

## Antiepileptic drugs: Energy-consuming processes governing drug disposition

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### 1. ABSTRACT

Diffusion is not the main process by which drugs are disposed throughout the body. Translational movements of solutes given by different energy-consuming mechanisms are required in order to dispose them efficiently. Membrane transportation and cardiac output distribution are two effective processes to move the molecules among different body sites. Gastrointestinal-blood cycling constitutes a supplementary way to regulate the distribution of molecules between the non-hepatic organs and the liver. Any change in the relative supply of drug molecules among eliminating organs could modify their clearance from the body. Either the nonlinear phenytoin (PHT) pharmacokinetic response or the influence that carbamazepine (CBZ) exerts on PHT exposure could be explained throughout their efflux transporter inducer abilities. Cardiac output distribution difference between the individuals might also explain the dual CBZ-over-PHT interaction response. Finally, valproic acid (VPA) pharmacokinetics can be understood by adding to these mechanisms of transportation its ability to cross the mitochondrial membrane of the hepatocyte.

### 2. BASIC PRINCIPLE FOR THE CORPORAL DRUG MOVEMENT

Diffusion is not the responsible mechanism by which drugs can enter and be disposed throughout the body. As it was pointed out by Treybal (1980) (1), the solute of a concentrated solution of sodium chloride placed in a cylinder of 0.75 m high and 1.5 m of diameter would invade the same volume of pure water placed above it, and homogenize the concentration in the total volume of solvent in 28 years. However, a simple agitation of 22 rpm could equilibrate the system in just 1 minute. Then, apart from the thermodynamic force governing the diffusion of solute, some supplementary energy must be introduced in order to move it efficiently. Drug release from solid pharmaceutical forms needs the energy contained inside the formulation to promote the dissolution of the active ingredient into the gastrointestinal fluids after their administration to the individuals. In the same way, the energy provided by the peristaltic movement of the gastrointestinal tract is required in order to approximate the molecules of drug to the membrane of the mucosa cells. To cross the membranes and cytoplasm of such cells, energy is

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also consumed, allowing the transportation of substances from the apical to the basal sites of the mucosal barrier. Once at the interstitial space, molecules continue flowing towards the rest of the body, either by lymphatic or blood vessels, propelled by the cardiac pump or muscular contraction respectively. In sum, translational movements of solutes given by different energy-consuming mechanisms are required not only for allowing drugs to reach their targets but also for allowing nutrients and oxygen to maintain the human organism alive.

### 2.1. Membrane transporters

Either in favor or against a concentration gradient, carriers (2) can facilitate the diffusion of molecules from one site to the other of a membrane. If such drug movement is against a concentration gradient, some consumption of energy is needed. Protein transporters are continuously synthesized and destroyed according to a characteristic turnover which also requires energy (3). Transportation through one or more membranes could save the molecule from an extensive enzymatic biotransformation, and hence its clearance from the body could be diminished. Conversely, drug molecule could be transported to a more active metabolic site and then its clearance increased.

Some drugs are substrates of one type of membrane carrier called efflux transporter, which drives the molecules outside the cells. Among these transporters, P-glycoprotein (Pgp) and multidrug-resistance-associated protein 2 (MRP2) were revealed as relevant for some antiepileptic drugs (4-5).

Being the isozyme CYP3A4 responsible for the major metabolic pathway of carbamazepine (CBZ) (6-7), and considering its abundant intestinal expression (8), it is reasonable to forecast an increased clearance when efflux transportation, both at the apical membrane of enterocytes and at the hepatobiliary membrane, becomes favored. Conversely, since CYP2C9 and 2C19 are more abundant at the hepatocyte (6-7, 9), phenytoin (PHT) clearance would be diminished once the expression of Pgp and/or MRP2 is induced. These events were theoretically envisaged in a previous paper (10) in order to postulate an alternative mechanism for understanding the metabolic autoinduction of CBZ and the Michaelis-Menten kinetics of PHT. Their sole role as efflux transporter inducers would explain consistently their particular pharmacokinetic behavior.

### 2.2. Cardiac output distribution

Unlike carriers located across the membrane that connect two sites, blood flowing within the cardiovascular apparatus connects several tissues and the drug could reach them according to the fraction of cardiac output destined to each site. So, the energy consumed by the heart, pushing the blood through the vessels, is distributed throughout the circulatory system according to the diameter of the arteries (11). After each cycle, the dissolved molecules pass by each organ in a determined fraction of the total circulating amount. This fraction of drug mass determines its distribution among the organs and its clearance from the body (12-13).

Cardiac output distribution ruled, in some way, the pharmacokinetic difference found between sexes, between physical activity and resting states, and between different physiopathological states of the cardiovascular system (14). As it has been reported recently, blood flow redistribution after graft implantation in renal transplanted patients could determine the clearance of immunosuppressant agents such as cyclosporine (15) and tacrolimus (16).

Both sexes show differences in muscular mass. Such differences determine a higher cardiac output fraction delivered to the splanchnic region of the body (excluding the liver) in female than in male subjects (17), and then, a higher intestinal clearance of drugs would be foreseen in women. Hepatic relative blood flow is quite constant among individuals and in different physical activity states, since the essential function of the liver must be preserved by means of the appropriate oxygen supply (14). When drugs are highly cleared by the intestine (CBZ), a significant steady state plasma concentration difference could be found between sexes (lower in woman) after the administration of the same daily dose to both genders (18). Conversely, when drugs are slightly cleared by the intestine, but mainly by the liver (PHT), significance in such sex plasma concentration difference might not be reached (19).

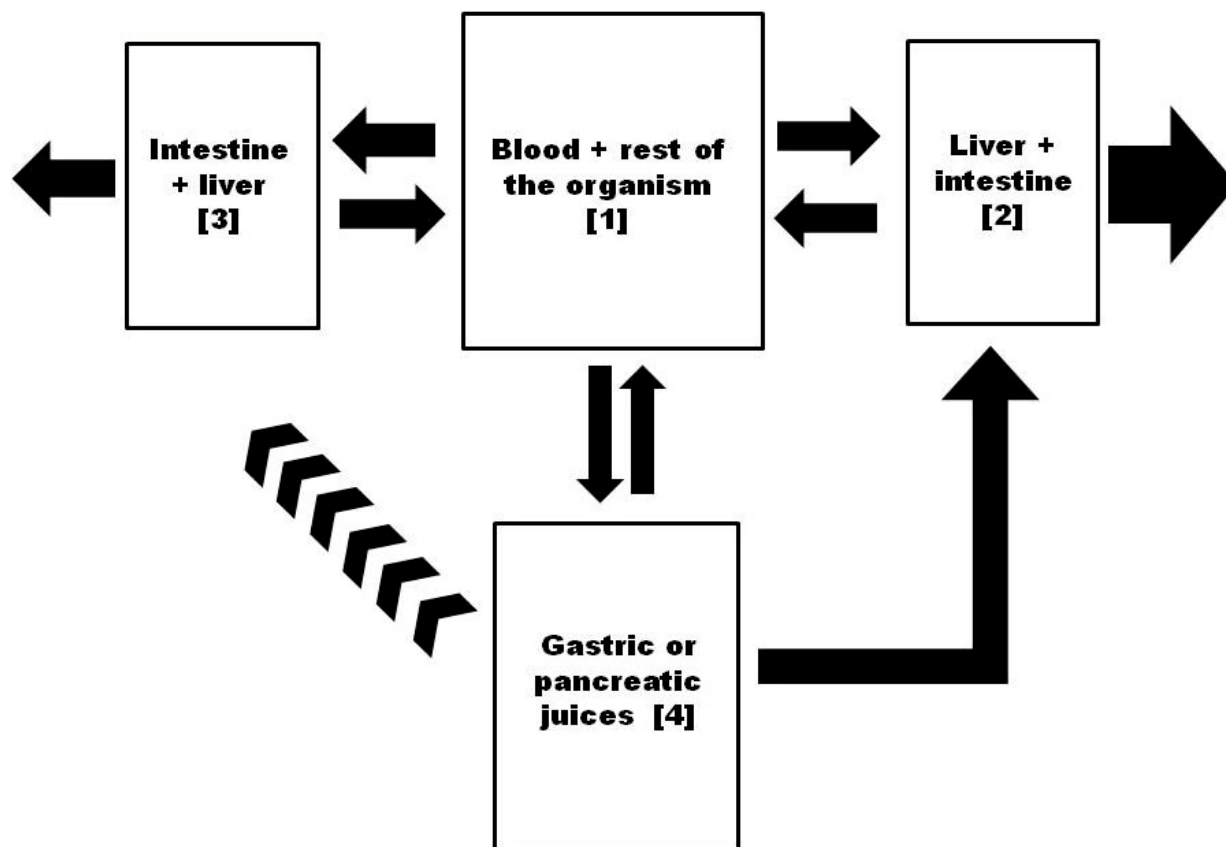
### 2.3. Gastrointestinal-blood cycling

Enterohepatic circulation is usually referred as the main mechanism by which drugs could be reabsorbed once they are secreted to the gastrointestinal tract. However, other fluids apart from the bile are secreted to the gastrointestinal lumen such as pancreatic and gastric juices. Independently of what efflux transporters are expressed in both the gastric mucosa and the apical membrane of acinar pancreatic cells (40-42), ionizable drugs could be highly excreted from plasma to a more alkaline or more acidic fluid (43). The efficiency of solute transportation to the gastrointestinal tract is determined by the cardiac output and the blood flow fraction destined to both organs of the splanchnic region (stomach and pancreas).

### 2.4. Drug distribution throughout the splanchnic organs

Figure 1 shows a simple compartmental model where blood and the whole organism are contained in compartment 1, except for the liver, the intestine, and the stomach or the pancreas, which are placed in compartments 2, 3, and 4, respectively. Arrows represent first order rate constants for the mass transferences between compartments, and the dashed arrow (from 4 to 3) means intermittent pulses of drug delivery. If a drug was extremely accumulated in compartment 4, each time the compartment 3 received the stored amount, a new entry of drug would take place and it would be visualized as a peak of concentration in plasma (compartment 1).

It should be considered that transference from one compartment to the other actually takes place when the substance enters the cells of extravascular tissues. For instance, if a fraction of drug flowing throughout the



**Figure 1.** Pharmacokinetic model displaying splanchnic circulation

liver does not enter the hepatocyte and goes back to the systemic blood circulation, it will not take part in the transference from 1 to 2. Again, if some portion of drug amount passes by the intestine without entering the enterocyte but it does enter the hepatocyte, it will be considered into the arrow that link 1 with 2 but not in that connecting 1 with 3. Arrow leading substance from 4 to 2 refers to the fraction of molecules that enters the hepatocyte once they have left the cells of the stomach or the pancreas.

Under these assumptions it is clear that compartments 2 or 3 are not exactly the liver or the intestine alone, but a combination between that which receives first the drug from 1 and the other that shares the stay of molecules before they could go back to the systemic blood circulation. Then, wherever the drug enters first, to the intestine or to the liver, these molecules will cycle between enterocytes and hepatocytes before their return to compartment 1. Due to a higher content of enzymes in the liver respect to the intestine, a first entrance in the hepatocytes will determine a higher extraction from compartment 2 than from compartment 3, and so, elimination from compartment 2 would be higher as well. This could be different if the level of expression of the involved CYP isoforms is higher in the intestine. As it was mentioned before, CYP3A4 is more abundant in the intestine. Both connections, between 1 and 2 and between 1 and 3, could be undertaken globally as shown in Figure 2.

When the elimination from the intestine is omitted, a higher extraction (1 - bioavailable fraction) could be inferred (10) by equations 1 and 2 when the molecules enter first to the liver than to the intestine:

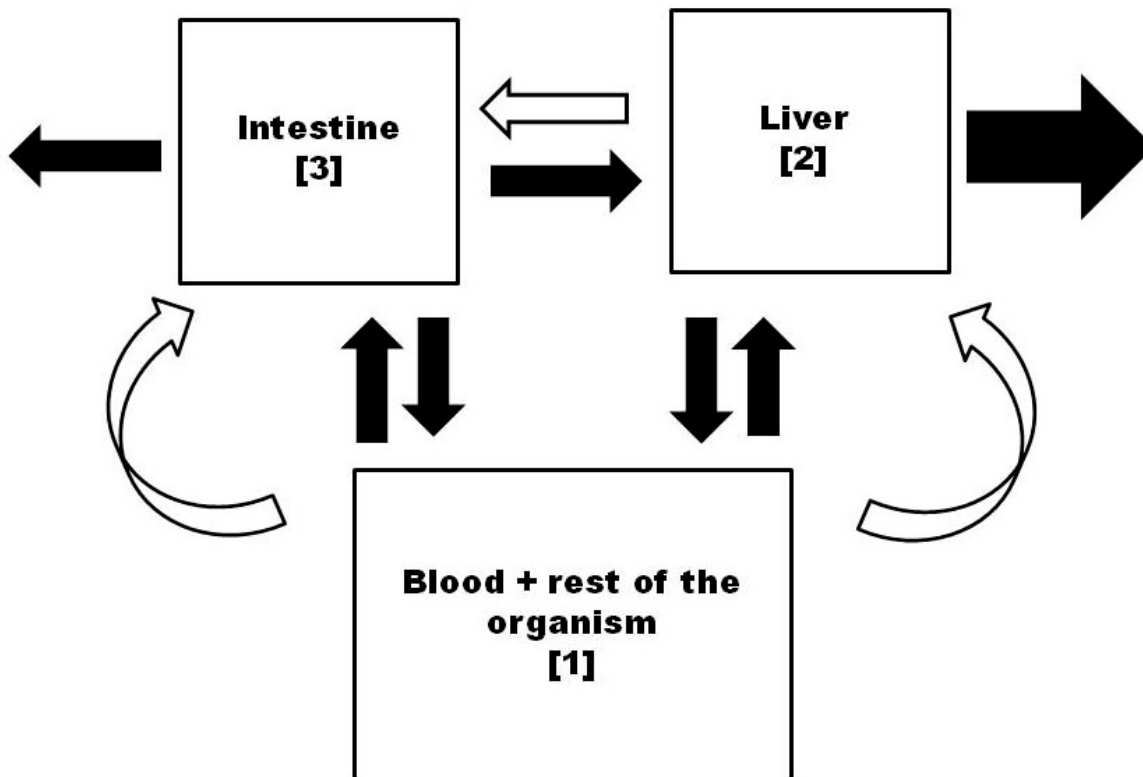
$$\text{Extraction of drug entering through the liver: } \frac{k_{20}(k_{32}+k_{31})}{((k_{21}+k_{20})(k_{32}+k_{31}) + k_{23}k_{31})} \text{ equation 1}$$

$$\text{Extraction of drug entering through the intestine: } \frac{k_{20}k_{32}}{((k_{21}+k_{20})(k_{32}+k_{31}) + k_{23}k_{31})} \text{ equation 2}$$

First order rate constants involved in the transference from compartment “x” to compartment “y” are symbolized as:  $k_{xy}$ . No transference from 0 must be considered since this is not a true compartment, but it is the exterior of the body, and hence,  $k_{x0}$  just symbolizes a first order elimination rate constant.

**2.5. Efflux transportation, blood flow fraction, and drug recycling**

Taking into consideration the three mechanism of drug distribution mentioned above, the model shown in Figure 3 could synthesize the most relevant pathways of a drug that follows elimination only through the splanchnic organs. In this model empty arrows mean that efflux transportation is involved.



**Figure 2.** Interconnection between intestine and liver with the rest of the organism

In order to evaluate the impact of different efflux carrier expression rates (10), Figure 4 illustrates the changes that would take place in the mass transference towards the exterior of a microsystem involving just two compartments. As it can be seen, the higher the expression of efflux carrier is towards one direction, the higher or the lower mass transference becomes, depending on what direction the movement of molecules is considered: to the same or to the opposite direction; respectively. According to Figure 3, transportation of substances to the intestine becomes favored when efflux transportation, by means of Pgp or MRP2, increases its activity. The inverse happens for the mass transportation to the liver. Hence, different consequences might be foreseen in drug depuration depending on the relative contribution that liver and intestine have in its clearance: a lower clearance for PHT (hepatic abundance of CYP2C9); a higher clearance for CBZ (intestine abundance of CYP3A4).

Another important consequence derived from the models (Figure 1 or 3) is the contribution that splanchnic blood flow fraction has on the amount of drug recycled throughout the gastrointestinal lumen. Because of a higher cardiac output fraction delivered to the non-hepatic organs of the splanchnic zone women have, a higher gastrointestinal cycling could be forecasted. Also, a higher intestinal clearance in relation with men might be expected. The increased drug extraction accounted in the intestine could diminish the contribution of the liver extraction in the total clearance of drug. The increase of the intestinal

clearance at the expense of the hepatic one when a preferred transit throughout the intestine is accomplished, by mean of hepatobiliary or pancreatic or gastric secretion (Figure 3), could lead to a significant change in the total clearance of a drug.

### 3. PHENYTOIN PHARMACOKINETICS

#### 3.1. Michaelis-Menten consideration

Non-linear pharmacokinetics of PHT was sufficiently demonstrated throughout the scientific literature, and parameters ranging from 17 to 23 mg/h and from 5 to 10 mg/L either for the maximum velocity of elimination ( $V_{max}$ ) or the Michaelis-Menten constant ( $K_m$ ), respectively, were assessed (24-26). Considering a complete gastrointestinal absorption of PHT, which is not far from the actual bioavailability of oral formulations (90%), steady state plasma concentration ( $C_{ss}$ ) increases and clearance (CL) decreases shown in Table 1 could be calculated when passing from a dose (D) of 200 mg every 24 h to 400 mg every 24 h. To perform this calculation the following equation at the steady state was used:  $D/24 = V_{max} C_{ss} / (K_m + C_{ss})$ . A strong reduction in CL is observed (more than two thirds) when daily dose is doubled.

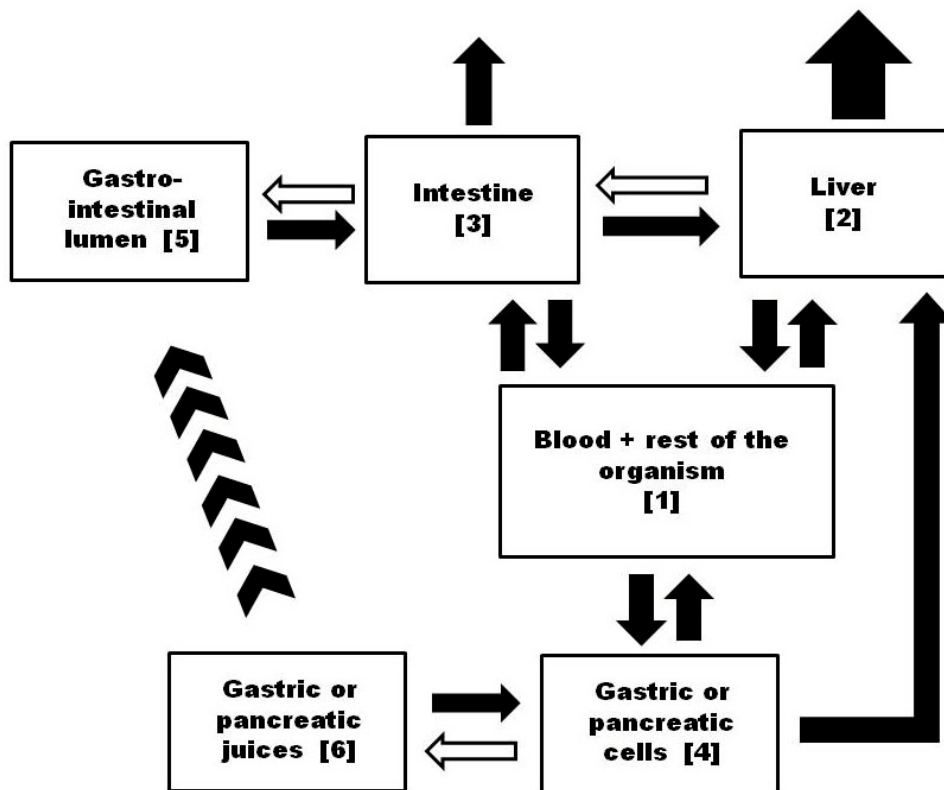
#### 3.2. Hepatic, intestinal, and renal contribution to phenytoin clearance

Despite the prevalence of the hepatic route in PHT elimination, it is known that both the intestine and the

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**Table 1.** Theoretical steady state plasma concentration ( $C_{ss}$ ) and clearance (CL) of phenytoin according to the daily dose administered, considering the following Michaelis-Menten parameters:  $K_m = 7.5$  mg/L;  $V_{max} = 20$  mg/h

PHT daily dose (mg)	$C_{ss}$ (mg/L)	CL (L/h)	% of CL
200	5.3.6	1.5.6	100
300	12.5.	1.0.0	64
400	37.5.	0.4.4	29



**Figure 3.** Expanded pharmacokinetic model for the splanchnic circulation

kidneys are also involved in PHT metabolism and excretion respectively (27). Neither the age nor the sex of individuals was reported to influence on the plasma protein binding rate (28) and the CL (29) of PHT. However, when PHT was administered by oral route some differences between sexes were assessed (19). The reason seems to be the lower bioavailability in women than in men (30), which, in turn, allow us to consider a higher presystemic clearance in female. Taking into account that minor differences between male and female were reported in both CYP2C content and hepatic or renal blood flow fractions (17), similar pattern of biotransformation and renal excretion could be foreseen regardless the sex of individuals. However, the lower bioavailability and the higher intestinal blood flow fraction that women have might preclude some dissimilar sex-related contribution between intestine and liver for the total splanchnic clearance of PHT. In order to hypothesize this gender difference, let us assume that men and women had 83:15:2 and 78:20:2 for the liver:intestine:kidney clearance composition, respectively. So, women would have a 1.33-fold higher intestinal clearance but global splanchnic and renal clearances similar to men. This could reflect the

compensation that the female intestinal blood flow fraction could have in response to the 30% lower cardiac output fraction delivered to the muscle (17). Then, more fraction of circulating molecules of PHT would become available directly from the blood to undergo intestinal metabolism, apart from those arriving from the liver, as in men, by means of the hepatobiliary route.

The sex of individuals is not the only variable to be considered, since their physical activity and genetics may influence the balance between the intestinal and hepatic clearances. Then, either within the women or men group differences between hepatic and intestinal clearances could vary among the individuals.

Considering this scenario of different abilities that individuals would have for metabolizing PHT at the enterocyte, any change produced in the level of intestinal enzyme expression, or in the efflux transporter expression, leading to an increased intestinal and a reduced hepatic metabolism, could differentiate the balance between hepatic and intestinal clearance displayed by both genders.

**Table 2.** Theoretical evolution of partial clearances composition (%) of phenytoin in relation with the daily dose administered. Percentage of the initial total clearance was retrieved from Table 1

PHT daily dose (mg)	CL hepatic		CL intestinal		CL renal		CL total
	Men	Women	Men	Women	Men	Women	Men or Women
200	83	78	15	20	2	2	100
300	45	40	15	20	4	4	64
400	8	3	15	20	6	6	29
200 + CBZ	45	40	30	40	4	4	79 or 84
300 + CBZ	8	3	45	60	6	6	59 or 69

**Table 3.** Mean ( $\pm$  standard deviation) plasma drug concentration, daily dose, and concentration / daily dose ratio for PHT and CBZ in patients receiving PHT or PHT+CBZ treatments. Significant differences ( $p < 0.5$ .) were found for men (\*) and women (#) respectively

	PHT		PHT+CBZ	
	Men	Women	Men	Women
Number of subjects	42	44	17	15
PHT plasma concentration (mg/L)	8.8. ( $\pm$ 4.3.)	11.4. ( $\pm$ 6.3.)	11.4. ( $\pm$ 7.3.)	8.1. ( $\pm$ 4.9.)
PHT daily dose (mg/kg)	4.6. ( $\pm$ 0.8.)	5.0. ( $\pm$ 1.5.)	4.0. ( $\pm$ 1.2.)	4.9. ( $\pm$ 1.8.)
PHT concentration / dose	1.9. ( $\pm$ 0.9.)*	2.2. ( $\pm$ 1.0.)#	2.8. ( $\pm$ 1.5.)*	1.6. ( $\pm$ 1.5.)#
CBZ plasma concentration (mg/L)			4.9. ( $\pm$ 3.7.)	5.0. ( $\pm$ 2.7.)
CBZ daily dose (mg/kg)			10.4. ( $\pm$ 4.6.)	12.0. ( $\pm$ 7.7.)
CBZ concentration / dose			0.5. ( $\pm$ 0.4.)	0.5. ( $\pm$ 0.4.)

It was argued that the mechanism by which PHT displays its Michaelis-Menten behavior is enzyme saturation by the drug itself. Recently, an alternative mechanism for explaining this nonlinear kinetics was postulated (10) based on the ability of PHT to induce both enzymes (31-33) and transporters (34). An intense induction of efflux transporters, that could extrude the molecules of PHT from the liver to the intestine, would be the cause for the progressive lowering of hepatic clearance in response to increasing daily doses. The increase of PHT concentration because of daily dose increase could saturate the enzymes and hence override their more expressed level either at the hepatocyte or at the enterocyte. Considering the inductive effect exerted by PHT on both Pgp and MRP2 (34), no sex-related differences would be foreseen for its nonlinear pharmacokinetics.

Our hypothesis of induction in the efflux transporter expression was recently tested for PHT in rats (35). Five days after the initiation of intraperitoneal PHT dosing the nonlinear increase in drug plasma concentration became evident (36), and according to our inductive mechanism the molecules of PHT would be carried from the hepatocyte to the enterocyte, avoiding hepatic metabolism. But once verapamil (Pgp inhibitor) was added at the fifth day of treatment the level of PHT decreased as a consequence of blocking its passage to the intestine (35). However, if verapamil was administered before the overexpression took place the result of the interaction would be the opposite. In fact, at the first (37) or the second (35) day of PHT dosing its plasma concentration increased after verapamil addition since the intestinal component of the splanchnic metabolism was blockade.

### 3.3. Interaction of carbamazepine on phenytoin pharmacokinetics

Table 2 was constructed in order to forecast the evolution of partial clearances with increasing PHT

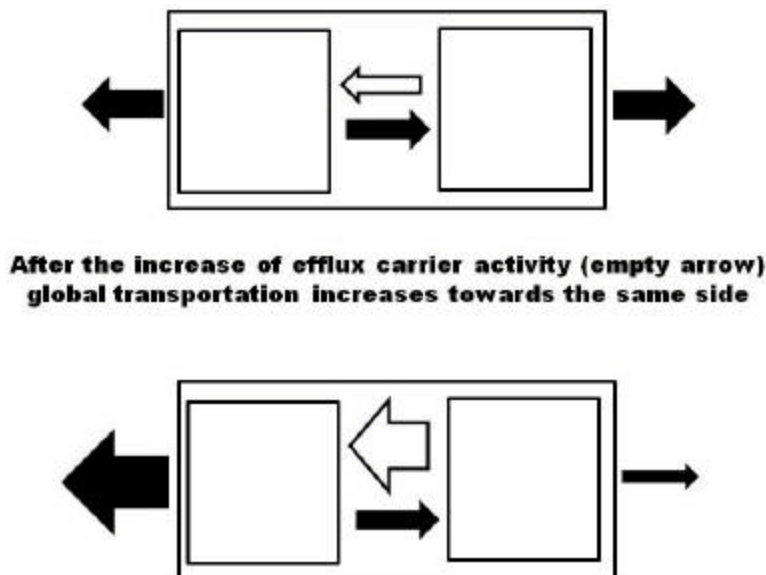
doses. To do this, a clearance reduction as shown in Table 1 was considered. Renal clearance was increased with increasing dosing because of inductive effect on the efflux transporter here overexpressed. The overexpression rate was linearly related with each 100 mg of increasing dose. The intestinal clearance was kept constant due to the enzyme inhibition provoked by the progressive increase of the local drug concentration, even though both efflux carriers and enzymes were overexpressed as well. Hepatic clearance was reduced as a consequence of the hepatobiliary overexpression of efflux transporter. This reduction was in such extent that the percentage of total clearance could satisfy the decrease shown in Table 1.

Table 2 also shows CBZ impact on the PHT clearance when it is added to the therapy. These predictions are just speculative since no experimental previous published data could support the extent of reduction/increase in partial clearances. Also these projections should be dependent on CBZ dose, or more precisely on the local CBZ concentrations at the sites where its induction would be taking place. Interestingly, Table 2 shows that some individuals could respond similarly as it was previously reported (38-39): increase of PHT concentration when CBZ was added to the therapy, while others do not respond or even respond in an inverse way. It was postulated that inhibitory (immediately after the administration) or inductive effects (several days after) of CBZ on CYP2C activity could lead to either a reduction or an enhancement of PHT metabolism (40). However, this hypothesis sounds inconsistent with clinical results (38-39) since all studied patients were kept for several days with CBZ once it was added to the PHT therapy.

## 4. VALPROIC ACID PHARMACOKINETICS

### 4.1. Nonlinear pharmacokinetics of free valproate

Valproic acid (VPA) is highly (41) and concentration-dependent bound to plasma protein, leading



**Figure 4.** Impact of efflux transportation on the kinetic parameter of mass exchange

to a lesser than proportional increase of its total plasma concentration when the dose increases. The higher plasma concentration of VPA is, the lower the capacity of the albumin to bind the drug becomes (42). Besides, free plasma concentration of VPA also responds no linearly to the administered dose. The reason of such behavior is the carnitine depletion caused by VPA (41), which prevents its entry to the mitochondria in order to follow  $\beta$ -oxidation as a fatty acid it is. Since  $\beta$ -oxidation is one of the major VPA elimination route, this non-linearity is a consequence of the drug clearance decrease. Hence, self-reduction of VPA ability to cross mitochondrial membranes highlights the fact that any change in drug transportation, even at the interior of the cell, could modify not only its own disposition but also the disposition of exogenous nutrients, such as fatty acid, or of endogenous metabolites, such as ammonia, leading to severe adverse reactions in patients (43).

#### 4.2. Gastrointestinal-blood cycling of valproate

Regarding the acidic property of the VPA (44) an important concentration of drug in the pancreatic juice could be foreseen. Difference of pHs between plasma (7.4) and pancreas duct (8.8) allows us to estimate a 25-fold higher pancreatic free drug concentration than that present in plasma. Recently (45), it was reported drug reabsorption from the gastrointestinal tract that precluded unchanged secretion of VPA to the gut. The mechanism here envisaged for VPA, following pancreatic secretion, becomes a great contribution to elucidate not only the relevant amount recycled (around 30% of dose) but also the significant difference between genders. Two-fold higher gastrointestinal-blood cycling in women is in accordance with gender differences in splanchnic blood flow fraction. As it was there reported (45) a lower clearance of VPA was detected in female, probably related with the liver-to-intestine switch because of both the higher cardiac output

fraction destined to non-hepatic organs and the higher MRP2 expression women have (46-49).

#### 5. CONCLUSION

Regarding the interaction of CBZ over PHT, a novel mechanism, different from the enzymatic inhibition, was proposed. The recognized inductive effect on efflux transporter was used to explain the nonlinear enhancement of PHT plasma concentration either by itself under chronic treatment or by CBZ INTRODUCTION to the treatment. Differences in CBZ-over-PHT interaction among individuals were explained by means of efflux transporter in combination with enzyme overexpressions. Dual effect put into consideration the role that efflux transporter could have on drug disposition.

Gastrointestinal drug recycling throughout the stomach and the pancreas becomes an important mechanism to redistribute the substance between the intestine and the liver. In the same way cardiac output redistribution could influence the clearance balance between two distant eliminating organs, gastrointestinal secretions could alter the clearance balance between two nearby eliminating sites such as the splanchnic organs. Moreover, efflux transporter contributes significantly to change the elimination pattern of a drug moving the molecules from one tissue to other (hepatocytes to enterocytes), with dissimilar enzymatic expression. Also, at the inner part of the same cell, changes in drug transportation between cytosol and mitochondria could modify the clearance and the elimination pathway of a drug.

In conclusion, simple pharmacokinetic models taking into account the route of drug movement could manage the impact that all these mechanisms could have on drug fate.

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## **Nonlinear pharmacokinetics of antiepileptic drugs**

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