

Influence of posture on pharmacokinetics

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Abstract

Introduction Body position may influence physiological characteristics, such as perfusion, gastrointestinal function and plasma volume. These characteristics may interact with key factors determining the pharmacokinetics of drugs (dissolution, absorption, distribution, metabolism, excretion). **Objectives** Based on a systematic literature search, current data on the effect of posture on physiological characteristics and/or pharmacokinetics are summarized, and the relevance of possible effects, such as those presenting in clinical practice and clinical pharmacokinetic studies, is assessed. **Results** Postures which favour rapid gastric emptying (sitting, standing, recumbent right) accelerate the absorption of orally administered drugs. Consequently, these postures favour a shorter time to reach peak plasma drug concentration (t_{\max}) and a higher maximum plasma drug concentration (C_{\max}) and—in the case of transient saturation of first-pass metabolism—total exposure (area under the concentration–time curve, AUC) in comparison to recumbent left and supine positions (e.g. nifedipine: AUC 30 and 38% higher in standing and right lateral position vs. left lateral position; C_{\max} 149 and 80% higher, respectively). The magnitude of these postural effects depends strongly on the nature and amount of liquids and food ingested before drug administration and is most pronounced in the

fasting state and after administration with a nonnutrient liquid. Changes in splanchnic–hepatic blood flow (e.g. reduction of estimated hepatic perfusion by 37% in standing vs. supine position) may substantially affect the metabolism of orally administered drugs, especially of those with a high/saturable first-pass metabolism. For highly protein-bound drugs (e.g. phenytoin, imipramine), the total plasma concentration has been found to be approximately 10% higher in standing than lying subjects due to changes in plasma volume.

Conclusions Positioning of a patient may be an effective method of enhancing or retarding absorption of some drugs in appropriate clinical situations (e.g. toxic ingestions, bedridden patients). In clinical pharmacokinetic trials, such as bioequivalence studies, defining and maintaining posture precisely is a useful approach for reducing within- and between-subject variability.

Keywords Absorption · Gastric emptying · Pharmacokinetics · Posture

Introduction

The influence of body position on physiological characteristics and pharmacokinetics has been investigated for several decades. The first study on this topic (effects of posture on gastric emptying) was reported to have been performed as early as 1918 [1] when it was observed that barium was emptied faster when subjects lay on the right side compared to other positions. Since then, a multitude of studies has addressed various aspects of postural effects, especially those on gastrointestinal motility, haematological parameters/perfusion and the pharmacokinetics of orally administered drugs.

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However, due to the variety of different postures, characteristics, and study procedures that have been chosen, a general consensus on the extent and relevance of postural effects has not yet been reached. Furthermore, the number of potential mechanisms of these effects is quite large, thus complicating a general assessment. In particular, the importance and magnitude of possible postural effects on orally administered drugs has not yet been completely elucidated.

In this review, we assess by which means posture can influence physiological characteristics and identify the links between posture, physiology and pharmacokinetics. We also examine the clinical relevance of postural effects and evaluate whether posture may affect the outcome of clinical pharmacokinetic trials by, for example, influencing the pharmacokinetic key characteristics [area under the concentration–time curve (AUC) and time to reach maximum plasma concentration (C_{max})] and/or affecting the within-subject and between-subject variability of these characteristics.

Data

In this review, we have summarized the results of clinical studies that have investigated the influence of posture on gastrointestinal function/motility, haematological parameters, plasma volume, splanchnic–hepatic blood flow and the pharmacokinetics of drugs.

To this end, a comprehensive Medline/PubMed search for reports on areas relating to this topic was carried out, using the key words “posture”, “body position”, “pharmacokinetics”, “gastric emptying” and “absorption”. In addition, we manually explored the references of original or review articles and found publications not captured by our systematic keyword research strategy. We only included peer-reviewed articles published up to April, 2008. Conference abstracts, data only given in the product information and information available only on the webpage of the U.S. drug registration agency (FDA) were not included.

Effects of posture on the gastric residence time of fluids and meals

For nonnutrient liquids, the mechanisms by which posture affects gastric motility and gastric emptying were clarified by Anvari et al. [2]. These researchers examined the effects of posture (sitting vs. left lateral) on gastric emptying, intragastric distribution and antropyloroduodenal motility following ingestion of 150 ml saline, both with and without coadministration of intravenous atropine (see Table 1). As expected, atropine slowed gastric emptying in both postures (time required for 50% total stomach emptying in sitting

position: 18 vs. 14 min; left lateral: 35 vs. 28 min). However, both with and without atropine, emptying of the saline solution was faster in sitting subjects. The authors concluded that posture influences the intragastric distribution of liquids due to the effect of gravity such that, for anatomical reasons, in the left lateral (= “pylorus up”) and supine posture, gravity cannot accelerate gastric emptying. Normally, the liquid is emptied according to a first-order process (exponentially): the larger the volume, the faster the emptying [3].

Moreover, the trial showed that the effects of gravity on gastric emptying of nonnutrient liquids are also likely to reflect changes in antropyloric motility. The sitting position was associated with increases in (antro-) pyloric pressure waves and in basal pyloric pressure and, hence, with more “active pumping”.

The importance of gravity for gastric emptying was further demonstrated by a trial of Horowitz et al., who co-administered 60 ml olive oil and 290 ml aqueous soup. They also compared sitting with left lateral position. Gastric emptying of the oil was slower in the sitting position; the aqueous phase, however, was emptied much slower in left lateral position (see Table 1), indicating that both phases were emptied according to their specific density due to intragastric “layering” of the nonemulsified oil and aqueous phase according to gravity [4]. Similar results were obtained by Burn-Murdoch et al., who studied the emptying of 750 ml of a saline drink in the sitting, left lateral and right lateral position. They found the emptying to be most rapid in the right lateral position (“pylorus down”), with the difference being significant compared to emptying in the left lateral position [5].

For high nutrient/high calorie liquids (e.g. glucose-containing drinks or olive oil), the effects of changes in posture are much less pronounced than those for non- or low-nutrient liquids (e.g. saline or low-nutrient beef consommé soup) [4, 5, 7]. In the trial cited above, Burn-Murdoch et al. did not find any significant influence of posture on the emptying rate of 750 ml of a glucose drink. Despite the force of gravity being the same for both kinds of liquids, corresponding studies confirmed this difference [6, 7]. Whereas intragastric volume and gravity appear to be the driving forces controlling gastric emptying of non-nutrient liquids [2, 5, 8], for nutrient liquids, feedback from small intestinal “nutrient” receptors is the decisive factor. These receptors, which are sensitive to, for example, carbohydrates and digestion products of fat, mediate the slowing of gastric emptying [2, 4, 5, 8]. This is also reflected in the emptying pattern, which is predominantly linear for nutrient liquids and exponential for nonnutrient ones [2]. Consequently, nutrient liquids are emptied slower, and the process is largely independent of posture [2, 5] (see results of Burn-Murdoch et al., Table 1).

Table 1 Influence of posture on gastric emptying and on haematological parameters of healthy volunteers

Author	Intervention; number of volunteers	Characteristic/parameter	Body position				Outcome/conclusion
			Lying on:				
			Left side	Right side	Supine	Prone	
Burn-Murdoch [5]	750 ml saline drink glucose drink (n=5)	Rate of gastric emptying	x	x			Gastric contents recovered at 10 min (saline), 20 min (glucose); Saline: right side 215 ml, left 431 ml (p<0.005); sitting: 308 ml Glucose: no significant differences (555, 589 and 564 ml)
Steingoetter [50]	300 ml water (n=12)	GE		x		x	Gastric emptying half time: 15.8 min (sitting) vs. 18.3 min (UPD) (p=0.07)
Asada [9]	Solid food (n=30)	GE			x		Emptying pattern: linear for UPD, exponential for sitting
Horowitz [4]	60 ml olive oil plus 290 ml soup (aqueous) (n=11)	GE	x				Gastric emptying delayed in supine position
				x			Sitting: emptying of oil slower than of aqueous phase
							Lag phase (oil) 44.3 min vs. 7.6 min (aqueous phase); p<0.01
							Left side: emptying of oil faster than of aqueous phase
							Lag phase (oil) 16.7 min vs. 160.9 min (aqueous phase); p<0.01
Doran [10]	Large and small meal (n=8)	GE		x			No effect on gastric emptying
Jones [7]	600 ml glucose drink (n=8)	GE			x		No effect on gastric emptying
Moore [8]	Standard beef meal, orange juice (n=8)	GE		x		x	Supine position slowed GE of beef, compared to both sitting (t _{1/2} 116.9 vs. 75.8 min; p=0.012) and standing (70.4; p=0.015)
Spiegel [12]	Tomato soup, egg sandwich (n=9)	GE			x		GE slower in supine position for both soup (p<0.05) and sandwich (p<0.025)
Anvari [2]	150 ml saline drink, with and without atropine i.v. (n=7)	GE, motility, intragastric distribution			x		Atropine slows gastric emptying (both postures; p<0.05). GE on left side slower, both with and without atropine (p<0.05)
Penev [27]	Change of body position (15 min per posture; n=32)	Haematological lab values			x		Values of haemoglobin, haematocrit, erythrocytes, leucocytes and platelets increase significantly with the change from recumbent to sitting and to erect
Dukova-Peneva [26]	Change of body position (15 min per posture; n=32)	Total protein, substrates, enzymes and electrolytes in serum			x		Significant increase of total protein, albumin, calcium and of activity of creatine kinase, alkaline phosphatase, gamma GTP

Table 1 (continued)

Author	Intervention; number of volunteers	Characteristic/parameter	Body position			Outcome/conclusion			
			Lying on: Left side	Right side	Supine	Prone	Sitting	Standing	Upside down
Maw [24]	Change of body position (30 min per posture; n=8)	Distribution of intra- and extravascular fluid volumes			x			x	Relative to seated: increase of blood volume in supine posture (mean: 89 ml), decrease while standing (406 ml), primarily due to plasma shifts between circulation and interstitium.
Hagan [25]	Change of body position (35 min per posture; n=7)	Haematological lab values, blood and plasma volume			x			x	In standing position vs. supine: increase of mean hct (10.3%), hb (10.8%), plasma proteins (20.8%); decrease of mean blood and plasma volume (9.5 and 16.2%, respectively)

GE, Gastric emptying; i.v. intravenous; hct, haematocrit; hb, haemoglobin; GTP, glutamyltranspeptidase

In terms of the effects of posture on the gastric emptying of solid food, conflicting results have been published. Whereas Asada et al. [9] found gastric emptying to be more delayed in the supine position versus the sitting position, Doran et al. did not see any relevant influence of posture (left lateral vs. sitting) following the administration of both a small and a large meal [10]. Doran et al. concluded that posture has only a minor influence on intragastric distribution and no effect at all on gastric emptying of solid food. Similar results were obtained by Mannell et al. [11]. Two trials investigating gastric emptying of a meal containing a nutritive liquid and solid food found the food to be emptied slower in the supine position compared to the sitting [8], [12] and standing position [8] (see Table 1). Both authors concluded that the effects of posture and gravity on the rate of gastric emptying are more pronounced after coadministration of solid food and nutrient liquid than after the administration of either component alone. After coadministration, propulsive motor activity apparently does not increase sufficiently to overcome the effects of gravity [12].

Posture and appetite

Somehow, surprisingly, appetite may also be influenced by posture. After ingestion of a 600-ml glucose test drink, hunger and prospective consumption were significantly less in the sitting position than in the supine position, continuously from 45 min until the end of the observation period 180 min after ingestion [7]. Horowitz et al. found a reduction of hunger in the left lateral decubitus position compared to sitting. After the administration of olive oil and soup, hunger was less in the subjects lying on their left side at both at 120 and at 180 min post-ingestion [4]. Corresponding results were obtained by Carney et al. for the same postures and a similar meal [13]. In contrast, Spiegel et al. found no posture-dependent differences in postprandial hunger after the ingestion of soup and a sandwich (seated vs. supine), which they explained by a different meal composition and a shorter observation period (0–120 min post-ingestion) [12]. After the ingestion of a solid meal (without liquid component), no statistical significant difference in satiety ratings for sitting and left lateral position could be observed [10].

Effects of posture on the absorption of orally administered drugs

The extent of absorption from the stomach is negligible for the vast majority of drugs [14, 15]. Thus, the rate of gastric emptying is the principal factor and one of the most important rate-limiting steps affecting the absorption of

orally administered drugs [16]. In the case of saturable absorption kinetics (e.g. amoxicillin [17]) and if there is a small “absorption window”, accelerated gastric emptying may decrease overall systemic bioavailability [1, 18].

Usually, as has been shown for a solution of acetaminophen (20 mg/kg), the first-order rate constant for drug transfer from the intestinal lumen into the systemic circulation is greater than the first-order rate constant for gastric emptying [19]. The mean half-time for drug transfer was 6.8 ± 0.9 min in this trial, whereas the mean gastric emptying half-time was 12 min. Consequently, gastric emptying, which is predominantly pulsatile, is the rate-limiting step in the early phase of absorption of orally administered drugs (provided the drug is well absorbed/highly soluble according to the Biopharmaceutics Classification System classification and given as a solution or rapidly dissolving dosage form; if dissolution is slow, it is rate-limiting). As posture is known to influence gastric emptying [1, 5, 18], in many cases the rate-limiting step for absorption can be influenced by posture. Moreover, in addition to the factors discussed above, it may also depend on posture as to whether the rate-limiting step is dissolution or gastric emptying, with respective consequences for the pharmacokinetic profile.

The resulting differences in the rate (and possibly extent) of absorption may affect various pharmacokinetic characteristics. As shown in Table 2, several studies, for example, with paracetamol [18, 20, 21], nifedipine [18], amoxicillin [22] and theophylline [23], have found an increase in the time to reach the maximum serum drug concentration (t_{\max})/mean residence time (MRT) and/or a decrease in maximum plasma drug concentration (C_{\max})/(early) AUC for left lateral and supine position compared to other positions (right lateral, prone, sitting, standing). The effects of the respective postures on pharmacokinetics correspond to their effects on gastric emptying, as discussed above (left lateral and supine positions tend to decrease the rate of gastric emptying). These differences were reported consistently by the studies; however, the extent of these postural effects on pharmacokinetics differs widely, ranging from “no effect” to an increase of 149% (C_{\max} of nifedipine in standing vs. left lateral position; see Table 2 [18]). For nifedipine, however, the additive postural effect on metabolism also has to be taken into consideration (see below). The extent of postural effects on absorption depends on several factors, especially on the dissolution and absorption characteristics of the drug/dosage form and on the quality/quantity of food and liquids ingested before or shortly after intake of the drug. Based on the considerations stated above, it can be expected that slow dissolution/absorption kinetics of the dosage form/agent and coadministration of solid food or nutrient liquids will diminish or abolish the effect of

posture on the absorption and pharmacokinetics of orally administered drugs.

Influence of posture on haematological parameters, plasma volume and distribution

Another way by which body position may affect pharmacokinetics is the postural influence on plasma volume and haematological parameters. Due to gravity, the standing position results in a high hydrostatic pressure in lower body parts, leading to an intravascular fluid loss caused by filtration of plasma into the interstitium [24]. This fluid loss accounts for approximately 9.5% of the blood volume and 16.2% of plasma volume, respectively (compared to the supine position; see Table 1) [25]. Thus, as the plasma concentrations of drugs can depend on plasma volume and its changes (especially in the case of high-molecular and highly protein-bound drugs), changes in pharmacokinetic characteristics (e.g. C_{\max}) up to a similar magnitude may be expected for some drugs.

The effects of posture in this context have been studied extensively over the past decades, with the results being largely consistent [24–27]. A change in body position from recumbent to sitting and to erect results in a significant increase in haematological laboratory values, such as haemoglobin, haematocrit, erythrocytes, leucocytes and platelets, due to reversible changes in the concentration and redistribution of the blood [25, 27]. Relative to the sitting position, blood volume increases by 89 ml (mean) after 30 min in supine posture and decreases by 406 ml while standing, with these differences being primarily the result of plasma shifts between the interstitium and circulation [24] (see Table 1). The haemo-concentration while standing is supposed to involve all blood compounds—and drugs—that cannot permeate the capillary membrane. Equivalent changes have been found for total protein, albumin and the activity of several enzymes [26].

Not surprisingly, the same mechanism applies to highly protein-bound drugs, such as phenytoin, imipramine and desipramine, whose total plasma concentrations increase significantly after standing for 40 min compared to lying (mean increase: 10.5, 9.8 and 11.5%, respectively) [28, 29]. In addition, the plasma level of endogenous hormones (thyroxine, cortisol) can be influenced to a similar extent (mean increase: 6.8 and 32.6%, respectively) [30, 31]. The large increase in cortisol is explained by a second effect of posture in this case: standing induces cortisol secretion as a physiological response to the resulting changes in plasma volume, circulation and blood pressure.

Apart from these effects on blood composition and plasma volume, it is likely that there is no further relevant influence of posture on the distribution of drugs. The results of Rumble et al. on paracetamol suggest that previously

Table 2 Influence of posture on the pharmacokinetic characteristics of orally administered drugs and endogenous hormones

Author	Study drug, number of volunteers	Characteristic	Body position			Sitting			Outcome/conclusion
			Lying on:	Prone	Standing	Ambulation			
			Left side	Right side	Supine	Left 20° head down	Right 20° head up		
Vance [20]	Paracetamol (80 mg/kg; $n=12$)	AUC_{0-2h}	x	x	x			x	Absorption (AUC_{0-2h}): delayed for both left side (6.0) and supine position (6.6) vs. prone (7.4), right side (9.0) and sitting (8.6 min mg/l; $p<0.05$) t_{max} : delayed on left side (both drugs; $p<0.05$) C_{max} : on left side (148.7) lower for nifedipine (right: 267.9; standing: 369.6 ng/ml; $p<0.01$) $AUC_{nifed.}$: ↓ on left side (354.1) vs. right (490.3; $p<0.01$) and standing (460.3 h ng/ml; $p<0.05$) Increase of heart rate: left < right ($p<0.05$) t_{max} : left 47, right 25 min (not significant)
Renwick [18]	Paracetamol (1 g) plus nifedipine (20 mg) ($n=8$)	t_{max} , C_{max} , AUC, Heart rate	x	x				x	
Wallden [21]	Paracetamol (1.5 g in 200 ml water) ($n=10$)	t_{max} , C_{max} , AUC_{0-1h}				x	x		
Wallden [21]	Paracetamol (1.5 g in 200 ml water) + remifentanyl i.v. ($n=10$)	t_{max} , C_{max} , AUC_{0-1h}				x	x		C_{max} : left 94, right 138 $\mu\text{mol/l}$ ($p<0.01$) AUC_{0-1h} : left 3793, right 5092 min $\mu\text{mol/l}$, $p<0.01$ Remifentanyl delays GE (t_{max} ↑, C_{max}/AUC_{0-1h} ↓); this delay is not significantly influenced by posture: t_{max} : left 109, right 94 min C_{max} : left 16, right 34 $\mu\text{mol/l}$ AUC_{0-1h} : left 197, right 962 min $\mu\text{mol/l}$ GFR: not influenced by posture Li^+ clearance: ↓ in walking vs. supine subjects (26 vs. 30 ml/min; $p<0.025$). Sitting: 29 ml/min No effect of posture (only minimal differences for all parameters)
Kamper [42]	16 mmol lithium (Li_2CO_3 orally) ($n=12$)	GFR, lithium clearance		x				x	x walk
Gupta [40]	Verapamil 240 mg (osmotically controlled formulation; $n=29$)	t_{max} , C_{max} , C_{min} , AUC							x

Roberts [22]	Amoxicillin 250 mg (<i>n</i> =8)	Amoxicillin: clearance, serum concentration	(x) bed rest	x	Higher Amoxicillin concentrations during ambulation; C_{max} 4.4 vs. 2.7 mg/l (bed rest) Lower apparent total serum amoxicillin clearance during ambulation: 0,37 vs. 0,51 kg h/l Higher Theophylline concentrations in the standing position at all times (measured hourly for 6 hours) AUC not influenced by posture (ratio of AUC: 0.98 ± 0.28)
Warren [23]	Theophylline 450 mg (slow release; <i>n</i> =6)	Plasma concentration	x	x	
Modi [33]	Propranolol 80 mg in 250 ml water (<i>n</i> =6)	AUC		x	
Abalan [29]	Phenytoin 100–300 mg (constant dose, <i>n</i> =11)	Total plasma concentration	x	x	Phenytoin plasma concentration increases by 10.5% while standing
Abalan [28]	Imipramine 150–300 mg (constant dose, <i>n</i> =16) Desipramine (metab.)	Total plasma concentration	x	x	Imipramine increases by 9,8% while standing, Desipramine by 11,5%
Abalan [30]	Endogenous thyroxine (<i>n</i> =15)	Total plasma concentration	x	x	Thyroxine increases by 6,8% while standing
Abalan [31]	Endogenous cortisol (<i>n</i> =16)	Total plasma concentration	x	x	Cortisol 32,6% higher in standing position

GFR, Glomerular filtration rate; AUC, area under the time–concentration curve; t_{max} , time to reach maximum serum drug concentration

reported changes in the volume of distribution do not exist [32]. As a general rule, because distribution is mainly determined by the physico-chemical properties of the administered drug, significant changes due to posture seem unlikely. The free (unbound) concentration of a drug in plasma is not supposed to be influenced by posture, provided the drug is able to permeate the capillary membranes. For high-molecular drugs unable to permeate the membrane (e.g. heparin), from a theoretical point of view the free concentration may also depend on posture.

Influence of posture on splanchnic–hepatic blood flow and metabolism

There is ample evidence that posture, as well as food and exercise, may influence splanchnic–hepatic blood flow [1, 33, 34]. In subjects standing upright for 15 min, estimated hepatic blood flow (clearance of indocyanine green) was reduced by 37% compared to supine position [35]. The authors of this study concluded that the influence of posture should be considered during pharmacokinetic assessment of high-clearance drugs. Similarly, Culbertson et al. also reported a mean 37% reduction of estimated hepatic blood flow in the standing compared to supine position [36].

Changes in splanchnic–hepatic blood flow may substantially affect the absorption and metabolism of orally administered drugs, especially of those with a high first-pass metabolism [1, 18]. In cases of partial saturation of first-pass metabolism, overall systemic bioavailability can depend on the rate of absorption [37] and, therefore, on posture as well.

As shown above, gastric emptying and intestinal motility affect the rate of absorption of drugs; this may also influence the extent of first-pass metabolism [38]. Postures which favour rapid gastric emptying (i.e. standing, sitting and recumbent right) may cause a transient saturation of first-pass metabolism due to the more rapid delivery of the agent to the metabolizing enzymes in the gut wall and liver. This is especially true if the administered drugs are absorbed rapidly after gastric emptying and undergo extensive presystemic elimination, as faster gastric emptying may increase the overall bioavailability of drugs with saturable first-pass metabolism, such as propranolol [39], nifedipine [18] and ethanol [51]. On the other hand, slower absorption may decrease overall systemic availability [37].

The possible effects of posture in this context can be illustrated by the results of the study by Renwick et al. [18] (see Table 2). These researchers co-administered nifedipine and paracetamol and compared the left lateral, right lateral and standing positions, with the respective posture being subsequently maintained for 4 h. In left lateral position, t_{\max} was prolonged for both drugs, indicating slower gastric emptying; C_{\max} and AUC were lower, but with this

difference being significant for nifedipine only. When the left lateral (= “pylorus up”) position was compared to the right lateral (= “pylorus down”) position, even one pharmacodynamic parameter (increase in heart rate following nifedipine administration) was significantly greater when the subject was lying on the right side.

The significantly higher AUC of nifedipine (but not of paracetamol) in the two postures that favour rapid gastric emptying (right lateral 38% higher, standing position 30%) suggests that there was an enhanced bioavailability of nifedipine due to a reduced first-pass extraction during transient saturation of first-pass metabolism [18].

In contrast to these findings, several other studies have found no significant effect of posture on the first-pass metabolism of highly extracted drugs [33, 40, 41]. These contradictory results can be explained by various differences between the studies, such as different elimination characteristics of the drugs used: if elimination is a saturable (mixed order) process, a significant effect of posture is possible; on the other hand, if elimination is a first-order process, posture will have no impact on bioavailability even though extraction may be high. Furthermore, differences between the postures (including their definition/duration of maintaining) and dosage forms may have contributed to the differing results. For example, in the case of osmotically controlled release (Gupta et al. [40]), the rate of drug release from the formulation is the limiting factor for the rate of absorption; hence, posture cannot influence the rate-limiting step within this setting.

Effects on renal elimination/clearance

Posture may also influence the renal elimination of drugs. After oral administration of lithium to volunteers who adopted either a supine or sitting position or walked around, lithium and sodium clearance tended to fall in the sitting position and fell significantly while the subjects were walking around (30, 29 and 26 ml/min, respectively) [42]. The decreased lithium clearance was not associated with any significant change in glomerular filtration rate, indicating an increase in both the absolute and the fractional proximal tubular reabsorptive rate (APR: walking 92, supine 83 ml/min; $p < 0.005$. FPR: walking 0.78, supine 0.73 ml/min; $p < 0.025$).

Effects on the skin pressure–vegetative reflex

In terms of the right and left lateral decubitus position, pharmacokinetic characteristics may be additionally affected by posture through an autonomic mechanism [16]. There are indications that pressure on the right side increases vagal tone due to the skin pressure–vegetative reflex, whereas lying on the left side increases sympathetic tone

[1, 18, 43]. As vagal and sympathetic tone affect gastrointestinal motility, this mechanism may have contributed to the fact that several studies [5, 18, 20] have shown faster gastric emptying/absorption in subjects lying on the right side compared to the left.

Posture and route of administration

The influence of posture on the pharmacokinetics of drugs depends also on the route of administration. Both the mechanism and extent of postural effects on pharmacokinetic characteristics differ between drugs administered orally, intravenously or intramuscularly.

Several studies failed to show any relevant postural effect on metabolism or elimination of the drugs administered intravenously [44–47]. As there is no absorption phase after intravenous application, the effects of posture on gastric emptying are not relevant. Effects on splanchnic–hepatic blood flow may occur, but in absence of a (potentially posture-sensitive) first-pass effect, these effects are less significant. The effects on C_{max} , such as higher peak plasma concentrations in the upright (18.3 mg/l) position versus the supine position (12.4 mg/l), which were seen initially after intravenous administration of theophylline [48, 52], are supposed to be based principally on the lower volume of the central compartment due to reversible haemo-concentration and, possibly, to vasoconstriction while standing [52]. Hence, these effects are usually short-time effects prior to the final distribution of the drug (except for drugs that are not distributed outside the systemic circulation). With the same exception, total exposure (AUC) is not supposed to be affected by posture after intravenous administration.

Rumble et al. studied the effects of posture on the pharmacokinetics of benzylpenicillin after intramuscular administration. Their results suggest that no significant changes occur (ambulation vs. supine: $t_{1/2}$ 52.5 and 50.9 min; AUC: 1175 and 1032 min mg/l, respectively). The authors concluded that these small differences are unlikely to be clinically relevant. Absorption seemed to be independent of posture; the major source of posturally determined (but not significant) pharmacokinetic differences after intramuscular application appeared to be clearance [49].

In summary, posture may influence the pharmacokinetics of orally administered drugs by affecting:

1. gastrointestinal motility/rate of gastric emptying
2. absorption
3. distribution/plasma volume
4. splanchnic–hepatic blood flow
5. metabolism/presystemic elimination
6. renal elimination/clearance
7. the skin pressure–vegetative reflex

It therefore appears that all pharmacokinetically relevant steps after oral ingestion of a drug can be affected by posture—with the exception of the dissolution of the agent from the pharmaceutical preparation (from a purely theoretical point of view, dissolution may be influenced indirectly by posture via effects on gastric motility and the rate of gastric emptying).

However, the magnitude of postural effects on pharmacokinetics of an orally administered drug depends on various factors, including (1) the physicochemical and pharmacological properties of the drug; (2) concomitant medication; (3) quantity, quality and temperature of ingested food or liquids; (4) pharmaceutical properties of the dosage form; (5) route of administration; (6) time of administration; (7) site, rate and extent of absorption, metabolism and elimination; (8) physical condition of individual/diseases; (9) age of individual; (10) sex of individual. This array of factors can interact with the postural influence by affecting any of the factors being influenced by posture, or via direct alteration of pharmacokinetic characteristics.

Implications for clinical practice

Compared to individual key factors that influence the pharmacokinetics of orally administered drugs and its variability (e.g. concomitant medication, phenotype of metabolizing enzymes/elimination, food intake), the effect of posture appears to be of minor importance. Generally, the occurrence of a clinically relevant effect of posture on pharmacokinetics might be expected if the drug has a steep concentration–response curve, is absorbed rapidly, undergoes saturable presystemic elimination, has a narrow therapeutic range, is administered orally in fasted state with a non-nutrient liquid, and if a rapid onset of the pharmacological effect is important. In these cases, in combination with prolonged maintenance of the same posture after intake, pharmacokinetic differences due to body position may be clinically relevant. For example, the positioning of a patient may be an effective method of enhancing or retarding drug absorption in appropriate clinical situations [16]. After the administration of acetaminophen (paracetamol) in an oral overdose model (80 mg/kg), Vance et al. found the AUC_{0-2h} to be significantly lower for both the left lateral (6.0) and supine posture (6.6) compared to the prone (7.4), sitting (8.6) and right lateral positions (9.0 min mg/l; see Table 2) [20]. Hence, mean absorption and total systemic exposure were (at least) during the first 2 hours significantly lower in these two former postures (up to 33% lower for left compared to right lateral position). Based on these results, the authors recommended the use of the left lateral decubitus position for initial management of patients with toxic ingestions. On

the other hand, for rapid onset of therapeutic effects, it would be advisable to avoid the left lateral and supine positions after the oral intake of a drug.

In normal clinical—especially ambulant—practice, however, daily activities of the patients are likely to cause a multitude of alterations in posture after drug administration. Therefore, and because for most of the drugs total AUC is not affected by posture, the clinical impact for mobile patients would seem to be quite limited. In terms of bedridden patients, particularly those with severe illness and/or those taking drugs with a narrow therapeutic range, the situation may be different: to position a patient in right lateral posture may accelerate the onset of therapeutic effects; on the other hand, avoiding the right lateral posture after intake may help to prevent toxic peak concentrations. Thus, in some cases, the adoption of a certain posture or adjustment of the dose regimen will be advisable for pharmacokinetic reasons. Additionally, in some cases (bisphosphonates), adoption/avoiding of certain postures after intake is required not for pharmacokinetic reasons, but to prevent side effects (oropharyngeal ulcer).

Implications for clinical pharmacokinetic studies

Pharmacokinetic data are commonly derived from subjects staying in bed and/or maintaining a standardized posture during the initial assessment of an orally administered drug. However, posture is not always defined strictly in these trials. As stated above, posture can influence the rate-limiting step in absorption (both whether it is gastric emptying or dissolution and, if it is gastric emptying, its rate), with respective consequences for the pharmacokinetic profile of orally administered drugs. The possible influences of posture on decisive pharmacokinetic characteristics, such as AUC and C_{\max} , clearly indicate that the posture of participating volunteers should be defined and maintained precisely, especially in the case of drugs which are absorbed rapidly and are subject to presystemic elimination [18]. At least throughout the phase of absorption, any change of posture should be avoided. This is especially relevant for bioequivalence studies, where the subjects should be carefully instructed and supervised. An inadequate definition and control of posture may result in an increase in both between-subject and within-subject variability of the various pharmacokinetic characteristics.

In bioequivalence trials, possible alterations in the key characteristics AUC and C_{\max} may cause a broader confidence interval, thus increasing the risk of failing to show bioequivalence. C_{\max} in particular, which is considerably sensitive to changes in the rate of absorption, can be notably influenced by posture. Hence, the precise definition of posture may help to reduce costs, for example, in the

number of subjects required, and/or improve the outcome of bioequivalence studies.

However, as shown in Table 2, the data available to date is limited, and the sample sizes in most of the trials are quite small. Experimental clinical trials, such as large bioequivalence studies comparing tight posture control versus no control, would be needed to confirm and assess quantitatively the impact of posture on pharmacokinetics and its variability.

References

- Oosterhuis B, Jonkman JH (1993) Pharmacokinetic studies in healthy volunteers in the context of in vitro/in vivo correlations. *Eur J Drug Metab Pharmacokin* 18(1):19–30
- Anvari M, Horowitz M, Fraser R, Maddox A, Myers J, Dent J et al (1995) Effects of posture on gastric emptying of nonnutrient liquids and antropyloroduodenal motility. *Am J Physiol* 268(5):G868–G871
- Golub AL, Frost RW, Betlach CJ, Gonzalez MA (1986) Physiologic considerations in drug absorption from the gastrointestinal tract. *J Allergy Clin Immunol* 78(4):689–694
- Horowitz M, Jones K, Edelbroek MA, Smout AJ, Read NW (1993) The effect of posture on gastric emptying and intragastric distribution of oil and aqueous meal components and appetite. *Gastroenterology* 105(2):382–390
- Burn-Murdoch R, Fisher MA, Hunt JN (1980) Does lying on the right side increase the rate of gastric emptying? *J Physiol* 302:395–398
- Hunt JN, Knox MT, Oginski A (1965) The effect of gravity on gastric emptying with various test meals. *J Physiol* 178:92–97
- Jones KL, O'Donovan D, Horowitz M, Russo A, Lei Y, Hausken T (2006) Effects of posture on gastric emptying, transpyloric flow, and hunger after a glucose drink in healthy humans. *Dig Dis Sci* 51(8):1331–1338
- Moore JG, Datz FL, Christian PE, Greenberg E, Alazraki N (1988) Effect of body posture on radionuclide measurements of gastric emptying. *Dig Dis Sci* 33(12):1592–1595
- Asada T, Sako Y, Fukushima Y, Kita T, Miyake T (1989) Effect of body position on gastric emptying of solid food—a study using a sulfamethizole capsule food method. *Nippon Shokakibyō Gakkai Zasshi* 86(8):1604–1610
- Doran S, Jones KL, Andrews JM, Horowitz M (1998) Effects of meal volume and posture on gastric emptying of solids and appetite. *Am J Physiol* 275(5):R1712–R1718
- Mannell A, Esser JD (1984) Gastric emptying of a solid meal. *S Afr Med J* 66(10):374–376
- Spiegel TA, Fried H, Hubert CD, Peikin SR, Siegel JA, Zeiger LS (2000) Effects of posture on gastric emptying and satiety ratings after a nutritive liquid and solid meal. *Am J Physiol Regul Integr Comp Physiol* 279(2):R684–R694
- Carney BI, Jones KL, Horowitz M, Sun WM, Penagini R, Meyer JH (1995) Gastric emptying of oil and aqueous meal components in pancreatic insufficiency: effects of posture and on appetite. *Am J Physiol* 268(6):G925–G932
- Davis SS, Hardy JG, Fara JW (1986) Transit of pharmaceutical dosage forms through the small intestine. *Gut* 27(8):886–892
- Heading RC, Nimmo J, Prescott LF, Tothill P (1973) The dependence of paracetamol absorption on the rate of gastric emptying. *Br J Pharmacol* 47(2):415–421
- Backon J, Hoffman A (1991) The lateral decubitus position may affect gastric emptying through an autonomic mechanism: the

- skin pressure-vegetative reflex. *Br J Clin Pharmacol* 32(1):138–139
17. Sanchez NA (2005) New formulations of amoxicillin/clavulanic acid: a pharmacokinetic and pharmacodynamic review. *Clin Pharmacokinet* 44(11):1097–1115
 18. Renwick AG, Ahsan CH, Challenor VF, Daniels R, Macklin BS, Waller DG et al (1992) The influence of posture on the pharmacokinetics of orally administered nifedipine. *Br J Clin Pharmacol* 34(4):332–336
 19. Clements JA, Heading RC, Nimmo WS, Prescott LF (1978) Kinetics of acetaminophen absorption and gastric emptying in man. *Clin Pharmacol Ther* 24(4):420–431
 20. Vance MV, Selden BS, Clark RF (1992) Optimal patient position for transport and initial management of toxic ingestions. *Ann Emerg Med* 21(3):243–246
 21. Wallden J, Thorn SE, Wattwil M (2004) The delay of gastric emptying induced by remifentanyl is not influenced by posture. *Anesth Analg* 99(2):429–434
 22. Roberts MS, Denton MJ (1980) Effect of posture and sleep on pharmacokinetics. I. Amoxicillin. *Eur J Clin Pharmacol* 18(2):175–183
 23. Warren JB, Cuss F, Barnes PJ (1985) Posture and theophylline kinetics. *Br J Clin Pharmacol* 19(5):707–709
 24. Maw GJ, Mackenzie IL, Taylor NA (1995) Redistribution of body fluids during postural manipulations. *Acta Physiol Scand* 155(2):157–163
 25. Hagan RD, Diaz FJ, Horvath SM (1978) Plasma volume changes with movement to supine and standing positions. *J Appl Physiol* 45(3):414–417
 26. Dukova-Peneva P, Penev M, Razsolkov M (1988) Effect of body position on substrates, enzymes and electrolytes in the serum of healthy subjects. *Vutr Boles* 27(4):81–85
 27. Penev M, Kereshka P (1988) Effect of body position on laboratory hematological indices. *Vutr Boles* 27(4):69–72
 28. Abalan F, Schweiger K, Hecquet D, Brachet-Liermain A, Sousselier M, Rigal F (1990) Effect of posture on imipramine and desipramine plasma concentrations. *J Clin Psychopharmacol* 10(4):301–302
 29. Abalan F, Vincon G, Ellisson W, Sousselier M, Demotes-Mainard F, Lachiver E et al (1990) Effect of posture on total phenytoin plasma concentration. *Eur J Clin Pharmacol* 38(5):526–527
 30. Abalan F, Hui Bon Hoa A, Dufrechou N, Ellisson W, Rigal F, Perey F et al (1991) Effect of posture on total thyroxine plasma concentration. *Horm Metab Res* 23(8):404–405
 31. Abalan F, Hui Bon Hoa A, Guillonneau D, Ruedas E, Calache M, Ellisson W et al (1992) Effect of posture on total cortisol plasma concentration. *Horm Metab Res* 24(12):595–596
 32. Rumble RH, Roberts MS, Denton MJ (1991) Effects of posture and sleep on the pharmacokinetics of paracetamol (acetaminophen) and its metabolites. *Clin Pharmacokinet* 20(2):167–173
 33. Modi MW, Hassett JM, Lalka D (1988) Influence of posture on hepatic perfusion and the presystemic biotransformation of propranolol: simulation of the food effect. *Clin Pharmacol Ther* 44(3):268–274
 34. Stromberg C, Vanakoski J, Olkkola KT, Lindqvist A, Seppala T, Laitinen LA (1992) Exercise alters the pharmacokinetics of midazolam. *Clin Pharmacol Ther* 51(5):527–532
 35. Daneshmend TK, Jackson L, Roberts CJ (1981) Physiological and pharmacological variability in estimated hepatic blood flow in man. *Br J Clin Pharmacol* 11(5):491–496
 36. Culbertson JW, Wilkins RW, Ingelfinger FJ, Bradley SE (1951) The effect of the upright posture upon hepatic blood flow in normotensive and hypertensive subjects. *J Clin Invest* 30(3):305–311
 37. Ludden TM (1991) Nonlinear pharmacokinetics: clinical Implications. *Clin Pharmacokinet* 20(6):429–446
 38. Pond SM, Tozer TN (1984) First-pass elimination. Basic concepts and clinical consequences. *Clin Pharmacokinet* 9(1):1–25
 39. Keller F, Kunzendorf U, Walz G, Haller H, Offermann G (1989) Saturable first-pass kinetics of propranolol. *J Clin Pharmacol* 29(3):240–245
 40. Gupta SK, Yih BM, Atkinson L, Longstreth J (1995) The effect of food, time of dosing, and body position on the pharmacokinetics and pharmacodynamics of verapamil and norverapamil. *J Clin Pharmacol* 35(11):1083–1093
 41. Challenor V, Waller DG, Gruchy BS, Renwick AG, George CF, McMurdo ET et al (1986) The effects of food and posture on the pharmacokinetics of a biphasic release preparation of nifedipine. *Br J Clin Pharmacol* 22(5):565–570
 42. Kamper AL, Strandgaard S, Holstein-Rathlou NH, Munck O, Leyssac PP (1988) The influence of body posture on lithium clearance. *Scand J Clin Lab Invest* 48(6):509–512
 43. Backon J (1991) Right lateral decubitus position via skin pressure vegetative reflex may prevent anxiety, adverse autonomic reactions, and syncope in blood donors. *Vox Sang* 60(4):242–243
 44. Hinderling PH, Gundert-Remy U, Forster D, Gau W (1983) The pharmacokinetics of furazolidin in healthy humans. *J Pharmacokin Biopharm* 11(1):5–30
 45. Breiby M, Aarbakke J, Sundsfjord J, Goussius G, Pape J (1983) Effect of posture on ampicillin pharmacokinetics, glomerular filtration rate and renal plasma flow in resting subjects. *Br J Clin Pharmacol* 16(6):691–694
 46. Rumble RH, Roberts MS, Scott AR (1986) The effect of posture on the pharmacokinetics of intravenous benzylpenicillin. *Eur J Clin Pharmacol* 30(6):731–734
 47. Kates RE, Harapat SR, Keefe DL, Goldwater D, Harrison DC (1980) Influence of prolonged recumbency on drug disposition. *Clin Pharmacol Ther* 28(5):624–628
 48. Warren J (1983) Theophylline concentrations and posture. *Lancet* 2(8354):850
 49. Rumble RH, Roberts MS, Scott AR (1988) The effects of posture on the pharmacokinetics of intramuscular benzylpenicillin. *Eur J Clin Pharmacol* 33(6):629–635
 50. Steingoetter A, Fox M, Treier R, Weishaupt D, Marincek B, Boesiger P et al (2006) Effects of posture on the physiology of gastric emptying: a magnetic resonance imaging study. *Scand J Gastroenterol* 41(10):1155–1164
 51. Holford NH (1987) Clinical pharmacokinetics of ethanol. *Clin Pharmacokinet* 13(5):273–292
 52. Warren J, Turner C, Dalton N, Thomson A, Cochrane G, Clark T (1983) The effect of posture on the sympathoadrenal response to theophylline infusion. *Br J Clin Pharmacol* 16(4):405–411