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Clinical Commentary

Effects of the abrupt switch from solution to modified-release granule formulation of valproate

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Background – A new modified-release (MR) granule formulation of valproate (VPA) has been recently developed for the treatment of children with epilepsy. It consists of tasteless microspheres that can be sprinkled on soft foods and easily swallowed. There are no data on the effectiveness of this formulation in pediatric age. *Aim of the study* – To evaluate the effects of the abrupt switch from solution to VPA MR granules in children undergoing chronic treatment. *Methods* – We enrolled children receiving VPA solution as sole or adjunctive therapy and switched them to MR granules at identical dosages. VPA blood level, treatment efficacy (clinical and EEG data), tolerability (adverse reactions), palatability, ease of administration, and compliance were evaluated before switching (T0) and after 4 weeks (T1). *Results* – Out of 112 enrolled children, 108 (96.4%) completed the evaluation. We observed no significant differences between the patients at T0 and T1 in VPA blood levels, treatment efficacy, tolerability, and compliance. MR granules were judged more palatable ($P < 0.05$) and easier to administer ($P < 0.05$) than solution by children and parents. At 6-month follow-up, all patients continued to use MR granules. *Conclusion* – Modified-release granule formulation of VPA may be a reliable alternative to solution for its convenience of use.

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Introduction

Valproate (VPA) is one of the most widely used anti-epileptic drugs for the treatment of epilepsy in children and adults (1). Since its introduction in 1967, several formulations have been developed to improve the management of therapy. An important advance has been the introduction of sustained-release preparations that provide stable VPA blood levels, allowing less frequent daily dosing, with inherent benefits in terms of adverse event profile and compliance (2, 3). However, these formulations are not adapted for children because they are available only in large tablets, which may cause swallowing difficulties and not allow tailoring dosage to the child's body weight. Traditionally, immediate-release liquid VPA is the most used formulation in infancy and childhood because it ensures accurate dosing and is easy to administer. However, the required multiple daily doses and its bitter taste may affect compliance (1, 4).

Recently, a new modified-release (MR) granule formulation of VPA (Depakine® Chronosphere ®) has been developed to provide a more palatable agent that can be given once or twice daily. It consists in tasteless microspheres that can be sprinkled on semi-solid foods, such as jam or yogurt, and easily swallowed. The microspheres

cannot be poured into hot food or hot beverages because heat damages the microspheres and, consequently, their modified-release properties. MR granules are bioequivalent to existing VPA sustained-release formulations, as demonstrated in adults (5).

The aim of our study is to evaluate the overall effects of the abrupt switch from solution to VPA MR granules in children with epilepsy.

Patients and methods

We performed a prospective, multicenter study, enrolling children referred to six pediatric neurological centers: Department of Pediatrics, Chieti; Department of Child Neuropsychiatry, L'Aquila; Department of Neurophysiopathology, L'Aquila; Department of Child Neuropsychiatry, Bologna; Department of Pediatrics, 'La Sapienza' University, Rome; and Department of Child Neuropsychiatry, Naples. We included children with any kind of epilepsy, treated for at least 6 months with 3 or 4 daily doses of VPA solution as sole or adjunctive therapy. Patients were consecutively recruited from March 2008 to January 2010.

Parents provided informed consent for their children, and the Ethics Committee of each institution approved the study.

On entry to the study, subjects were abruptly switched from solution to MR granule formulation of VPA at identical dosages, but their regimens were changed to twice daily. Concomitant medications remained unchanged. We evaluated VPA blood levels, treatment efficacy, tolerability, palatability, ease of administration, and compliance before switching (T0) and after 4 weeks of therapy (T1). Demographic and clinical data of each child were also collected.

Blood samples were collected after an overnight fast and before the morning dose and then centrifuged at 1500 ***g*** for 10 min; the plasma was separated and stored at −20°C until analysis. Serum VPA was measured by fluorescent polarization immune assay (Abbott Laboratories Valproic acid kit, North Chicago, IL, USA).

The efficacy of treatment was assessed by seizure frequency (number of seizures per month), seizure control rate (percentage of seizure-free patients), and EEG characteristics (normal; focal/generalized abnormalities).

The tolerability of treatment was evaluated by monitoring clinical adverse reactions (i.e. gastrointestinal symptoms, central nervous symptoms, appetite increase, hair change/loss, and rash) and abnormalities in selected laboratory values [platelet count, aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase (γ-GT), ammonia level, prothrombin time (PT), activated partial thromboplastin time, amylase, and lipase].

We analyzed the palatability of treatment in children older than 4 years of age, who were able to comply with the instruction of a palatability test. We obtained a score, asking children 'how much did you like the taste of this medication?' and encouraging them to indicate their preference by pointing to the appropriate face on a previously used facial hedonic scale that depicted various degrees of pleasure: 5 = really good; 4 = good; 3 = not sure; 2 = bad; and 1 = really bad (Fig. 1) (6–8). We indirectly assessed palatability even in parents, questioning them about the reaction of the child to the administration of the drug: 'On the basis of reaction/facial expression of your child, do you think that the medication is: pleasant = 3; not sure = 2; or unpleasant = 1?' (9).

We investigated the ease of administration, asking parents 'Do you sometimes have problems in giving the medication to your child because he refuses to take it or throws it up? (Yes/No)' (10).

The compliance of treatment was assessed in parents through an interview that comprised three questions: 'Was the medication missed in the past 2 days? (Yes/No)', 'Was the medication missed in the past week? (Yes/No)', and 'Was the medication missed in the past month? (Yes/No)' (10).

After 6 months, we examined the persistence to treatment in patients. Statistical analysis was performed with SPSS statistical package (version 17.0, SPSS Inc, Chicago, IL, USA). Normal distribution of the variables was verified with the Kolmogorov–Smirnov test. The results were expressed as means (±SD) for continuous variables and as absolute numbers/percentage for categorical variables. Comparisons between categorical data were evaluated by chi-square test and Fisher's test whereas continuous variables were compared using Student's *t* test. Statistical significance was defined as a *P* value 0.05.

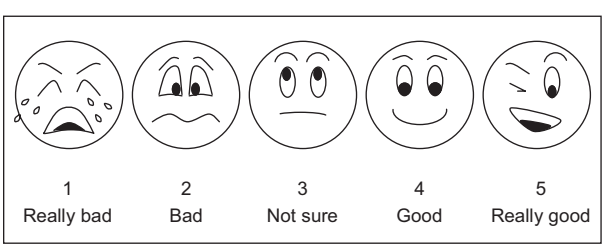

Figure 1. Facial hedonic scale used for palatability test in children.

Results

One hundred and twelve subjects were initially recruited. Out of them, four discontinued VPA MR granules before the second evaluation. The reasons for discontinuation of therapy were child dislike for MR granules ($n = 2$) and parent fear that the complete dose was not ingested with the food ($n = 2$). Therefore, the final analysis was performed on 108 patients (96.4%); their epidemiological and clinical data are reported in Table 1.

Comparing patients at T0 and T1, we observed no statistically significant changes in VPA blood levels, seizure frequency, seizure control rate, EEG characteristics, laboratory parameters, and clinical adverse reactions (Table 2).

Fifty-three children were judged to be able to comply with the instruction of the palatability test; their overall palatability score of MR granules was significantly higher than solution ($P < 0.05$) (Table 2). Also, the parents assigned a better palatability score to MR granules ($P < 0.05$) and reported significantly less troubles in giving medication to their children with MR granules ($P < 0.05$) (Table 2). Compliance was similar between patients at T0 and T1 (Table 2).

At 6-month follow-up, all 108 children continued to use MR granule formulation.

Table 1 Epidemiological and electroclinical characteristics of enrolled subjects

Characteristics	
Age (years)	6.7 ± 3.6
Sex	
Male	59 (54.6%)
Female	49 (45.4%)
Seizure type	
Focal	29 (26.9%)
Typical absence	31 (28.7%)
Generalized tonic–clonic	9 (8.3%)
Myoclonic	5 (4.6%)
Spasms	4 (3.7%)
Mixed	30 (27.8%)
Epilepsy type	
Idiopathic	
Generalized	49 (45.4%)
Focal	26 (24.1%)
Symptomatic	21 (19.4%)
Epileptic encephalopathy	12 (11.1%)
EEG	
Normal	38 (35.2%)
Abnormal	70 (64.8%)
Therapy	
Monotherapy	75 (69.4%)
Polytherapy	33 (30.6%)
Levetiracetam	9
Clobazam	6
Carbamazepine	4
Ethosuximide	4
Oxcarbamazepine	2
Phenobarbital	2
Topiramate	2
Zonisamide	2
Acetazolamide	1
Stiripentol	1
Seizure control (previous 3 months)	
Seizure free	89 (82.4%)
Not seizure free	19 (17.6%)

Data are expressed as mean ± SD, absolute numbers, and percentage.

Table 2 Study variables

	T0	T1	*P*
VPA blood levels (μg/ml)			
Patients in monotherapy	65.89 ± 14.26	68.48 ± 15.59	NS
Patients in polytherapy	67.62 ± 18.23	72.78 ± 12.48	NS
Tot	66.57 ± 15.85	68.96 ± 14.70	NS
Efficacy			
Seizure frequency	1.16 ± 3.01	1.02 ± 3.30	NS
Seizure control rate	82.4%	84.3%	NS
EEG characteristics			
Normal	38 (35.2%)	40 (37.0%)	NS
Generalized abnormalities	51 (47.2%)	49 (45.4%)	NS
Focal abnormalities	19 (17.6%)	19 (17.6%)	NS
Tolerability			
Adverse events			
Restlessness	6 (5.6%)	5 (4.6%)	NS
Aggressiveness	2 (1.8%)	3 (2.8%)	NS
Drowsiness	6 (5.6%)	4 (3.7%)	NS
Postural tremor	2 (1.8%)	3 (2.8%)	NS
Headache	4 (3.7%)	3 (2.8%)	NS
Learning difficulty	2 (1.8%)	3 (2.8%)	NS
Nausea and/or vomiting	10 (9.3%)	7 (6.5%)	NS
Diarrhea	3 (2.8%)	5 (4.6%)	NS
Appetite increase	15 (13.9%)	13 (12.0%)	NS
Hair change/loss	2 (1.8%)	1 (0.9%)	NS
Rash	2 (1.8%)	2 (1.8%)	NS
Laboratory values			
Platelet count ($\times 10^9$/l)	332.43 ± 87.59	325.45 ± 82.51	NS
PT (s)	12.21 ± 0.54	12.54 ± 0.87	NS
aPTT (s)	31.77 ± 5.23	33.41 ± 5.35	NS
Ammonia (μmol/l)	36.62 ± 9.34	34.23 ± 7.45	NS
ALT (U/l)	22.67 ± 5.36	24.56 ± 4.31	NS
AST (U/l)	21.84 ± 6.67	23.58 ± 8.42	NS
γGT (U/l)	24.75 ± 5.26	28.55 ± 5.97	NS
Amylase (U/l)	34.76 ± 7.69	37.26 ± 5.26	NS
Lipase (U/l)	13.54 ± 3.26	12.67 ± 4.13	NS
Palatability			
Palatability score in children (range 1–5)	2.09 ± 0.86	3.83 ± 0.96	<0.05
Palatability score in parents (range 1–3)	1.35 ± 0.60	2.45 ± 0.69	<0.05
Ease of administration			
Parents reporting troubles	74 (68.5%)	17 (15.7%)	<0.05
Compliance			
Missed medication, past 2 days	12 (11.1%)	9 (8.3%)	NS
Missed medication, past week	17 (15.7%)	14 (13.0%)	NS
Missed medication, past month	37 (34.3%)	31 (28.7%)	NS

Data are expressed as mean ± SD, absolute numbers, and percentage.
VPA, valproate; PT, prothrombin time; aPTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, γ-glutamyltransferase; NS, not significant.

Discussion

Our study demonstrates that the abrupt switch from solution to MR granule formulation of VPA is not associated with any significant change in VPA blood levels, efficacy, tolerability, and compliance of treatment; in addition, MR granules are more palatable and easier to administer than solution.

The palatability of a medication is of great value to achieve treatment objectives, especially in children. Indeed, an unpleasant tasting or a difficult to swallow preparation may affect the ease of administration and influence compliance and effectiveness (11). Therefore, children require appropriate pediatric dosage forms that simplify the administration, as pointed out even by the World Health Organization (12).

In line with the previous results obtained by Motte et al. (6), our data confirm the palatable property of VPA MR granule formulation and its positive influence on the convenience of use as the rate of the parents reporting troubles in the administration of VPA with MR granules was significantly lower than with solution. For its microsphere formulation, MR granules may be useful even in adults with difficulties in swallowing tablet formulation of VPA, as recently described (13).

Furthermore, in our study, MR granules were well tolerated because the incidence of adverse reactions between patients at T0 and T1 was similar and no subject required premature discontinuation to the study because of a treatment-related adverse event.

Moreover, at 6-month follow-up, all patients continued to use MR granules. This preference may be due not only to improved palatability or to simplified handling but also to the twice-daily regimen probably because it avoids to children the social stigma of taking medicines in public, for example at school, as suggested by some authors (3, 14). Even if the less frequent dosing should enhance compliance (15), we did not observe a significant improvement in compliance in our study; the compliance was good with both the treatments although it might be overestimated for self-report bias associated with interview.

When formulations are switched from a multiple to a twice-daily dosing, it is important to verify that desired plasma concentrations are attained. The consistency of VPA levels in our patients suggests that no dosage adjustment is required to ensure effective exposure, even in children on polytherapy, in whom inducer drugs may shorten VPA half-life (1). This finding is confirmed by the absence of deterioration in seizure frequency, seizure control rate, and EEG characteristics in our children. Thus, it is not necessary to evaluate VPA plasma level after switching from solution to MR granules.

In conclusion, our data indicate that VPA MR granules are as effective as solution, even after switching from multiple to twice-daily dosing without adjusting daily dosage. Besides, their convenience of use makes MR granules a reliable addition to the array of VPA formulation, particularly in children.

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Conflict of interest

This study was not supported by any grant or other funding sources. None of the authors has any conflict of interest to disclose.

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