REVIEW

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Rabeprazole: pharmacokinetics and pharmacokinetic drug interactions

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Rabeprazole is the most recently approved proton pump inhibitor in Germany. The substance has an absolute bioavailability upon oral administration of approximately 52% which is robust against food intake or administration of antacids. Maximal plasma concentrations are reached after approximately 3–4 h. Concentrations increase proportionally with the dose. Rabeprazole undergoes an almost complete, mainly non-enzymatic metabolism with renal elimination of the metabolites. CYP3A4 and CYP2C19 contribute to the fraction of metabolism mediated enzymatically. Elimination half-life is about 1 h. The extent of rabeprazole concentration increase by old age, poor metabolizer status for CYP2C19 and impairment of liver function is not greater than two-fold, impaired renal function does not affect the elimination. Even in patients with delayed elimination, no relevant accumulation of rabeprazole was observed upon long-term administration. In *in vivo* studies, rabeprazole had no noteworthy effect on the metabolism of other drugs. This statement however must be made with reservation because of shortcomings in published studies with respect to the methods used and presentation and because of lacking investigations about possible effects on the cytochrome P-450 enzymes CYP3A4 and CYP2D6. A slight reduction in ketoconazole absorption and a moderate increase in digoxin concentrations should be taken into account for concomitant therapy, but is expected to be clinically relevant only in isolated cases. Based on these partially incomplete data, in summary it is to be expected that rabeprazole can be administered at a standard dose for the respective disease in almost any patient for the entire duration of therapy, and that usually no dose adjustment of other drugs is required when rabeprazole is coadministered.

1. Introduction

The insights in the role of *Helicobacter pylori* and the availability of proton pump inhibitors have lead to a considerable amelioration of the pharmacologic treatment options for gastric and duodenal ulcers. Correspondingly, nowadays surgical interventions for these indications like partial gastric resections or vagotomia have only to be carried out in exceptional situations. Proton pump inhibitors also represent for the first time a suitable therapeutic approach for the symptomatic acute as well as chronic treatment of gastroesophageal reflux disease [1–3].

Proton pump inhibitors cause a sustained decrease in gastric acid production. The mechanism of action of all substances in this therapeutic class is a specific inhibition of the H^+,K^+-ATPase, the enzyme responsible for the terminal step in the secretion of gastric acid. Proton pump inhibitors bind by disulphide linkage specifically and virtually irreversibly to extracellular cystein residues of this transport protein [4]. Therefore, pharmacologic peculiarities of the single compounds can only be attributable to additional drug targets or to distinct pharmacokinetic behaviours. While additional mechanisms of action are unknown, further drug targets are represented by xenobiotic metabolising enzymes, with the possibility to cause drug drug interactions. Additionally, pharmacokinetic characteristics of proton pump inhibitors differ largely. This is not only true for the time course of plasma concentrations and the mechanisms of elimination [5, 6], but also for binding characteristics to the target enzyme H^+,K^+-ATPase [4, 7].

Knowledge of these particular characteristics of an individual proton pump inhibitor is crucial to avoid surprises in individual patients who have pharmacokinetics differing considerably from the population means. In these patients, an individually adapted dose should be chosen. Patient groups which are particularly susceptible to altered pharmacokinetics and hence adverse drug effects include patients with:

- concomitant intake of other medications (risk of interactions)
- genetic variations in drug metabolism
- low age (children)
- higher age (>65 years)
- renal dysfunction
- hepatic dysfunction
- critical illness

Whether these groups of patients show particular characteristics for a single compound has therefore to be studied specifically.

Rabeprazole is the proton pump inhibitor most recently released for use in Germany. Indications include the acute *Ulcus duodeni* and the acute, benign *Ulcus ventriculi*, symptomatic erosive or ulcerative gasroesophageal reflux disease, long-term therapy of gastroesophageal reflux disease and (in combination with appropriate antibiotics) the eradication therapy against *Helicobacter pylori* in patients with peptic ulcer [8, 9]. A detailed review of the efficacy of the substance has recently been published [10]. Main pharmacokinetic characteristics of rabeprazole comprise an absolute bioavailability of approximately 52% after oral administration which is independent of influencing factors like food intake; a time to reach maximal plasma concentrations of 3 to 4 h; a linear increase of concentrations dependent on the dose administered; and an extensive, probably non-enzymatic biodegradation with a short elimination half-life of roughly 1 h, thereby preventing accumulation after long-term administration.

2. Investigations in healthy volunteers

2.1. Absorption and bioavailability

Due to their instability in acidic milieu, proton pump inhibitors are marketed as enteric coated oral dosage forms. Correspondingly, absorption of rabeprazole after oral intake starts with some delay, independent of the dose admi-

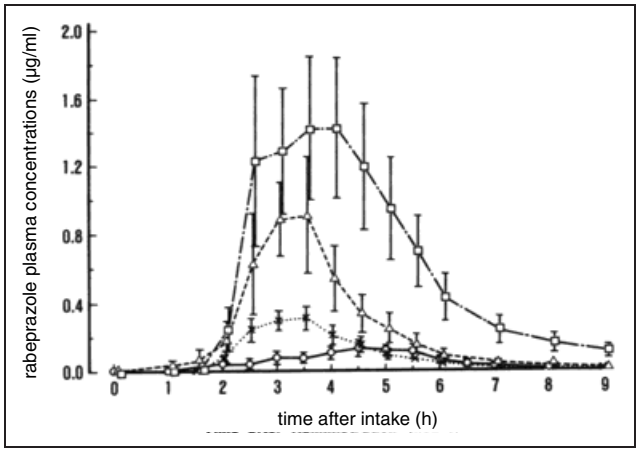


Fig.: Concentration vs. time course of rabeprazole after oral single dose administration.
Each point corresponds to the mean ± SEM of 4 persons in the 40 mg – study and of 6 persons for the other doses. ○ = 10 mg, × = 20 mg, Δ = 40 mg, □ = 80 mg (taken from Yasuda et al. 1994 [11], with the permission of Dustri Verlag, Deisenhofen, Germany)

Table 1: Pharmacokinetic parameters (means ± SD) of rabeprazole in 6 healthy Japanese [11][a] and in 8 healthy, mostly Caucasian males [12][b]

Dose	AUC (ng/ml · h)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
10 mg[a]	440 ± 59	247 ± 59	3.8 ± 1.3	0.85 ± 0.09
10 mg[b]	315 ± 211	184 ± 135	2.9 ± 0.6	0.73 ± 0.16
20 mg[a]	809 ± 456	406 ± 156	3.1 ± 0.4	1.02 ± 0.39
20 mg[b]	545 ± 215	294 ± 101	2.9 ± 0.4	0.70 ± 0.16
30 mg[b]	1182 ± 536	615 ± 228	2.9 ± 0.4	0.86 ± 0.29
40 mg[a]	2153 ± 628	1351 ± 453	2.9 ± 0.5	1.06 ± 0.09
40 mg[b]	1554 ± 211	800 ± 536	2.8 ± 0.9	1.01 ± 0.36
80 mg[a]	5212 ± 2158	2499 ± 618	3.3 ± 0.9	1.21 ± 0.32

nistered. Maximal plasma concentrations are reached between 2.8 and 5.1 h postdose (means of published studies) [11, 12]. In trials investigating dose-proportionality, concentration vs. time courses of rabeprazole and its metabolites were studied after single-dose administration of 10 to 80 mg [11] (Fig.) and 10 to 40 mg [12], respectively. Maximal plasma concentrations, C_{max}, as well as the area under the concentration vs. time curve, AUC, increased linearly with dose (Table 1). This shows that there exists neither a saturable first-pass metabolism, which would lead to non-proportional increases in plasma concentrations after high doses [13], nor a limitation of the capacity to liberate or absorb high doses, as it would be the case for a poorly soluble substance.

The absolute bioavailability of rabeprazole is reported to amount to 52% after administration of a 20 mg dose [8]. On the basis of the renal elimination of metabolites of rabeprazole, a bioavailability of at least 30% has been estimated [11].

The intake of rabeprazole within 30 min after a standard breakfast (526 kcal with 22.7 g fat and 23.2 g protein) delayed the absorption of 20 mg of rabeprazole compared with drug intake in the fasting state and reduced the apparent elimination half life in a crossover study in 12 healthy Japanese volunteers, but did not have an effect on bioavailability [11, 14]. With food intake, maximal plasma concentrations were reached 1.7 h later. Probably, these differences are merely caused by a delay in stomach emptying after the meal.

2.2. Distribution

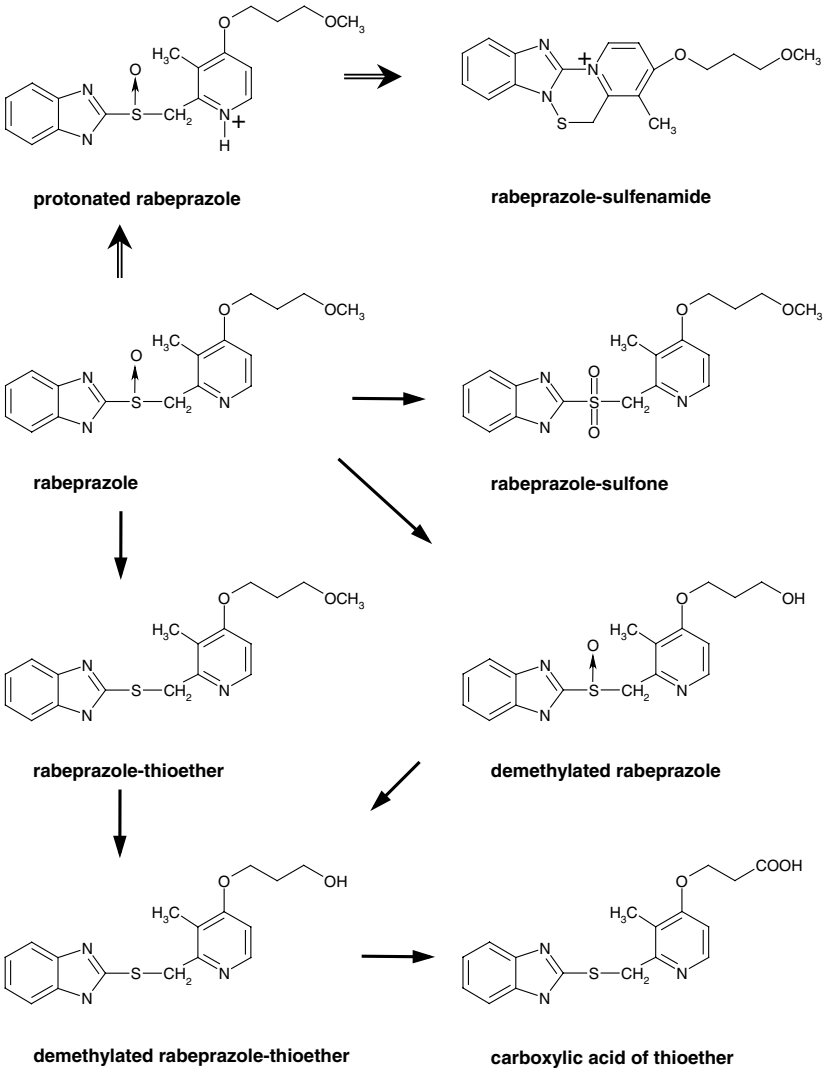
In healthy volunteers, rabeprazole is bound to plasma proteins to 94.8–97.5% [8, 15]. Data concerning the volume of distribution in man (Vd or Vd/F) are not available.

Table 2: *In vivo*-studies on the effect of rabeprazole on the pharmacokinetics of other drugs[a]

Substance examined			Rabeprazole	Statistically significant effect of rabeprazole on the kinetics of the substance examined
Relevant for pharmacokinetics[b]	Drug (number of volunteers)[c]	Dose and route of administration	Dose and route of administration	
CYP1A2	Theophylline (n = 12)	250 mg orally single dose	1 × 20 mg orally for 7 days	None
CYP2C9	Phenytoin (n = 12)	2 × 100 mg orally for 3 days + 1 × 250 mg i.v. on day 4	1 × 20 mg orally for 13 days	None
	Warfarin (n = 10)	0.75 mg/kg orally single dose	1 × 20 mg orally for 7 days	None
CYP2C19	Diazepam (n = 15)	0.1 mg/kg i.v. single dose	1 × 20 mg orally for 23 days	None
CYP3A	Desmethyldiazepam (n = 15)	diazepam 0.1 mg/kg i.v. single dose	1 × 20 mg orally for 23 days	AUC + 16%
	Cortisol (n = 12)	endogenous	1 × 20 mg orally for 14 days	None (renal elimination of 6-β-hydroxycortisol not increased)
p-Glycoprotein	Digoxin (n = 8)	0.25 mg orally daily in steady state	1 × 20 mg orally for 14 days	Increased concentrations: trough value + 22%, C_{max} + 29%
Gastric pH	Ketoconazole (n = 9)	400 mg orally single dose	1 × 20 mg orally for 7 days	33% decrease of concentrations

[a] As far as assessable because of flaws in design and presentation of the studies, see introductory remarks in paragraph "Interactions with concomitantly taken drugs" (references are also given there).
[b] A detailed state-of-the-art review of substrates of the various cytochrome P450 enzymes is given in ref. [5].
[c] The number of volunteers who were actually included in the comparison is indicated. In several studies an additional group participated which did not receive rabeprazole in any of the periods.

Scheme: Metabolism of Rabeprazole in man [4, 16, 42]



2.3. Metabolism and elimination

In healthy volunteers, the elimination half life averages approximately 1 h (range 0.7 to 1.5 h), the mean clearance after oral intake is about 7 ml/min/kg [11]. The mean total body clearance is reported to amount to 283 ml/min [8]. It should be noted that, albeit rabeprazole is eliminated rapidly, its effect lasts much longer than concentrations in plasma are detectable, because of the stable binding of rabeprazole to the H^+,K^+-ATPase.

After ingestion of a single oral dose of 20 mg of ^{14}C radiolabelled rabeprazole no unchanged compound was detected in urine. About 90% of dose were excreted renally as four metabolites, comprising besides the mercapturate conjugate and the carboxylic acid (Scheme) two non-identified metabolites [16]. The remaining radioactivity was detected in faeces. In man, thioether and carboxylic acid are the two most prominent metabolites in plasma, while sulfone, demethylated thioether, and mercapturate conjugate metabolites were found only in low concentrations (Scheme) [8]. Original data endorsing these statements are however not published.

In overview articles (e.g. [5]), the formation of thioether is referred to as being the most important primary metabolic step which is said to take place non-enzymatically. A primarily non-enzymatic degradation of rabeprazole is principally advantageous, because – in contrast to other proton pump inhibitors [17] – it cannot be altered by inhibitors of drug metabolising enzymes. Concerning the primary biotransformation steps towards rabeprazole sulfone and towards demethylated rabeprazole, detailed investigations in human liver microsomes have been published [18]. These investigations revealed that the high affinity binding site for the formation of the sulfone is represented by CYP3A4 (K_M approx. 4 μM), while demethylation of rabeprazole is mediated by CYP2C19 (K_M approx. 15 μM).

The formation of sulfenamide [4] which takes place in the acidic milieu of the stomach only represents a quantitatively very small portion of the entire metabolism, though

being essential for the pharmacologic action of the substance. This metabolite is not detected in plasma or urine.
The comparison between pharmacokinetic parameters after single dose and after long-term administration did not result in any relevant difference regarding accumulation of rabeprazole or auto-induction of metabolism [11].

2.4 Pharmacokinetics at the pharmacologic site of action, the H^+,K^+-ATPase

Rabeprazole is a weak base accumulating in the acidic milieu of the stomach, which is maintained by the activity of the H^+,K^+-ATPase. The substance is protonated there and undergoes an acid-mediated transformation leading to the cationic sulfenamide, which forms stable disulfides with extracellular cysteine residues of the H^+,K^+-ATPase, thereby inactivating this enzyme. The sulfenamide formation of rabeprazole is accomplished significantly faster compared to other proton pump inhibitors [7]. Correspondingly, rabeprazole showed the fastest inactivation of H^+,K^+-ATPase in an *in vitro* investigation [4].
Despite the short elimination half-life of approximately 1 h, the effect of rabeprazole on gastric pH and on gastric acid secretion is fully present for at least 24 h, and is still detectable the third day after withdrawal [19], while active metabolites of rabeprazole are not detected in plasma any longer [16]. These findings elucidate that rabeprazole remains bound to the H^+,K^+-ATPase after elimination from the plasma and suppresses effectively the function of the proton pump.

3. Investigations in special populations

3.1. Interactions with concomitantly taken drugs

For the registration of rabeprazole, several investigations have been carried out concerning interactions with other compounds, which show a certain specificity for particular elimination pathways, and with which interactions would be of clinical relevance. The data available from these studies feature some particularities relevant for proper interpretation which, therefore, will shortly be explained here. Most of these investigations have only been published as abstracts of presentations at scientific meetings, hence the information included therein can only be judged with precaution. In most studies, an unusual parallel group design has been used, firstly determining the pharmacokinetics of the possible interaction partner of rabeprazole after administration without rabeprazole. Thereafter, the population to be studied was randomly assigned to the additional intake of rabeprazole and placebo, respectively. The results are mostly presented as differences of pharmacokinetic parameters obtained in the second part of the study to the respective values before addition of placebo and rabeprazole. Absolute values for the single study periods as well as the magnitudes of changes are not published, so statements regarding the absolute extent of change observed with rabeprazole cannot be given. The assessment of the interaction is done by statistical comparison of differences between the groups after placebo and rabeprazole intake. Since sample size considerations are mostly not reported, it is questionable whether the power of these investigations was sufficient to detect existing differences. Apparently, the null hypothesis was "no interaction present", which could not be rejected when values varied over a wide range even if an interaction existed.

3.1.1. Effects of rabeprazole on the pharmacokinetics of other drugs

In investigations with human liver microsomes, an inhibition of the metabolism of cyclosporine (2 μM) by rabeprazole with an IC_{50} – value of 62 μM was shown [20]. Cyclosporine is a substrate of CYP3A4. Another study revealed a competitive inhibitory effect of rabeprazole on the cytochrome P450 enzymes CYP3A4 and CYP2C19 [18]. A K_i-value of 59 μM for 1′-hydroxylation of midazolam (CYP3A4) and of 9 μM for 4′-hydroxylation of S-mephenytoin (CYP2C19) was reported. Additionally, a weak mixed-type inhibition was found for CYP2D6 (K_i-value for 1′-hydroxylation of bufuralol 101 μM). The effect of rabeprazole on other enzymes was not studied. The authors of this study predicted on the basis of these values that rabeprazole would diminish the activity of CYP3A4 *in vivo* by 2% and that of CYP2D6 by 11% [18]. Since *in vitro/in vivo* extrapolations are not very exact even in the case of solid *in vitro* information, the effect of rabeprazole on these enzymes *in vivo* has to be studied carefully.
Further *in vitro* studies examined the potency of rabeprazole to induce enzymes of the cytochrome P450 system. Regarding omeprazole, the observed induction of the cytochrome P450 subfamily CYP1A was initially judged to have possible clinical consequences [21]. However, until now this effect revealed to be irrelevant in clinical practice. In an investigation on CYP1A1 induction in the human hepatoma cell line HepG2, rabeprazole provoked an increase in mRNA concentration, in protein expression and in enzyme activity of CYP1A1, but these effects were less pronounced compared to the reference substance omeprazole [22]. In primary human hepatocytes, no induction of CYP1A2 and CYP2D6 was observed, while one of three cell cultures presented a weak induction of CYP2E1 and a more distinct induction of CYP3A4 in the presence of rabeprazole (50 μM) [20]. This observation, however, has to be confirmed in further studies, since results of investigations with primary human hepatocytes are often very variable.

3.1.1.1. Digoxin

In 2×8 healthy volunteers, the effect of placebo and 20 mg rabeprazole, respectively, once daily for two weeks on the steady-state pharmacokinetics of 0.25 mg digoxin daily was examined [23]. The authors indicated that a difference of 25% was detectable with a power of 80% and $\alpha = 0.05$. Rabeprazole caused a significant increase in AUC, in maximal plasma concentrations, and in elimination half-life of digoxin. Trough concentrations increased by 22% with rabeprazole [8], and maximal concentrations by 29% [24]. So far, it has been assumed that this type of interaction at the absorption site is mediated by an increase in gastric pH caused by proton pump inhibitors, but new findings challenge the mechanism of this interaction. It may be possible that rabeprazole causes a certain inhibition of the activity of p-glycoprotein, a transmembrane carrier mediating intestinal secretion of digoxin and also playing a role in the renal elimination of the compound [25]. Therefore, a possible effect of proton pump inhibitors on p-glycoprotein should be investigated for rabeprazole as well as for the other compounds in this therapeutic class.

3.1.1.2. Diazepam

This interaction has been tested in 15 healthy Japanese men in a change-over design, among them six "poor meta-

bolizers" and nine "extensive metabolizers" for CYP2C19 [26]. Rabeprazole (20 mg), omeprazole (20 mg) or placebo were administered once daily for 23 days each. On day 8 of the respective intake period, 0.1 mg/kg diazepam were given intravenously. Because of the long elimination half-life of diazepam and its metabolites, concentrations were monitored up to 16 days after application. As expected, the clearance of diazepam in "poor metabolizers" was roughly half of that observed in "extensive metabolizers" for CYP2C19. In contrast to omeprazole, in either groups rabeprazole did not influence the concentration vs. time course and the pharmacokinetic parameters of the parent compound diazepam. Only in "poor metabolizers" a small but significant increase in AUC of desmethyldiazepam by 16% was seen. The authors interpreted this finding as a hint at an inhibition of CYP3A4 which plays a role in the further metabolism of this diazepam metabolite [26].

3.1.1.3. Phenytoin

To elucidate this possible interaction, two groups of 12 healthy volunteers each were examined [27]. Phenytoin, a substrate of the cytochrome P450 enzyme CYP2C9, was given orally in a dose of 100 mg twice daily for three days. The fourth day, 250 mg were administered intravenously. In the comparison period, rabeprazole in a dose of 20 mg and placebo, respectively, was given each to 12 volunteers for 13 days once daily. No significant changes compared to the sole administration of phenytoin were observed.

3.1.1.4. Theophylline

The effect of placebo or 20 mg rabeprazole once daily for 7 days, respectively, on the pharmacokinetics of a single dose of 250 mg theophylline was investigated in 2×12 healthy volunteers [28]. No statistically significant differences were seen between the groups in the changes of kinetic parameters of theophylline after vs. before intake of rabeprazole and placebo, respectively. Since theophylline metabolism is primarily mediated by the cytochrome P450 enzyme CYP1A2 [29], interactions between rabeprazole and other substrates of this enzyme like caffeine, tacrine, clozapine, and triamterene [30] are not likely to be expected.

3.1.1.5. Warfarin

A study with warfarin was carried out in 2×10 healthy volunteers. The impact of placebo and 20 mg rabeprazole once daily for seven days, respectively, on the pharmacokinetics and pharmacodynamics (prothrombin time) following a single dose of 0.75 mg/kg warfarin was investigated [28]. The authors indicated that there were no statistically significant differences between the groups regarding the changes in parameters of warfarin compared to the respective values in the groups before administration of rabeprazole or placebo. However, in the abstract cited here, prothrombin time values were chosen as parameters for comparison, while pharmacokinetic data are not shown. Warfarin is mainly biotransformed by the cytochrome P450 enzyme CYP2C9 [31], therefore, interactions between rabeprazole and other substrates for this enzyme like tolbutamide or diclofenac seem unlikely.

3.1.1.6. Ketoconazole

In a study with parallel group design, the effect of placebo and 20 mg rabeprazole once daily for seven days, respectively, on the pharmacokinetics of a single dose of 400 mg ketoconazole was investigated in 2×9 healthy volunteers [32]. Rabeprazole led to a significant decrease in AUC and C_{max} of ketoconazole. Unfortunately, the study is only published as an abstract not reporting the magnitude of decrease. In the manufacturer's information leaflet (German "Fachinformation"), a decrease in ketoconazole concentrations by 33% caused by rabeprazole is mentioned [8].

3.1.1.7. Miscellaneous

In a study in 12 healthy men, the effect of 20 mg rabeprazole once daily for two weeks or placebo on endocrine functions was examined [19]. Rabeprazole caused no relevant changes in the homeostasis of sex hormones, mineralo- and glucocorticoids, thyroid hormones, PTH, insulin, glucagon, renin, and somatotrophic hormone. Particularly, there was no impact on the excretion of 6-beta-hydroxycortisol in urine. Formation of this metabolite of cortisol is mediated by enzymes of the cytochrome P450 subfamily CYP3A, and is markedly increased when enzyme activity is induced [33]. Therefore, a pronounced induction of CYP3A enzymes by rabeprazole is not to be expected in man.

In conclusion, for rabeprazole no noteworthy influence on the metabolism of other drugs was shown *in vivo*, while the absorption/intestinal secretion of drugs was impaired to a certain degree. This conclusion, however, can only be drawn with precaution because of the flaws in study design and presentation of the results [34]. Moreover, no adequate studies on the effect of rabeprazole on the activity of the cytochrome P450 enzymes CYP3A4 and CYP2D6 are published. These two enzymes are among the most important enzymes in the metabolism of xenobiotics in man.

3.1.2. Effect of other drugs on the pharmacokinetics of rabeprazole

3.1.2.1. Ketoconazole

Ketoconazole is a highly potent inhibitor of the cytochrome P450 enzyme CYP3A4. In the above mentioned study on the effect of rabeprazole on the pharmacokinetics of ketoconazole, rabeprazole concentrations have also been determined [11]. A comparison period without ketoconazole intake is, however, missing. The authors compare their results with the pharmacokinetics of rabeprazole derived from other studies and conclude that at least a pronounced impact of ketoconazole on rabeprazole pharmacokinetics is not to be expected. This would also make unlikely that interactions between other inhibitors of CYP3A4 and rabeprazole occur.

3.1.2.2. Antacids (Mg/Al hydroxide)

In a cross-over-study in 12 healthy Japanese men, 20 mg rabeprazole were administered alone, together with the antacid, and 1 h after the antacid [14, 35]. Maalox® was used as antacid in a dosage of 30 ml (448 mg $Al(OH)_3$ and 400 mg $Mg(OH)_2$). In both regimens, no significant influence of the antacid on the pharmacokinetics of rabeprazole was detected. Only for the AUC, the power of the

study was above 80%, so that the lack of interaction could be substantiated with sufficient reliability.

3.2. Individuals with genetic variations in drug metabolism

The genetically polymorphic cytochrome P450 enzyme CYP2C19 contributes to the metabolism of all proton pump inhibitors. Depending on the population studied, between 1% (Afro-Americans) and 23% (Japanese) of patients are so-called "poor metabolizers" with a homozygously deficient form of the enzyme. In so-called "Caucasians", a term also including central Europeans, "poor metabolizers" for CYP2C19 account for 2–6% of the population [5]. Patients with this deficiency show a correspondingly decreased elimination of substrates of this enzyme.

In an investigation in 15 volunteers (4 homozygous extensive and poor metabolisers each, and 7 heterozygous extensive metabolisers), the pharmacokinetics of rabeprazole (20 mg) were clearly less dependent on the CYP2C19 metaboliser status than those of omeprazole and lansoprazole [36]. Compared to homozygous extensive metabolisers, the area under the concentration vs. time curve of rabeprazole was increased 1.11 fold in heterozygous extensive metabolisers, and 1.39 fold in homozygous poor metabolisers.

Another study compared the pharmacokinetics of omeprazole and of rabeprazole between six poor metabolisers and nine (homozygous and heterozygous) extensive metabolisers of CYP2C19 [16]. The substances were given in a dose of 20 mg daily for seven days, and pharmacokinetic parameters were determined after the first and after the seventh dose. Again, a significant influence of CYP2C19 genotype on the pharmacokinetics of rabeprazole became evident: Mean AUC and mean elimination half-life were increased in poor metabolisers by 1.8 fold compared to extensive metabolisers (corresponding increases for omeprazole amounted to 6.3 fold and 3.5 fold, respectively, with additional remarkable differences in the kinetics of metabolites). While discrete changes in the metabolite pattern of rabeprazole were observed on the seventh day, the differences between CYP2C19 phenotypes were essentially unchanged.

Overall, only relatively small differences in the pharmacokinetics of rabeprazole were observed between the different genotypes and phenotypes of CYP2C19. These findings can be explained by the fact that, in contrast to other proton pump inhibitors, only a minor metabolic pathway of rabeprazole, i. e. demethylation (see above, Scheme), is mediated by CYP2C19. Correspondingly, in a comparative study no difference in intragastric pH between CYP2C19 genotypes was found during therapy with 20 mg rabeprazole daily [37].

3.3. Effects of age

3.3.1. Children

No data on pharmacokinetics of rabeprazole in children is available.

3.3.2. Elderly people

In a study in two groups of 20 persons (10 men and 10 women each), differences related to age were investigated [38]. The mean age in one group was 23.3 ± 3.9 years, and in the other group 71.1 ± 4.9 years. On the seventh day of administration of 20 mg rabeprazole once daily, the AUC in the elderly was almost twice as high as in the young volunteers, and maximal plasma concentrations and elimination half-life were 57% and 29% greater, respectively. However, no evidence for accumulation of rabeprazole was found.

3.4. Influence of diseases

3.4.1. Renal dysfunction

A study in ten healthy men (creatinine clearance > 90 ml/min/m^2) and in 10 patients with stable chronic end-stage renal failure on hemodialysis (creatinine clearance ≤ 5 ml/min/m^2) has been carried out [39]. A single dose of 20 mg rabeprazole was administered to the healthy volunteers, the patients with end-stage renal failure were given the same single dose once daily after hemodialysis, and on a second occasion during hemodialysis. No statistically significant difference in any of the pharmacokinetic parameters studied was observed neither for the patients compared to the healthy men nor in the patients following or during hemodialysis. However, due to a pronounced variability of the parameters together with a small power of the study, the existence of real differences cannot be excluded with sufficient probability. In fact, the mean AUC and C_{max} values in patients were approximately 35% lower than in healthy volunteers. Based on these data and on the known elimination pathways of rabeprazole, in can be assumed with some precaution that the dosage of rabeprazole needs not to be adapted to renal function [8, 9].

3.4.2. Hepatic dysfunction

In a comparative study in 13 healthy men and 10 men with compensated chronic liver cirrhosis [40], the oral clearance of a single dose of 20 mg rabeprazole was reduced to roughly 40%. Maximal plasma concentrations in patients were approximately doubled. An average terminal elimination half-life of 3.7 h is even in these patients not in favour of an accumulation risk of rabeprazole when administered once daily. Unfortunately, the publication does not mention the exact degree of liver cirrhosis [40], so, based on this study, it cannot easily be determined which patients with hepatic dysfunction should not be treated any more with rabeprazole, irrespective of the favourable outcome of this study.

In another investigation not published in detail [8], carried out in patients with chronic mild to moderate hepatic dysfunction, the AUC after intake of a single dose of 20 mg rabeprazole was doubled in comparison to healthy volunteers, and the half-life of rabeprazole increased two- to threefold. The increase in AUC after 20 mg rabeprazole daily for seven days was 1.5 fold, while C_{max} increased 1.2 fold. The terminal elimination half-life of rabeprazole in steady-state in patients with deteriorated hepatic function amounted to 12.3 h compared to 2.1 h in healthy volunteers. However, the pharmacodynamic effect on gastric pH was similar in both groups.

3.4.3. Severe diseases and critically ill patients

No data on rabeprazole pharmacokinetics in patients with severe systemic diseases like e.g. septicemia are available.

4. Conclusions

The pharmacokinetic behaviour of the new proton pump inhibitor rabeprazole shows only minor differences in most populations with particular medical conditions compared to healthy young volunteers.

The plasma concentrations of rabeprazole were increased up to not more than twofold by higher age, poor metaboliser status for CYP2C19, and hepatic dysfunction, while renal dysfunction and the intake of antacids did not influence the pharmacokinetics of the proton pump inhibitor. None of the groups investigated showed any relevant accumulation of rabeprazole during long-term treatment.

In published investigations, which however should be amended, rabeprazole did not cause metabolic drug interactions. Some impairment in absorption of ketoconazole and a moderate increase in digoxin concentrations should be considered when the drugs are used concomitantly with rabeprazole, however, these interactions may become clinically relevant only in individual cases.

On the basis of these data it can be expected that rabeprazole can be administered to almost all patients for the entire duration of treatment in a standard dose appropriate to the individual disease [41], and that in general no dose adaptation of other pharmacologic entities is necessary when rabeprazole is added to a given treatment.

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