Short-term efficacy and safety of valproate sustained-release formulation in newly diagnosed partial epilepsy (VIPe-study)

A multicenter observational open-label study

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ABSTRACT

Objective: To evaluate the efficacy and safety of valproate (VPA) sustained-released in monotherapy across all ages in newly-diagnosed epileptic patients with partial seizures (PS) with or without secondary generalization.

Methods: This was a multicenter, prospective, observational, open-label, non-comparative study involving the Gulf Cooperation Council (GCC) countries except the Kingdom of Saudi Arabia, and was performed between November 2004 and May 2006. Adults and children (6 years or older with newly diagnosed partial epilepsy [PE]) with or without secondary generalization were enrolled. The primary efficacy parameter was 6 month-remission rate (proportion of seizure-free patients in relation to total number of retained patients). Secondary efficacy parameters included: 6 month-retention rate, investigator's clinical global impression rating, maximal effective dose and safety profile.

Results: Seventy-seven patients were enrolled; 56% adults and 44% children, with average duration of epilepsy of 5 months in the pediatric and 17 months in the adult group. Seizures type distribution: PS with secondary generalization (62%), complex PS (53%) and simple PS (14%). The majority had idiopathic seizures (48%). Sixty-six patients completed the study (treatment retention rate 80.5%). At 6 months, 87% of patients became seizure free with VPA sustained-release monotherapy (average dose 22 mg/kg/day). Adverse drug reactions (hair loss and tremor) were recorded in <20% of patients, mostly affecting adults.

Conclusions: In this population, short-term treatment with VPA sustained-release in monotherapy provides good seizure control and is well tolerated.

Saudi Med J 2007; Vol. 28 (9): 1402-1407

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Received 7th January 2007. Accepted 25th April 2007.

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Epilepsy is a chronic neurological disorder characterized by unprovoked, intermittent seizures, which are the expression of abnormal paroxysmal hypersynchronous discharges of cortical neurons. Epidemiological studies indicate that 40-70 individuals per 100,000 will develop epilepsy annually.[1,2] The incidence rate of epilepsy is higher in developing countries (>65/100,000) compared with that in industrialized countries (43.4/100,000).[1,2] Complete seizure control, with minimal or no adverse drug reactions (ADRs) is the single most important determinant of good quality of life for epileptic patients.[3] This requires often life-long therapy with antiepileptic drugs (AEDs) in monotherapy in most cases.[4] However in up to 30% of patients, seizures are refractory to treatment with a single AED despite optimal AED therapy, and others have the unacceptable side effects.[4] Accurate diagnosis of the type of seizure is essential because AEDs are selective. Because of its broad spectrum of antiepileptic activity, valproate (VPA) has been extensively and successfully used in epilepsy and this in all age groups for the past 4

Disclosure: This study was sponsored by an educational grant of Sanofi-Aventis. All investigators received a financial compensation for completing the case record forms and recruiting the patients. Additional expenses related to investigations, travel expenses of patients and so forth were paid.

decades.[5] Its indications include both partial and generalized epilepsy, and it is the drug of choice in the treatment of all forms of generalized seizures. However, despite a number of published comparative clinical trials showing that VPA and carbamazepine (CBZ) are equally effective in controlling partial seizures in an out-patient population, a common practice and approach were to use VPA for the control of generalized seizures while CBZ was recommended for partial seizures.[6-8] Valproate sustained-release formulation (Depakine Chrono®) is almost completely absorbed in the stomach, and provided the peak concentrations 5-10 hours after intake, compared with 2-3 hours for the regular capsule and 3-5 hours for the enteric-coated tablets. Studies indicate that the sustained-release formulation (Depakine Chrono®) not only improves pharmacokinetics but that switching from immediate release VPA to sustained-release formulation results in an increase in seizure-free rates, a reduction in reported side effects, an improvement in the level of compliance, and an improvement in patient satisfaction.[9] As for other AEDs, data on efficacy and tolerability of VPA in epileptic patients are almost exclusively based on Western or Japanese populations. Based on genetic and environmental factors, pharmacokinetic, pharmacodynamic as well as disease-related processes differ amongst populations,[10,11] possibly leading to distinct population-dependent tolerability and, possibly, efficacy profiles of AEDs. Therefore, the aim of this observational study was to collect, under daily practice conditions, additional clinical data on the efficacy and safety of the oral VPA sustained-release (Depakine Chrono®) used as first-line monotherapy in a cohort of newly or recently diagnosed partial epileptic patients (pediatric and adult patients) in 5 Gulf Cooperation Council (GCC) countries (Bahrain, Kuwait, Oman, Qatar, the United Arab Emirates).

Methods. This study was a multicenter, prospective, observational, open-label, non-comparative study involving 5 GCC countries (Bahrain, Kuwait, Oman, Qatar, the United Arab Emirates), and was performed between November 2004 and May 2006. The inclusion criteria were the following: a) all patient - adults and children 6 years or older - with newly or recently diagnosed partial epilepsy, with or without secondary generalization, and requiring a first antiepileptic treatment (women of childbearing potential were included, provided they took efficient contraceptive measures); b) having had an electroencephalographic (EEG) and CT or MRI brain maximum 6 months prior to study entry; c) not taking any AEDs (previous short-term treatment with benzodiazepines were allowed but these should have been discontinued at least one week prior to the study); d) ability of the patient to complete the diary seizure card and to follow the study procedures, and they gave their informed consent; e) normal cell blood count and basic biochemistry (liver and renal function tests and glucose levels).

Newly/recently diagnosed partial epilepsy was defined as having had at least 2 or more and 10 or less partial seizures (complex partial and/or simple seizures of the motor type), with or without secondary generalization, during the preceding 6 months. Patients with one partial seizure, with or without secondary generalization, were allowed to enter the study only if analyses of clinical and ancillary data (EEG, CT or MRI brain) strongly supported the diagnosis of epilepsy. The clinical data required a clearly witnessed seizure and clinical description or clinical findings (such as sequel of tong bite in case of partial seizure with secondary generalization) compatible with a seizure. The EEG had to show signs of focal paroxysmal activity at least on 2 occasions. Neuroimaging could be either normal or abnormal. Exclusion criteria included: patients with primary generalized seizures or a generalized epilepsy syndrome (for example juvenile myoclonic epilepsy), history of: non-epileptic seizures, acute or chronic hepatitis, or liver disease, hepatic porphyria, active central nervous system infection, demyelinating disease, or any central nervous system disease deemed to be significantly progressive during the course of the study (for example low-grade tumor was allowed), drug or alcohol abuse; severe acute or chronic illness (for example hematological, renal, cancer, AIDS, and so forth); patients taking benzodiazepines for anxiety; women pregnant at time of enrollment or having a pregnancy wish or those who were lactating; patients who have taken the investigational drug(s) within 30 days prior to the first study visit. The study was approved by the Medical and Ethics Committee of the different institutions involved, and included strict confidentiality for all information collected. Patients had to sign an informed consent form in their own language in order to collect their data.The following data were collected: demographics (age, gender, and weight), result of neurological examination (dichotomized; either normal or abnormal), type and etiology of the epileptic syndrome (for example idiopathic, cryptogenic, symptomatic), age at onset of seizures, topographical origin of the seizures (temporal, extratemporal, or not determined), duration of disease, seizure frequency at enrollment, and at each visit. The type of epileptic seizure was grouped according to the revised classification of the International League Against Epilepsy:[12,13] complex partial, simple partial, tonic-clonic, absence, myoclonic, clonic, tonic, atonic, and status. The following etiologies were considered: idiopathic, cryptogenic, symptomatic (such as brain

tumor, degenerative, febrile seizures, meningitis/encephalitis, perinatal anoxia, cerebrovascular causes, mesial temporal sclerosis, systemic disease, dysplasia and other malformations and cranial trauma and post-neurosurgical intervention) or undetermined cause.

The study lasted 6 months with 2 intermediary visits (at 2 and 3 months). During the observational study no other antiepileptic drugs were allowed. The primary efficacy parameter included remission rate, defined as the proportion of seizure-free patients at 6 months in relation to total number of retained patients. Secondary efficacy parameters consisted of: a) the treatment retention rate (proportion of patients who completed the 6-month study); b) brief neurological evaluation; c) the investigator's clinical global impression (CGI) scale (including efficacy and tolerability) (marked = vast improvement, moderate = partial improvement, minimal = slight improvement and none = unchanged or worse); d) dose to reach maximal efficacy; e) efficacy according to the type, etiology, topographic localization of partial epilepsy, and age at inclusion (under and above 15 years). Regarding the dose regimen, the following data were collected: compliance, effective dose regimen at first visit and follow-up visits (2, 3, and 6 months). Tolerability was assessed through monitoring of ADRs (spontaneous reporting or leading to drop out) and was assessed for potential relationship to the study drug and intensity (mild, moderate, severe).

Intention to treat analysis was performed whereby any patient who had at least one dose and completed at least one follow-up visit was included in the analysis. All data for continuous variables are expressed as mean ± standard deviation (SD) and as frequency (%) for categorical variables with their 95% confidence intervals (CI). All data were treated using MS access and graph pad software.

Results. Seventy-seven patients fulfilled the criteria for inclusion in this study. The demographic characteristics of the study population are given in **Table 1**. The mean age was 25.5 ± 14.3 (range 6 - 62) years with 56% adults. Patients were diagnosed as suffering from epilepsy for an average of 11.7 ± 35.3 (range 0-200) months (in the adult group 17.3 ± 44.6 (range 0-200) months and in the children's group 4.7 ± 15.8, range 0.1-91.8 months). The average weight was in children

Table 1 - Demographic data of the study population (n=77).

Parameters	Age (years)	Gender n (%)			Duration of epilepsy
		Male	Female	Total	(months)
Children	13.0 ± 3.1 [6-18]	18 (53)	16 (47)	34 (44)	4.7 ± 15.8 [0.1-91.8]
Adults	35.6 ± 11.1 [19-62]	28 (65)	15 (35)	43 (56)	17.3 ± 44.6 [0-200]
Total	**25.5 ± 11.1 [19-62]**	**46 (60)**	**31 (40)**	**77 (100)**	**11.7± 35.3 [0-200]**

Table 2 - Type of seizures (n=77). Note that many patients had several seizure types. Number of seizures (median) in previous 6 months and number of patients with only one seizure.

Seizure type	Children (n=34)	Adults (n=43)	Total (n=77)
	n (%)	n (%)	n (%)
Partial seizures with secondary generalization	20 (59)	28 (65)	48 (62) median 3.0 (5 patients had 1 seizure) (12 patients had 2 seizure) (9 patients had 3 seizure)
Complex partial seizures	20 (59)	21 (49)	41 (53) median 4.0 (1 patients had 1 seizure) (11 patients had 2 seizure) (7 patients had 3 seizure)
Simple partial seizures	2 (6)	9 (21)	11 (14) median 10.0 (no patients had 1 seizure) (1 patients had 2 seizure) (2 patients had 3 seizure)

Table 3 - Efficacy of valproate sustained release (Depakine Chrono®) in monotherapy at the end of the study (6 months). Note that there are missing data for clinical global impression in 22% of patients.

Parameters	Seizure free N=62 number of patients (%)	Retention rate N=62 number of patients (%)	Clinical global impression N=74* number of patients (%)			
			Marked	Moderate	Minimal	NA
Children	26 (93)	28 (82)	25 (76)	-	1 (1)	7 (21)
Adults	28 (82)	34 (79)	23 (56)	11 (27)	-	7 (17)
Total	**54 (87)**	**62 (81)**	**48 (65)**	**11 (15)**	**1 (1)**	**14 (19)**

NA - not available. *Three patients dropped-out after baseline visit.

Table 4 - Adverse drug reaction (ADR) profile of valproate sustained release (Depakine Chrono®) in monotherapy during the study (n=77).

Description of ADR	Number of events	Severity	Relationship with study medication	Action taken	Outcome
Drowsiness	1	moderate	related	discontinuation	recovered
Hair loss	4	mild to severe	related	3 patients discontinued*	ongoing
Headache	1	moderate	related	paracetamol treatment	ongoing
Weight gain	1	mild	related	no action taken	ongoing
Tremor	3	mild to moderate	related	1 patient discontinued* 2 patient no action taken	ongoing
Overdose (9000 mg/day)	1	moderate	related	Temporary discontinuation	recovered

There were 5 additional patients with ADRs but these were not specified.
*One patient discontinued because of 2 ADRs.

50.0 ± 16.9 kg and adults 73.7 ± 13.7 kg. Seventy-five percent of patients had no relevant medical history and 96% had normal neurological examination (one patient had dysphoria, one patient presented bilateral cerebellar and pyramidal syndrome, and one patient had upper limb paresis with behavioral abnormalities). The types of epileptic seizure are summarized in **Table 2**. Across all age groups, partial seizures with secondary generalization seizures were most frequently observed and accounted for 62% of all types of epileptic seizures, closely followed by complex partial seizures (53%) and less frequently simple partial seizures (14%) (**Table 2**). Idiopathic/cryptogenic epilepsy was the most common etiology of epileptic seizures (56%) while symptomatic causes accounted for 19%, most of them following cranial trauma and post-neurosurgical intervention. The remaining etiologies (25%) were listed as undetermined. The suspected topographical location of the seizures was temporal in 43% of patients, and extra-temporal in 32%. The remaining seizures were of undetermined topography. From the 77 patients enrolled, 62 completed the trial, corresponding to a treatment retention rate across both age groups of 81%. This figure was almost comparable in both age groups (**Table 3**). Reasons for drop out were the following: 3 patients discontinued after the baseline visit; 3 because of ADRs; one due to lack of efficacy; one because of pregnancy wish; 5 were lost to follow-up and 2 due to poor compliance.

Irrespective of the age group and type of seizures (**Table 3**), 87% of patients became completely seizure-free. This rate was higher in the pediatric group (93%) than in the adult group (82%). Eighty-two percent of patients were seizure-free within 2 months of starting the treatment. The therapeutic efficacy as measured by the investigator's CGI is shown in **Table 3**. Marked to vast improvement without ADR was observed in 67% (95% CI: 48-82%) of the children and in 51% (95% CI: 35-67%) of adults. At the end of the study, 76% of physicians decided to continue the study drug. In both age groups, the average dose taken was 22 mg/kg/day. Broken down for the different age groups it revealed the following values: in the adult group; median 1,000 mg bid, (range 500 mg od - 2,000 mg bid), and in the child group; median 500 mg od, (range 250 mg bid - 1,500 mg bid). Overall, 15 patients (19.5%) reported ADRs during the course of the study. The distribution of ADRs is given in **Table 4**.

Discussion. This multicenter, observational study of VPA sustained-release (Depakine Chrono®) in

monotherapy in adults and children with newly-onset partial epilepsy provides for the first time data on efficacy and tolerability in patients from the Arabian Gulf countries. In this rather young epileptic population (average age 24 years), partial seizures with secondary generalization were most frequently encountered (62%) and this based on an idiopathic/cryptogenic background (56%). These findings are consistent with a recently published study in epileptic patients from one of these Arabian Gulf countries, the Sultanate of Oman, in which over two-thirds of the patients were younger than 30 years.[14,15] In addition, in that study all forms of epilepsy, tonic-clonic and partial seizures with secondary generalization were most frequently encountered and idiopathic/cryptogenic etiologies were most common. Also in this study as well as in the study reported by Hanssens et al,[15] approximately 20% of patients had a symptomatic underlying cause. Similar findings were reported in epidemiological surveys from other countries in the geographical region[16] as well as in a large hospital-based study performed in the Kingdom of Saudi Arabia.[17] As previously reported,[15] and consistent with the findings in this clinical trial, the rate of cryptogenic and inherited forms was higher than in studies on epileptic patients originating from the West. This is probably explained by a higher rate of consanguinity in the region.

Since each patient population (newly versus chronic epileptic patients), study design (add-on therapy for refractory seizures versus monotherapy; duration of the trial) or parameters of antiepileptic efficacy are different, it is difficult to compare studies on epileptic patients with one another. Depending on the duration and type of clinical study, several parameters have been used as measure of antiepileptic efficacy such as (a) time to the achievement of a period of prolonged remission, one year or more; (b) time to first seizure; (c) change in seizure counts and 50% reduction in seizure frequency; and (d) withdrawal time of the AED due to lack of efficacy (poor seizure control) or intolerable side-effects whichever is the earliest. The latter parameter being a composite-endpoint is known as the retention time on treatment. In this 6-month efficacy and tolerability study remission (seizure-free after 6 months) and retention rate was preferred as a practical measure of clinical efficacy and utility of the drug studied. Both parameters indirectly add in evaluating quality of life in an epileptic population. In addition, the CGI was included as secondary parameter.

In our epileptic population with partial seizures, the retention rate over the 6 months studies the period was high (81%) which probably explains why VPA is one of the most commonly prescribed AEDs in monotherapy in certain Arabian Gulf countries.[14,15] Valproate's broad-spectrum antiepileptic properties and favorable side effect profile support its use. Studies in epileptic populations performed in the early nineties, with the conventional formulations of VPA, revealed retention times up to 90%.[7] In this study, the average effective dose of VPA sustained-release (Depakine Chrono®) was 22 mg/kg/day for both age groups and corresponds with the usual effective dosage in other ethnic adults (10-30 mg/kg/day) and pediatric (20-40 mg/kg/day) groups.[6] Eighty-seven percent of patients became seizure-free, with a predominance for the pediatric population. More important, the CGI indicated that while on treatment with VPA sustained-release over 51% of adults and 67% of children had marked improvement to vast improvement with no ADRs. The results of our study correlate with findings from Western populations which revealed seizure control while on VPA monotherapy in 50-70% of patients.[18-19]

Up to 60 percent of patients with seizures report ADRs with AEDs.[3] In this study, the incidence of reported ADRs was in both age groups was less than 20%, with only 5 patients having to discontinue the therapy because of lack of efficacy or ADRs. Hair loss and tremor were the most commonly encountered ADRs, which correlates with findings from the European trial.[20] Many AEDs are known to increase body weight. In this study, weight was not included as a clinical parameter because ADRs was based on spontaneous reporting, hence, underreporting might have occurred. However, despite this only one patient reported the significant increase in weight gain which did not necessitate change in therapy.

Pharmacoeconomic data on newly therapeutic practice have clearly shown that in diagnosed epilepsy optimal cost-effectiveness can be achieved with conventional AEDs.[21] This conclusion is supported by evidence that in these patients, new AEDs are not more effective than older ones.[22] The relative small number of patients, the open, non-blinded, and non-controlled, (non-comparative) design are considered important limitations of the design of this study. Hence, it could be argued that the reduction in seizure frequency was related to chance, rather than to the effect of VPA sustained-release. In addition, the inclusion of 6 patients with one seizure some of them with normal neuroimaging could raise the question whether these patients really needed any therapy. However, there is strong evidence indicating that patients with a single idiopathic unprovoked seizure and with abnormal EEG, have a 75% risk of seizure recurrence mostly within 3 months of the first seizure. Furthermore in such population, AED therapy reduces the chances of developing a second seizure with 34%.[23]

In conclusion, the genetic variability is one of the contributing and perhaps the major underlying cause of differences in AED response and resistance.[15] This study in partial epilepsy provides for the first time long-term efficacy and tolerability data of VPA sustained- release (Depakine Chrono®) in monotherapy in a population of the Arabian peninsula, often deprived from early stage clinical trials. The data indicate a high adherence to the therapy with good efficacy. In addition, VPA sustained-release proved to have a good safety profile.

Acknowledgement. *We would like to thank the sponsor of this study, Sanofi-Aventis for their continuous support and unlimited help during the flow of this study.*

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