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Actual Bioavailability of Divalproex Sodium Extended-release Tablets and Its Clinical Implications

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ABSTRACT

Divalproex sodium extended-release dosage form (divalproex-ER) has been promoted as innovative formulation for the treatment of epilepsy and manic disorders, and for migraine headache prevention, with the advantage of being dosing once a day. Due to a significant decreasing in the peak-trough fluctuation of plasma valproic acid levels, in comparison with the twice-daily dosing of conventional delayed-release formulations (divalproex-DR), concentration-dependent side effects would be prevented. However the main constraint for divalproex-ER usage is the need to be administered in a higher daily dose, because of its lower bioavailability, in order to prevent eventual breakthrough seizures when patients are switched from the twice-daily divalproex DR regimen. Taking into account free plasma drug levels, divalproex ER/DR relative bioavailability could be assessed as low as 75% in fasting condition. In order to overcome the need of increase divalproex-ER daily dose, maintenance of the twice-daily regimen is suggested. Divalproex-ER administered every 12 hours not only increases steady state trough concentration to a higher value in comparison with divalproex-DR, avoiding inefficacy of the treatment, but also achieves the safest manner to treat patients with valproic acid because of reaching practically a plateau profile of drug levels.

Key words: divalproex sodium, extended-release formulations, bioavailability.

RESUMEN

Real biodisponibilidad del divalproato de sodio en comprimidos de liberación prolongada y sus implicancias clínicas

Divalproato de sodio de liberación prolongada (*divalproex-ER*) es un producto innovador que ha sido promovido tanto para el tratamiento de la epilepsia y de los desórdenes maníacos como también para la prevención de la migraña, con la ventaja de poder administrarse una sola vez al día. Dado que la fluctuación de niveles plasmáticos de ácido valproico resulta menor que la originada por la administración dos veces al día del producto convencional de liberación retardada (*divalproex-DR*), se estarían previniendo los efectos secundarios dependientes de la concentración del fármaco. Sin embargo, y considerando la menor biodisponibilidad del producto, el uso de *divalproex-ER* tiene el principal inconveniente de necesitar una mayor dosis diaria a los efectos de evitar una eventual reaparición de crisis cuando los pacientes cambian de tratamiento desde *divalproex-DR*. Teniendo en cuenta los niveles plasmáticos libres del fármaco, la biodisponibilidad relativa *divalproex ER/DR* podría afirmarse que sea aún más baja, tanto como 75% cuando los estudios son realizados en ayunas. A los efectos de no incrementar la dosis diaria de *divalproex-ER* se sugiere mantener un régimen de administración cada 12 horas. La administración de *divalproex-ER* dos veces al día no sólo incrementa las concentraciones de valle, respecto a *divalproex-DR*, sino que logra un perfil de niveles de ácido valproico prácticamente de meseta, lográndose así un tratamiento eficaz y con la mayor seguridad para los pacientes.

Palabras claves: divalproato de sodio, medicamento de liberación prolongada, biodisponibilidad.

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INTRODUCTION

Valproic acid and its derivatives are indicated for the treatment of different types of epilepsy, for the treatment of acute manic or mixed episodes associated with bipolar disorder, and for prophylaxis of migraine headaches. Particularly, a complex constituted by a 1:1 molar relationship of valproic acid and sodium valproate (divalproex sodium) has recently reached some preference in the market. Divalproex sodium is marketed by Abbott Laboratories as conventional delayed-release (DR), enteric-coated, dosage forms (Depakote tablets, and Depakote sprinkle capsules), and as innovative extended-release (ER) tablets (Depakote ER). Both tablets (divalproex-DR and divalproex-ER) are supplied in dosage strengths containing divalproex sodium equivalent to 250 and 500 mg of valproic acid, and the DR form is supplied containing divalproex sodium equivalent to 125 of valproic acid as well. In Uruguay and Argentine the brand names for divalproex tablets are Valcote and Valcote ER.

Divalproex-ER has the advantage of diminishing the peak-trough fluctuation (PTF) of plasma valproic acid concentrations at the steady state after multiple dose administration, and hence its concentration-dependent side effects may be substantially reduced. Furthermore, technological properties of the dosage form allow it to be administered once a day, making more comfortable its use by the patients. Information about PTF is in someway confusing, on the one hand the peak-to-trough fluctuation in plasma valproate concentrations is claimed to be 10-20% lower than that of regular Depakote given twice a day,[1] and on the other hand a reduction of 42-48% in this parameter was obtained when the ER product is given once-daily in comparison with the twice-daily DR product administration.[2] We are of the opinion that the confusion comes from that PTF is reported as a percentage of the steady state average plasma drug concentration, and then the former data reports the difference of absolute values while the later gives the ratio.

However, the main constraint of divalproex-ER is its lower bioavailability in comparison with divalproex-DR. This fact is highlighted by the manufacturer, which gives guidance for changing the total daily dose when the treatment of patients is converted from DR to ER regimen. We will return on this point in next sections.

Before going deeper inside the bioavailability it should be remembered that valproic acid has a saturable plasma protein binding, which produces a nonlinear relationship between the total valproate concentration in plasma and the dose administered.[3,4] Conversely, free plasma drug concentration is linearly related with the dose, and the free drug clearance seems to be constant throughout the therapeutic concentration range. The free fraction of valproate in plasma increases from 10%, at 40 mg/L of total plasma concentration, to 18.5% at 130 mg/L.[1]

BIOAVAILABILLITY OF DIVALPROEX EXTENDEND-RELEASE TABLETS

It has been reported that the absolute oral bioavailability of divalproex-ER is 89%, while the oral absorption is practically 100% for divalproex-DR.[5] Steady state 24-hour average plasma valproate concentration after once-daily administration of divalproex-ER was between 81 and 89% (fasting and non fasting conditions respectively) of that obtained after twice-daily dosing of divalproex-DR.[6] A meta-analysis of divalproex-ER once-daily/divalproex-DR twice-daily relative bioavailability across five multiple-dose studies, under different meal conditions, revealed a mean value for AUCss (area under the steady state total plasma drug concentration curve) ER/DR ratio of 0.89.[7]

The last two reports could be summarized saying that divalproex-ER (given once-daily) yields lower amount of drug absorbed than divalproex-DR (given twice-daily): approximately 10% less when they are co-administered with meals and 20% less when they are given in fasting condition, both at the same daily dose. However, these studies compared average total drug levels in plasma assuming constant clearance, but, as it was already said, the clearance for total drug is not constant due to the variable plasma protein binding of valproic acid. For this reason we have recalculated the ratio of steady state average valproic acid concentrations taking into account free plasma drug levels and hence we have arrived to a more confident relative bioavailability factor.

Equation 1 relates steady state average plasma drug concentrations (Cssav), reached after equal multiple daily dosing of both formulations (DR and ER), with the fraction of dose absorbed (F) and with the actual drug clearance (CL).

$$\frac{Cssav_{ER}}{Cssav_{DR}} = \frac{(F_{ER} * CL_{DR})}{(F_{DR} * CL_{ER})} \qquad (1)$$

Being the unbound drug clearance a constant, the ratio of average free plasma concentrations ($C_{free}ssav$) becomes a reliable estimator of drug-product relative bioavailability (Equation 2).

$$\frac{C_{free}ssav_{ER}}{C_{free}ssav_{DR}} = \frac{F_{ER}}{F_{DR}} \qquad (2)$$

In order to calculate free plasma valproic acid concentration Equation 3 was used. Free fraction of valproate in plasma (f) was deduced from the mass balance of a 1:1 molar relationship for the valproate – plasma protein complex.

$$f = \frac{[D]}{[D_t]} = \frac{(Kd + [D])}{[([P_t] + Kd + [D])} \quad (3)$$

Being,
Kd: dissociation constant for the drug-protein complex
[D]: free plasma drug concentration
$[D_t]$: total plasma drug concentration
$[P_t]$: total plasma protein concentration.

Feeding the equation with valproic acid binding data a close to the real molar concentration for the total plasma protein is obtained, which validates the assumption of a 1:1 molar relationship for drug-protein binding. Equation 4 gives the values for Kd and ($[P_t]$+Kd) parameters in milligram per liter.

$$\frac{[D]}{[D_t]} = \frac{(15.2 + [D])}{(188 + [D])} \quad (4)$$

Mean plasma valproic acid concentrations obtained in the literature[6,7] were comprised within the commonly assumed therapeutic range for this substance (50-100 mg/L of total drug). If we take 75 mg/L as the mean plasma concentration for divalproex-DR, 67 mg/L (89%) and 61 mg/L (81%) could be the values for divalproex-ER in both non-fasting and fasting condition respectively. Using equation 4 the following free plasma valproic acid concentrations were obtained: 9.3, 7.9 and 6.9 mg/L. Consequently, divalproex-ER/divalproex-DR relative bioavailabilities of 85% (7.9/9.3) and 74% (6.9/9.3) should be assessed.

According to Duta et al.,[8] valproic acid absorption from divalproex-ER starts immediately after administration and a slow process with constant rate is followed for more than 20 hours. During such an extended period of time may be part of the drug was not even released or was released in portions of the gut where absorption is not favored. Both possibilities could give rise to a loss of bioavailability. This presumption is supported by the fact that food co-administration increases the ER formulation bioavailability. Because of gastrointestinal transit retardation when foods are given, tablets might be more retained in appropriate zones of the gut and hence the efficiency of the absorption process could be improved.

CONVERSION FROM DELAYED-RELEASE TO EXTENDED-RELEASE DOSAGE FORM. A CLINICAL POINT OF VIEW

It was suggested that patients whose treatments are switched from twice-daily divalproex-DR to once-daily divalproex-ER should increase 8 to 20% the dose they are receiving,[1,7] in order to compensate the difference of bioavailability between both formulations. We estimate the increasing of dose could be made up to 25% according to our recalculated relative bioavailability (1/0.8 = 1.25).

In our opinion, changes in the daily dose would not be necessary if divalproex-ER were also administered twice a day. As it was recently reported a twice-daily dosing of divalproex-ER yielded a degree of PTF in valproic acid concentration even smaller than that obtained with conventional divalproex-DR given every 6 hours.[9] So, it could be inferred that even though twice-daily divalproex-ER multiple dose administration yields a lower mean steady state plasma drug concentration than that after the same twice-daily divalproex-DR dosing, its trough concentration rises to a higher value. Hence, eventual breakthrough seizures caused by a switch from formulations would be prevented. Furthermore, divalproex-ER given twice-daily assures not only efficacy but also increases the safety of the treatment due to a strong reduction in the steady state peak plasma valproate concentration.

In conclusion, despite having lower bioavailability than conventional delayed-release tablets the same-daily-dose every-12-hour extended-release divalproex sodium administration enhances notably the performance of valproic acid therapy, keeping the patients free from seizures and reducing the risk of side effects. Then, taking into account the need for dose changing respect the twice-daily divalproex-DR regimen, a more comfortable use of once-daily divalproex-ER dosing should not be maintained as the main issue for this formulation. Instead, a more effective and safer way to treat the patients, maintaining both the dose and the regimen of administration they are receiving, makes the switch from conventional to extended-release dosage forms a more reasonable goal. Due to the lack of the strength of 125 mg for the extended-release formulation, its daily dose should be higher than that of the delayed-release form just by this amount of drug when necessary. For instance, a DR dose of 1125 mg given twice daily should be switched to a ER dose of 1250 mg under the same regimen of administration.

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