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A physiologically based pharmacokinetic model for Valproic acid in adults and children

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ABSTRACT

Valproic acid is an anti-convulscant drug that is widely used in the treatment of different types of epilepsy and since its introduction the clinical use has increased rapidly both as a sole agent and in combination therapies. The mechanism of action has been linked to blockade of voltage-dependent sodium channels and potentiation of GABAergic transmission. The most widely used route of administration of Valproic acid is oral, although it can also be given intravenously and rectally and its pharmacokinetics has been studied extensively. The aim of this work was to develop a physiologically based pharmacokinetic model for plasma and tissue/organ prediction in children and adults following intravenous and oral dosing of Valproic acid. The plasma/tissue concentration profile will be used for clinical trial simulation in Dravet syndrome, a rare form of epilepsy in children where the combination of Valproic acid, stiripentol and clobazam has shown remarkable results. A physiologically based pharmacokinetic model was developed with compartments for gut lumen, enterocyte, gut tissue, systemic blood, kidney, liver, brain, spleen, muscle and rest of body. System and drug specific parameters for the model were obtained from the literature from *in vitro* and *in vivo* experiments. The model was initially developed for adults and scaled to children using age-dependent changes in anatomical and physiological parameters and ontogeny functions for enzyme maturation assuming the same elimination pathways in adults and children. The results from the model validation showed satisfactory prediction of plasma concentration both in terms of mean prediction and variability in children and adults following intravenous and oral dosing especially after single doses. The model also adequately predicts clearance in children. Due to limited distribution of Valproic acid into tissues, the concentration in plasma is about 8–9 times higher than tissues/organs. The model could help to improve clinical outcome in the treatment of Dravet syndrome through dose optimisation.

1. Introduction

Valproic acid (VPA) is an anti-convulscant drug that is widely used in the treatment of different types of epilepsy including simple and generalised epilepsies (Levy et al., 1990). Since it was introduced over 50 years ago, its clinical use has increased rapidly both as a sole agent and in combination with other anti-epileptic drugs. The mechanism of action of VPA is still unknown although it has been linked to blockade of voltage-dependent sodium channels and potentiation of GABAergic transmission (Suzuki et al., 2011). The most widely used route of administration of VPA is oral, although it can also be given intravenously and rectally. Oral formulations include syrup, oral solutions, plain tablets, capsules, enteric-coated tablets and slow release formulations (Zaccara et al., 1988).

The pharmacokinetics (PK) of VPA has been investigated using different formulations. The absorption of VPA is rapid from the gastrointestinal tract, the maximum concentration in plasma is reached within 4 h of administration of a tablet formulation (Zaccara et al., 1988). Absorption after oral administration from the gastrointestinal tract is also complete as with other extravascular administrations (Bialer et al., 1985; Zaccara et al., 1988). VPA distributes mainly into the extracellular space with minor tissue uptake and low apparent volume of distribution (Klotz and Antonin, 1977). The volume of distribution at steady state (V_{ss}) is around 10*L* (8.4 ± 3.4*L* (Klotz and Antonin, 1977), 12.6 ± 1.2*L* (Nitsche and Mascher, 1982) and 8.2*L* (6.9 – 10*L*) (Bryson et al., 1983)). The metabolism of VPA is complex and it is mainly by glucuronidation and oxidation, and more than 15 metabolites of VPA have been detected in urine, these accounted for 85% ± 19.5% of the

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administered dose with almost no excretion of the unchanged drug (Levy et al., 1990). Glucuronidation is the most important route for the elimination of VPA, it accounts for 30–70% of the administered dose (Argikar and Remmel, 2009). VPA is glucuronidated by UGTs to form acyl glucuronides that are excreted in urine. Mitochondria β-oxidation is another important route for the elimination of VPA, it accounts for 20–40% of the administered dose (Argikar and Remmel, 2009). CYP450 enzymes (CYP2A6, 2B6 and 2C9) are responsible for elimination of about 10% of the administered dose (Argikar and Remmel, 2009; Levy et al., 1990). The half-life of VPA is around 12 h in adults (Klotz, 1977; Klotz and Antonin, 1977; Nitsche and Mascher, 1982; Perucca et al., 1978a; Perucca et al., 1978b). VPA is highly bound (over 90%) mostly to albumin in plasma: two binding sites have been identified on the albumin molecule for VPA binding (Zaccara et al., 1988). The binding of VPA in plasma is saturable with the free fraction of the drug higher at high total plasma concentration and there have been a number of attempts in the literature to characterise the non-linear binding kinetics of VPA (Cloyd et al., 2003; Scheyer et al., 1990; Suzuki et al., 2011; Ueshima et al., 2009, 2011). Although VPA is considered to be generally safe, it has been associated with rare but fatal hepatotoxicity which is associated with a number of risk factors (Ho et al., 2003). Although the mechanism of the toxicity remains unknown it has been associated with one of the metabolites: 4-ene-VPA which is produced via CYP450 enzymes (Ho et al., 2003; Levy et al., 1990; Sadeque et al., 1997). Therapeutic drug monitoring is therefore often used in the clinical use of VPA to monitor plasma concentration, especially free plasma concentration, to prevent toxicities.

In a clinical study, a remarkable result was achieved by a combination of VPA, stiripentol (STI) and clobazam (CLB) in the treatment of Dravet Syndrome (DS) (Chiron et al., 2000). DS also known as severe myoclonic epilepsy in infants is a rare form of epilepsy that affects at least 1 in 40,000 children up to the age of 7 years and accounts for about 7% of severe forms of epilepsy in children under the age of 3 years (Hurst, 1990; Morse, 2011). DS is associated with serious deleterious effects on cognitive and motor development and the seizures associated with DS are known to be some of the most resistant to conventional therapies. The effectiveness of the combination of VPA, STI and CLB represents an important breakthrough in the treatment of DS.

The aims of this work were to develop a physiologically based pharmacokinetic model (PBPK) for VPA to predict plasma and tissue concentration in adults and children and to investigate changes in plasma and tissue concentrations with age. This work forms part of the CRESim (Child Rare Euro-Simulation) project designed to investigate the use of modelling and simulation in the development of drugs for the treatment of rare diseases. In this case the focus is on DS and the drugs under investigation are CLB, STI and VPA. The PBPK model developed for the prediction of plasma and tissue concentrations of VPA in the present study will be used in combination with the PBPK model developed for STI and CLB and combined with DS disease model developed under other work packages to obtain a PBPK-PD model for clinical trial simulation.

2. Methodology

The approach used in the development of a PBPK model for adults and children is to develop and validate the model first in adults and then scale to children using age-dependent changes in anatomical and physiological functions such as organ/tissue flows and volumes and enzyme maturation functions. This is similar to a workflow published recently to support the paediatric research and development using a PBPK model and Lorazepam as a case study (Maharaj et al., 2013).

2.1. PBPK model development and assumptions

The PBPK model developed for VPA is made up of 10 compartments: gut lumen, enterocyte, gut tissue, systemic blood, kidney, liver, brain, spleen, muscle and rest of body. The rest of body compartment is used to account for mass balance of the system. Tissues/organs of the PBPK model were modelled using flow limited assumption described using Eq. (1)

$$V_T \frac{dC_T}{dt} = Q_T \left(C_b - \frac{C_T}{K_{p,T}} \right) \quad (1)$$

where V_T, C_T, Q_T and $K_{p,T}$ are the volume, concentration, blood flow, tissue/blood concentration ratio for the different tissues and C_b is the systemic blood concentration. For intravenous dosing, the drug is added directly to the systemic blood compartment and for oral dosing the drug is added to the gut lumen compartment from where it is absorbed by a first order process via the gut wall and the liver into the systemic circulation. It was assumed that VPA is metabolised by glucuronidation, β-oxidation and CYP450 enzymes. Glucuronidation of VPA is assumed to be by UGT2B7 and it occurs in the gut, kidney and liver (Argikar and Remmel, 2009; Soars et al., 2002). β-oxidation and CYP450 metabolism take place in the liver. It was assumed that VPA is metabolised by β-oxidation into 2(E)-ene-valproic acid (2(E)-ene-VPA) and by CYP2C9 into three metabolites: 4-ene-valproic acid (4-ene-VPA), 4-hydroxyl valproic acid (4-OH VPA) and 5-hydroxyl valproic acid (5-OH VPA) (Levy et al., 1990; Sadeque et al., 1997). The saturable non-linear binding of VPA to plasma albumin was accounted for by a two site binding model taken from the literature (Cloyd et al., 2003).

2.2. System parameters

Systems parameters for adults (assumed to be 18–20 years old and 70 kg weight) were obtained from the literature (Valentin, 2002). These include organ/tissue weights and volumes, cardiac output (CO), body surface area (BSA), height (HT), body weight (BW) and haematocrit (HCT). Table 1 shows organ/tissue volumes and blood flows for adults.

2.2.1. Drug specific parameter

Tissue/blood concentration ratios (K_p) for the tissues were predicted using the equations proposed by Rodgers and Rowland and

Table 1
Organ/tissue volumes (V), blood flows (Q) and tissue/blood concentration ratio (K_p) obtained using Rodgers and Rowland equation for different tissues/organs in adults.

Parameters	Organs/tissues								
	Systemic blood	Kidney	Liver	Gut	Enterocyte	Brain	Spleen	Muscle	Rest of body
V (L)	5.3	0.31	1.8	1.7	0.12	1.45	0.15	29	–[a]
Q (L/h)	356.31[b]	79.5	25.38	54.6	21.38	46.8	11.7	66.3	–[c]
K_p	–	0.32	0.23	0.36	–	0.17	0.25	0.52	0.40

[a] $70 - \Sigma V_T$.
[b] Cardiac output.
[c] $CO - \Sigma Q_T$.