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Pharmacokinetic variability of valproate during pregnancy – Implications for the use of therapeutic drug monitoring

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ABSTRACT

Background and purpose: Use of valproate (VPA) in women of childbearing age is restricted due to dose-dependent risk of teratogenicity. The purpose of this study was to characterise pharmacokinetic variability of VPA in pregnancy, and discuss use of therapeutic drug monitoring (TDM) as guidance to exposure in women.

Method: Measurements of trough total and unbound VPA concentrations before, during and after pregnancy, at assumed steady-state were collected from the TDM-database (2006–2016) at the National Center for Epilepsy in Norway. Additional clinical data were obtained from the Oppland county Perinatal Database (1994–2011).

Results: Data from 51 pregnancies in 33 women aged 19–40 years were included. Each woman underwent 1–4 pregnancies, and 1–7 measurements per pregnancy were performed. The variability in total concentration/dose (C/D)-ratios between women was 13-fold, and intra-patient variability extensive. Total C/D-ratios were reduced by 46% from before pregnancy to third trimester (0.48–0.29 μmol/L/mg). Unbound concentrations of VPA were only requested in 10% of the pregnancies. Repeated measurements from two pregnancies in one women revealed increased unbound concentration of VPA during pregnancy. There were 19 with idiopathic generalized epilepsy and two focal based on clinical data from 21 women and 38 pregnancies; 1 major congenital malformation was noted.

Conclusion: There is pronounced pharmacokinetic variability of VPA during pregnancy. Unbound concentrations are rarely requested. TDM should be used by measurements of both total and unbound concentrations since total concentrations may be misleading for efficacy and fetal exposure of VPA.

1. Introduction

The use of valproate (VPA) in women of childbearing age is restricted, because of the risk of teratogenicity and possible cognitive consequences (European Medicines Agency, 2014, 2017; Tomson et al., 2015a,b; Tomson, 2015, Perucca et al., 2015, Bromley et al., 2016). In some women with generalized epilepsy VPA may be the most or the only effective antiepileptic drug (AED) (Marson et al., 2007). VPA is also widely used in psychiatric conditions (Baftiu et al., 2016). The risk of malformations is higher with VPA than with other AEDs, it is dose-dependent, and doses < 700 mg/day carry lower risk (Tomson et al., 2011, 2015a). A dose response effect is also probably present concerning IQ decline in VPA exposed children (Meador et al., 2009). An increased risk of autism spectrum disorders has also been documented in a population-based study in the offspring of mothers who used VPA during pregnancy (Christensen et al., 2013). There is, however, a 10-fold variability in serum concentration and dose relationships with such doses (Johannessen Landmark et al., 2017). Major physiological changes occur during pregnancy, affecting the pharmacokinetic processes, from absorption and distribution to metabolism and excretion. The volume of distribution, blood flow and capacity for elimination all increase, while albumin and thus protein binding may decrease during pregnancy (Tomson et al., 2013). As VPA readily crosses the placenta, the measured maternal serum concentration can

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be an indicator of fetal exposure of the drug. Since VPA is a highly protein bound drug, it is assumed that measurement of the unbound concentration is likely to be a better marker of exposure than the total concentrations. This assumption has been based on theoretical aspects and in vitro studies (Perucca and Crema, 1982, Yerby et al., 1992, Johannessen, 1992). In addition, one prospective clinical study from the 1980′s in nine women using VPA where total and unbound concentrations and albumin were measured monthly, showed that protein binding changes during pregnancy (Koerner et al., 1989). Recommendations on therapeutic drug monitoring (TDM) from the International League Against Epilepsy and other reviews thus suggest that both unbound and total serum concentrations of VPA should be measured during pregnancy (Patsalos et al., 2008, 2017, Aguglia et al., 2009, Johannessen Landmark et al., 2012a, 2016, Tomson et al., 2013, Deligiannidis et al., 2014). Systematic data on pharmacokinetic variability and changes during pregnancy are not available from the large international pregnancy registries. Various clinical studies have demonstrated that extensive changes may occur, and consequently increase in clearance through pregnancy of other commonly used AEDs (lamotrigine, levetiracetam, oxcarbazepine and topiramate) (Aguglia et al., 2009, Tomson et al., 2013, Johannessen Landmark et al., 2012a). There is a need for more research in this regard also for other AEDs. Based on the current knowledge of risks of malformations in relation to dose and cognitive decline in offspring, it seems timely to re-evaluate these aspects in a clinical setting. The purpose of this study was to characterise pharmacokinetic variability of VPA in pregnancy, and to discuss clinical implications of how TDM should be used as guidance to exposure in women.

2. Material and methods

2.1. Study material

2.1.1. Data from the TDM database

Anonymized retrospective data from a TDM-database (2006–2016) were used, covering patients admitted to the National Center for Epilepsy, as well as outpatient samples from all parts of the country. Inclusion criteria: Women using VPA in an oral formulation (tablets or retard formulation from Desitin, Germany) with at least one serum concentration measurement at assumed steady-state (no dosage adjustments last week), trough values from samples taken drug-fasting in the morning, before intake of the morning dose, as is standard in the country, with information on pregnancy and the dose of VPA provided on the request form. A baseline value (the last measurement up to one year before pregnancy), all samples during pregnancy (first, second and third trimester) including measurement of unbound VPA concentrations, and post-partum (the first available measurement after giving birth, days to several weeks) were noted.

Drug analyses were routine measurements with validated methods at the Section for Clinical Pharmacology, National Center for Epilepsy, Oslo University Hospital, as measured by immunoassay (COBAS C111, Roche Diagnostics Switzerland, interval for measurements 5–1040 μmol/L). The reference range for total concentration of VPA is given as 300–700 μmol/L, while the reference range for unbound concentrations usually is given as the free fraction of VPA *100%, i.e. that the unbound concentration is about 10% of the total concentration (Patsalos et al., 2008).

2.1.2. Data from oppland county perinatal database (OPD)

OPD contains prospectively collected data regarding 95% of pregnancies in Oppland county. Out of 166 women with a validated epilepsy diagnosis during 1989–2011, data on women who used VPA were included (Farmen et al., 2015) as an additional source to evaluate clinical information such as seizure type, frequency, seizure freedom, comedication, dosage adjustments and pregnancy outcome (major malformation) and use of TDM, collected from medical records. The data were anonymized, and date of serum concentration measurement, year of birth, dose and serum concentration were used to avoid duplication of data from the TDM-database. The study was approved by the Regional Ethics Committee.

2.2. Calculations

2.2.1. Serum concentration and dose relationships

Serum concentrations, doses and concentration/dose (C/D)-ratios are presented as mean values, and standard deviation (SD) and range (minimum-maximum values), were used to express variability. The C/D-ratio may be used in retrospective TDM-based studies as a surrogate for inverse oral or apparent clearance (CL/F). Changes in C/D-ratios may serve as an indication of pharmacokinetic variability, which includes all host factors contributing to variability in pharmacokinetics and consequently efficacy/tolerability among patients (Johannessen Landmark et al., 2012b). A decrease in the C/D-ratio mirrors an increase in clearance, based on the following equation: CL/F (mL/kg/min) = daily dose (mg/kg)/C_{ss} (mg/Lx1000) × 1440 as utilized in a previous publication (Johannessen Landmark et al., 2012a,b), where oral clearance is CL/F; CL = clearance, F = oral bioavailability, C_{ss} = serum concentration at steady-state, 1440 = min/24 h. C/D-ratios for all pregnant women, from the TDM database and OPD were combined and compared from baseline, all trimesters and post-partum.

The free fraction (unbound concentration/total concentration) is presented as the percentage unbound (unbound concentration/total concentration * 100). As a practical approach to express pharmacokinetic variability based on the TDM-data available, the relationship between the maximum and minimum measured serum concentrations between women, is presented according to our previous publication (Johannessen Landmark et al., 2017).

2.2.2. Statistical analyses

For statistical analyses IBM SPSS Statistics version 22 (SPSS Inc, Chicago, IL, USA) was used. Univariate analysis was used for linear regression. To compare changes in C/D-ratios during pregnancy a non-parametric test, Friedmans' two-way analysis of variance by ranks, was used. A p-value of < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

In total, data from 51 pregnancies in 33 women with epilepsy were included; 1–4 pregnancies per woman, mean age 29 years (range 19–40) (Tables 1 and 2). There were 33 women (65%) who used VPA in monotherapy, and one third used 1–2 concomitant AEDs. Lamotrigine was the most commonly used comedication (Table 1).

Data regarding use of VPA from OPD with additional clinical information are shown in Table 2, including 38 pregnancies in 21 women, mean age 27 years (19–36), seizure type and frequency. Twenty-three were seizure free (60%), and 11 had one or more seizures during pregnancy. In seven cases (18%) the dosage was increased during pregnancy, by 33–100%. One major malformation (cleft palate) was noted at a low dosage and low serum concentration (Table 2).

3.2. Variability in C/D-ratios

There was extensive variability in dose and total serum concentration relationships, as shown in Fig. 1a. The overall variability in total C/D-ratio between women was 13-fold, and 8-fold in the low-dose interval < 700 mg/day (n = 25). The variability between women with at least three measurements (n = 15) was extensive (1.21–3.23). Comedication with enzyme inducers (carbamazepine/phenytoin) were only used in four patients and thus not analyzed separately and did not affect the variability in C/D-ratios in total when excluded.