enzymes were evaluated in 45 patients. An increase in serum glutamic-oxaloacetic transaminase (SGOT) from 16 to 56 U/ml was detected in one patient and an increase in serum glutamate pyruvate transaminase (SGPT) from 8 to 56 U/ml in another. In a third patient, who was concomitantly prescribed colchicine for the treatment of FMF, SGOT increased from 22 to 60 U/ml and SGPT increased from 28 to 108 U/ml.

Compliance

Compliance was considered acceptable if the patient did not miss a dose of treatment more than twice during the first four-week evaluation period for each treatment regimen or more than four times during the subsequent eight-week evaluation period. For the standard valproate treatment period, 82.2% of patients showed acceptable compliance after four weeks and 88.1% did so after a further eight weeks. For the valproate-CR treatment period, compliance increased from 86.3% after four weeks to 97.4% after the subsequent eight weeks. The difference in compliance between visits was statistically significant ($p = 0.001$).

Due to the small number of patients in whom plasma valproate concentrations were determined, these could not be used systematically as an independent indicator of compliance. In 36 patients screened at the second study visit (standard valproate treatment period), the average serum valproate concentration was 68.2 mg/L. In 32 patients screened at the fourth study visit (valproate-CR treatment period), the corresponding value was 88.1 mg/L. This difference was statistically significant ($p = 0.050$).

Determinants of treatment compliance amongst baseline variables were assessed. No association was observed between, on the one hand, compliance and, on the other, gender, marital status, vocational status, aetiology of epilepsy and previous antiepileptic drug use. In contrast, compliance was 20-30% lower in patients who had frequent seizures. An interaction was observed between formulation and educational level, age, seizure type and duration of treatment. The gain in compliance upon switch from standard valproate to valproate-CR was 38% in secondary school graduates, 28% in ages 31-50 years group, 12% in patients with secondary generalised epilepsy and 41% in the group that had taken treatment for 13-36 months.

Patient-reported outcome

The proportion of patients who reported being satisfied or very satisfied with their epilepsy treatment increased from 63.9% at the end of the standard valproate treatment period (Visit 3) to 77.7% at the end of the valproate-CR treatment period (Visit 5). This difference was statistically significant ($p = 0.001$).

Patients who declared that taking treatment more than once daily was a problem decreased from 36.1% at Visit 3 to 18.5% at Visit 5. From the point of seizure control, 90.3% of the patients at Visit 3 and 97.3% of the patients at Visit 5 reported treatment efficacy to be good or very good ($p = 0.683$). At Visit 3, 78.3% of patients declared that they never forgot to take their drugs or they forgot to take the drug less than once a month, compared to 89.5% at Visit 5 ($p < 0.010$). The proportion of patients who declared that they took more drug than the physician recommended was 2.4% (two patients) at Visit 3 and 6.5 % (five patients) at Visit 5 ($p = 0.395$). Only one patient declared that it was not important to take the drug according to the physician's recommendation.

At the end of the study, patients responded to five additional questions aimed at ascertaining relative compliance and satisfaction with the valproate-CR formulation. The majority (70.3%) of patients declared that they took the drug once a day during the last three months. The remaining patients were taking the drug two or three times a day. Overall, 77.4% of patients found the valproate-CR formulation easy to use.

When asked about the most desirable frequency to take the drug, 86.8% of patients replied that they preferred to take the drug once a day and the remaining 13.2% preferred to take the drug twice a day. None wanted to take the drug more frequently. Three patients who were taking more than four tablets daily at the fifth visit (one patient taking 2250 mg and two patients taking 3250 mg/day) declared that they would prefer to take valproate once a day. All the remaining patients, including the patients preferring to use the drug twice a day, were using less than four tablets daily. Patients who preferred to take the drug once a day gave their reasons as "not to forget to take it" in 40.9%of cases, as "it is easier for me" in 27.3% of cases and as "since it was recommended

by the physician'' in 6.1%of cases. Four out of ten patients who preferred to take the drug twice a day gave their reason as ''since I believe it is more effective'' and two patients gave it as ''since it was recommended by the physician''.

In the questionnaire completed at both the third and fifth visit, there were nine items related to patients' opinions on taking the drug once a day. Apart from a 15% decrease in the number of patients who agreed with the statement ''I would have forgotten it less if I had to take it only once a day'', no significant differences were found in the other statements between the two visits ($p<0.005$), (Table 5). With respect to questionnaire items related to problems or side effects considered by the patients to be caused by antiepileptic drug use, nervousness, weight gain, tremor, and hair loss were most frequently cited. Even though there was a decrease in the incidence of these side effects between third and fifth visits, no statistically significant difference was found.

Table 5. Treatment satisfaction.

	Percentage of patients who said I strongly agree / I agree	
Satisfaction Indicators	**Valproate**	**Valproate-CR**
I prefer to take my antiepileptic drug only once a day	71.1%	71.1%
It is more appropriate to take an antiepileptic drug once a day	70.7%	68.4%
Frequent use of an antiepileptic drug causes it to be forgotten more often	75.9%	67.1%
Taking an antiepileptic drug only once a day reduces the risk of side effects	40.0%	38.3%
It is easier to take an antiepileptic drug only once a day	79.5%	80.0%
Taking the antiepileptic drug once a day means that it is less effective	13.4%	10.6%
If I had to take my drug once a day, I would be less likely forget to take it	71.6%	56.0%
Taking an antiepileptic drug frequently causes more side effects	30.1%	35.6%
Taking an antiepileptic drug once a day would suit my lifestyle better	74.0%	68.4%

End of study evaluation

At the end of the study, 84.9 % of the patients said that they were satisfied with their treatment. Patients were classified by treatment response and by impact of side-effects using the general clinical evaluation scale (Table 6). Of the 74.4% of patients who were classified as improving most, side effects were observed in 25.2%. Overall, side effects were observed in 41.4% of patients, for 34.1% of whom, these did not interfere with functions whereas, in 6.1%, function was significantly affected. In one patient who had shown slight improvement, side effects including nausea, weight gain and hair loss, were considered to overshadow the benefits of treatment. This patient failed to tolerate the 1000 mg/day dose of valproate-CR and she withdrawn at the fourth study visit.

Treatment discontinuation

Seventy seven patients completed the study (81.9%). The reasons for premature study discontinuation are presented in Table 7.

Discussion

In our series of 94 patients with partial epilepsy in whom treatment with valproate (500-3250 mg/day) was initiated and pursued for 24 weeks, a decrease in seizure frequency was observed in 64% of cases. This improvement in seizure control was further amplified following a switch to the valproate-CR formulation. After initiation of valproate treatment, the proportion of patients with controlled seizures increased by 32%. These findings support the findings of other studies showing the efficacy of VPA in partial epilepsy.[4,5,16,17]

Table 6. Clinical General Impression Side-effects Scale

Side Effects	None Number (%)	Do not affect patient functioning Number (%)	Significantly affect patient functioning Number (%)	Overshadow the therapeutic benefits of the drug Number (%)	Total Number (%)
Very improved	42 (51.2)	15 (18.3)	4 (4.9)	-	61 (74.4)
A little improved	3 (3.7)	11 (13.4)	1 (1.2)	1 (1.2)	16 (19.5)
No difference	2 (2.4)	2 (2.4)	-	-	4 (4.8)
Worsened	-	-	-	-	-
Not evaluated	-	-	-	-	1 (1.2)
Total	47 (57.3)	28 (34.1)	5 (6.1)	1 (1.2)	82 (100.0)

Table 7. Premature study discontinuation

	Number of patients	Percentage (%)
Completed study as planned	77	81.9
Patient lost to follow up	8	8.5
Left the study due to side effects	4	4.3
Physician changed the drug for ineffectiveness and patient left the study	3	3.2
Patient left the study due to another disease or operation	2	2.1
Total	94	100

Valproate was discontinued due to lack of efficacy in three patients only. No change in seizure presentation or increase in seizure frequency was observed, consistent with previous observations that paradoxical seizure exacerbation, that are sometimes reported with other antiepileptic drugs, are infrequent with valproate.[4,5]

The switch to valproate-CR treatment was associated with a decrease in the incidence of adverse events; these were observed in 35 patients during the standard valproate period and in 19 patients during the valproate-CR treatment period. Part of this decrease may be due to the previously reported reduction in the incidence of acute adverse events, such as somnolence, stupor, gastrointestinal irritation and hypersensitivity reactions, which occurs in the days immediately following initiation of valproate treatment.[18] The severity of adverse events did not differ between the two treatment periods. The incidence of the most frequent adverse event, nausea, decreased by 8% following switch to valproate-CR, whereas the incidence of hair loss increased by 4.3%. Other frequently reported adverse events were tremor and weight gain. The nature and frequency of adverse events observed in this study are consistent with the previous studies.[15,18] The proportion of adverse events attributed to valproate treatment decreased from 42.6% to 31.3% following the switch to valproate-CR. These results suggest that switching from standard valproate to valproate-CR is associated with a significant reduction in the incidence of adverse events, in support of other recently-published findings.[11,15]

No significant differences in physician- or patient-rated tolerability were observed. Although no serious side effects were observed, four patients discontinued the study due to adverse events, and dose reduction was necessary in 28 patients. The incidence of severe adverse events was reduced by a factor of two between the end of the standard valproate

treatment period and the end of the valproate-CR treatment period. No significant changes in haematocrit, haemoglobin or leukocyte counts were observed in either treatment period. Thrombocytopenia, possibly related to valproate treatment, was observed in one patient and an increase in transaminases over two times the upper limit of normal reported in 3 patients. Long term tolerability could not be assessed due to the relatively short study duration (three months).

No association was observed between gender, marital status, educational level, vocational status or epilepsy aetiology and patient compliance. With respect to age, the 31-50 age group showed the greatest compliance, reaching 95% for the valproate-CR formulation. Compliance was 18% greater in patients with secondary generalised seizures than in patients with simple partial seizures. These determinants may not be independent due to the heterogeneous distribution of seizure type with age. The relationship between seizure frequency and compliance was not possible to evaluate, since lack of response to treatment is known to be detrimental to good compliance.[15] An important finding of the study was that treatment compliance increased upon switch to the valproate-CR form. Demographic variables, medical antecedents and characteristics of epilepsy did not influence compliance. Previously described variables influencing compliance include attitudes to the importance of respecting prescribing recommendations, dosage frequency and concomitant medication.[19,20]

Between the end of the standard valproate treatment period and the end of the valproate-CR treatment period, a 14% increase in the preference for a once daily treatment regimen was observed. A concomitant decrease of 17.6% was seen in the proportion of patients declaring that taking treatment more than once daily was problematic. The proportion of patients who believed that their antiepileptic drug treatment controlled their seizures increased by 7%. These variables covaried with the decrease in seizure frequency.

In addition, the proportion of patients who forgot to take the drug decreased by 11% following the switch to the valproate-CR formulation. At the end of the valproate-CR treatment period, 70.3% of patients were taking the drug once a day, 77.4% of the patients found the once-daily dosage easy to use and 86.8% of the patients preferred to take the drug once daily. Three patients using more than 2000 mg/day declared that they would have preferred to take the drug once a day. The ability of the patient to remember to take the drug and its simple delivery were important reasons given for preferring the valproate-CR formulation. Nonetheless, 30% of patients who were taking low daily doses ($<$ 2000 mg or $<$ four tablets/day), justified using the drug more than once daily by their belief that this regimen was more effective or that it was recommended by the physician. These results indicate that the number of tablets to be taken each day per se was not the only criterion determining the preference for a once-daily administration. The results illustrate the need to educate the patient about therapy and epilepsy, in particular with respect to the importance of using the drug as prescribed, and support the notion that administration of the drug the fewest times a day possible considerably increase patient compliance, consistent with previous reports.[20,21]

Concerning treatment satisfaction, no significant difference in responses between the two treatment periods was observed for eight out of nine questions. The exception was a 15% decrease in a positive answer to the item "I would not have forgotten my drug if I had to take it only once daily" following a switch to the valproate-CR formulation.

The decreased probability of forgetting to take the drug and the positive impact of a once-daily treatment regimen on quality of life reported here were consistent with findings from previous studies.[15,22] At the end of the study, 84.9% of patients were satisfied with treatment and 81.9% had completed the entire study. These proportions matched those reporting a decrease in seizure frequency, compliance to treatment and treatment satisfaction. The major reason for premature study discontinuation was loss to follow up. Most of these discontinuations occurred before the first study visit after four weeks of treatment (100 patients; 12%). The explanation for these premature discontinuations may include lack of efficacy, the occurrence of adverse events or inappropriate inclusion; however, these reasons could not be elucidated in the majority of cases, since patients had been loss to follow up.

The present study was an observational study rather than a randomised controlled study. For this reason, some caution should be exercised in the interpretation of the results, notably with respect to efficacy, adverse events and compliance. Nevertheless, to our knowledge, this is the first study that

has evaluated, under standard conditions of epilepsy care, treatment compliance, efficacy and tolerability in a cohort of patients with partial epilepsy switched to a controlled release formulation of valproate.

The study illustrates the need for more comprehensive, long-term comparative studies of the utility of valproate and its controlled-release formulation in the treatment of partial epilepsies. In particular, pharmacogenetic classification of patients presenting side effects will be especially informative.

In conclusion, this study demonstrated that standard valproate and valproate-CR are effective for the treatment of partial epilepsy. Treatment satisfaction and compliance were found to be high and to improve following the switch to the valproate-CR formulation.

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