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# Cefpodoxime-proxetil hydrolysis and food effects in the intestinal lumen before absorption: in vitro comparison of rabbit and human material

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**Abstract**

The luminal and mucosal deesterification of the prodrug ester cefpodoxime-proxetil was studied in human duodenal washings in vitro. Enzymatic hydrolysis of the ester, releasing the active third generation cephalosporin, was observed in luminal washing in the same way as it had previously been observed in the rabbit. Eserine and PMSF and $HgCl_2$ were potent inhibitors of cefpodoxime-proxetil hydrolysis in luminal washing, suggesting the participation of a cholinesterase in the hydrolysis of cefpodoxime-proxetil. These results are in agreement with our previous findings performed in the rabbit. Moreover, cefpodoxime-proxetil directly decreases the acetylcholinesterase activity when tested by a specific enzymatic method. These observations support the hypothesis that the partial oral bioavailability of cefpodoxime-proxetil results from hydrolysis by luminal cholinesterases. In vitro experiments run with rabbit duodenal washing with food components were compared with the pharmacokinetics of cefpodoxime-proxetil in humans. Amino acids, trace elements and vitamins were potent inhibitors for cefpodoxime-proxetil hydrolysis in duodenal washings. Otherwise, lipids (LTC and mixed LCT/MCT) did not interact. In the human, cefpodoxime-proxetil bioavailability is significantly enhanced when tablets are administered with food. The correlation found between animal results and human results in vitro for prospective investigation of a new prodrug ester could be very useful. An in vitro hydrolysis in intestinal animal washings could allow the potentially degraded condition and the food effect of the luminal tract to be assessed before absorption. © 1997 Elsevier Science B.V.

*Keywords:* Absorption; Cefpodoxime-proxetil; Human duodenal washing; Cholinesterase; Amino acids; Trace elements; Vitamins; Lipid

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## 1. Introduction

Cefpodoxime-proxetil is an orally absorbed broad spectrum third generation cephalosporin ester. This prodrug ester is deesterified in vivo into its active metabolite cefpodoxime. In humans, the absolute bioavailability of cefpodoxime-proxetil administered as a 100 mg tablet is about 50% (Borin, 1991). Moreover, in the faeces, cefpodoxime-proxetil accounted for less than 0.5% of the administered dose, most of it being recovered as free cefpodoxime. This suggests that a degradation of the prodrug ester occurs in the intestinal lumen.

The degradation of cefpodoxime-proxetil was previously studied in rabbit duodenal washings (Crauste-Manciet et al., 1997). The rabbit was selected as a model because of it human similarity in activity of intestinal esterase which hydrolyze the ester-type drugs (Inoue et al., 1979a). In our previous study performed in vitro in the rabbit we observed a hydrolysis of the ester, leading to the release of free cefpodoxime. This hydrolysis is clearly related to an enzymatic activity since we did not observe any spontaneous hydrolysis at temperatures as high as 50°C and pH values in the range 6–8. Enzymatic activity was high in the luminal washing and was inhibited both by diisopropylfluorophosphate (DFP) and eserine. Therefore, this enzyme can be classified as a B esterase according to Aldridge's classification (Aldridge, 1953) and a cholinesterase according to Walker and Mackness, 1983.

The aim of the present work was to check in vitro in human duodenal washings that a similar cefpodoxime hydrolysis occurred and to investigate in vitro the impact of food on cefpodoxime-proxetil bioavailability. In human, cefpodoxime-proxetil bioavailability was found to be enhanced by food (Hughes et al., 1989; Borin and Forbes, 1995; Borin et al., 1995a,b). The objective of the present work was to correlate the influence of nutrients such as lipids, amino acids, trace elements and vitamins on the intestinal esterase activity in vitro.

## 2. Materials and methods

### 2.1. Materials

Cefpodoxime-proxetil was kindly provided by Roussel Uclaf, France. Cefuroxime-axetil, eserine, phenylmethylsulfonyl fluoride (PMSF), acetylthiocholine, acetylcholinesterase from the electric eel and 5,5′-dithio-bis(2-nitrobenzoic acid (DTNB) were purchased from Sigma (La Verpillière, France). Injectable macronutrients used for competition were the long chain triglycerides (200 g/l) emulsion, IVELIP® 20% (Clintec Nutrition Clinique, Sèvres, France). The mixed medium chain triglycerides (100 g/l) and long chain triglycerides (100 g/l) emulsion, MEDIALIPIDE® 20% (B. Braun Medical, Boulogne, France) and a mixed amino acids injectable solution, VAMINE®, (Kabi Pharmacia, St. Quentin en Yvelines, France). The amino acids composition is given in Table 1a. Injectable micronutrients as a trace element mixture, were also tested, namely, NONAN® (Aguettant, Lyon, France) and mixed hydrosoluble liposoluble vitamins, CERNEVIT® (Clintec Nutrition Clinique). Trace elements and vitamin compositions are given in Table 1bTable 1c, respectively. All other reagents were of the highest grade available.

### 2.2. Methods

#### 2.2.1. Human intestinal washings

Human duodenal washing samples were obtained from overnight fasted healthy volunteers in accordance with the Helsinki Declaration. 5 ml Duodenal washings were collected by tube from 6 male volunteers. The samples collected were spun down at $3800 \times g$ for 10 min to remove particulate material, pooled and frozen at $-22$°C.

#### 2.2.2. Rabbit intestinal washings

Male New-Zealand rabbits weighing 2.5–3 kg were fasted overnight before being sacrificed by i.v. injection of 2 ml/kg sodium pentobarbital. After an abdominal mid-line incision, the small intestine was exposed and a 20 cm segment be-

Table 1
Composition of Vamine®, Nonan® and Cernevit®

a: Amino acids composition of Vamine®

| Amino acids | Concentration (g/l) |
|---|---|
| L-Alanine | 3.8 |
| L-Arginine | 4.2 |
| L-Aspartic acid | 5.2 |
| L-Cystein | 1.7 |
| L-Phenylalanine | 7.0 |
| L-Glutamic acid | 11.5 |
| Glycine | 2.7 |
| L-Histidine | 3.1 |
| L-Isoleucine | 5.0 |
| L-Leucine | 6.7 |
| L-Lysine | 5.0 |
| L-Methionine | 2.4 |
| L-Proline | 10.3 |
| L-Serine | 9.6 |
| L-Threonine | 3.8 |
| L-Tryptophane | 1.3 |
| L-Tyrosine | 0.6 |
| L-Valine | 5.5 |

b: Trace element composition of Nonan®

| Trace elements | Concentration |
|---|---|
| $Fe^{2+}$ | 0.450 mM |
| $Cu^{2+}$ | 0.175 mM |
| $Mn^{2+}$ | 0.450 mM |
| $Zn^{2+}$ | 1.525 mM |
| $F^{2+}$ | 1.9 mM |
| $Co^{2+}$ | 0.625 $\mu$M |
| $I^{2+}$ | 0.300 $\mu$M |
| $Se^{2+}$ | 12.675 $\mu$M |
| $Mo^{2+}$ | 6.500 $\mu$M |

c: Vitamin composition of Cernevit®

| Vitamins | Concentration |
|---|---|
| Retinol | 700 000 I.U./l |
| Cholecalciferol | 44 000 I.U./l |
| Alphatocopherol | 2240 I.U./l |
| Ascorbic acid | 25 g/l |
| Thiamine | 0.702 g/l |
| Riboflavine | 0.828 g/l |
| Pyridoxine | 0.906 g/l |
| Cyanocobalamine | 0.0012 g/l |
| Folic acid | 0.0828 g/l |
| Biotine | 0.0138 g/l |
| Nicotinamide | 9.2 g/l |
| Panthotenic acid | 3.45 g/l |

The influence of nutrients on the cefpodoxime-proxetil hydrolysis was performed in the rabbit. Qualitative and quantative composition of the mixtures used are: a, the amino acid mixture; b, the trace element mixture; c, the vitamin mixture.

ginning 5 cm distal to the pylorus was ligatured at both ends. The segment was filled with 5 ml washing buffer (10 mM Hepes buffer pH 7, 300 mM mannitol) which was left inside for 10 min. The intestine was then evacuated, the washing was spun down at $3800 \times g$ for 10 min to remove particulate material, aliquoted and frozen at $-22$°C.

### *2.2.3. Assay of cefpodoxime-proxetil esterase activity*

The enzymatic preparation (5 $\mu$g protein) was preincubated at 37°C for 5 min in 200 $\mu$l of 10 mM Hepes buffer pH 7, 300 mM mannitol. The reaction was started by the addition of 50 $\mu$l of cefpodoxime-proxetil (final concentration of 100 $\mu$M). After 30 min incubation, the reaction was stopped by the addition of trifluoroacetic acid (TFA) and the samples were centrifuged at $10\,000 \times g$ for 15 min and the amount of cefpodoxime released was measured by HPLC analysis of the supernatant.

The effect of eserine, paramethyl sulfoxide (PMSF), on the hydrolysis of cefpodoxime-proxetil in the human intestinal washings was measured by preincubating the enzymatic preparation with the above mentioned compound for 15 min at 37°C.

The specificity of cefpodoxime-proxetil esterase was studied in human and in rabbit duodenal washings by adding cefuroxime-axetil simultaneously to the cefpodoxime-proxetil at final concentrations in the range 0.01–1 mM.

The influence of the nutrients on cefpodoxime-proxetil hydrolysis was tested in the rabbit by adding elementary compound mixtures namely: amino acids, lipidic emulsions, vitamins and trace elements with a dilution factor from 1 (undiluted mixture) to 0.01. Injectable nutrients were selected for the in vitro study in order to study separately the impact of each class of nutrient on the hydrolysis of cefpodoxime-proxetil. The initial concentration (undiluted) of each mixture can be made to match the daily needs of proteins, lipids, vitamins and trace elements in humans. The dilution (0.1 and 0.01) of each mixture were performed in order to improve the concentration effect on the enzymatic activity.

*2.2.4. Cholinesterase activity inhibition by cefpodoxime-proxetil*

Acetylcholinesterase activity: acetylcholinesterase activity was measured at 37°C and pH 8 by the photometric method of Ellman et al., 1961. The reaction mixture contained 2.86 ml 0.1 M phosphate buffer pH 8, 0.10 ml 0.01 M DTNB, 20 $\mu$l 0.075 M acetylthiocholine and 20 $\mu$l acetylcholinesterase (7.5 U/ml). The blank consisted of a buffer, acetylcholinesterase and a DTNB solution. The reaction was started by addition of the substrate to the reaction mixture. Acetylcholinesterase activity was determined by measuring the change in absorbance at 412 nm for 10 min with a spectrophotometer (Spectronic 1201 Milton Roy, Bioblock Scientific, Illkirch, France).

Competition assay with cefpodoxime-proxetil: The reaction mixture contained 2.84 ml 0.1 M phosphate buffer pH 8, 0.10 ml 0.01 M DTNB, 20 $\mu$l acetylcholinesterase (7.5 U/ml) and 20 $\mu$l 0.5 mM cefpodoxime-proxetil, the solution was pre-incubated for 10 min at 37°C. The blank consisted of buffer, acetylcholinesterase, 0.5 mM cefpodoxime-proxetil and DTNB solution. The reaction was started by the addition of the substrate (20 $\mu$l 0.075 M acetylthiocholine).

Acetylcholinesterase activity was determined by measuring the change in absorbance at 412 nm for 10 min with a spectrophotometer.

*2.2.5. HPLC analysis of cefpodoxime*

The enzymatic incubation media were diluted with a 2% trichloracetic acid solution. The dilution was analyzed on an optimized system composed of a Supelcosil LC18 (250 mm × 4.6 mm, 5 mm particulate size) column (Supelco, St Germain en Laye, France) and of a ternary mobile phase (acetate buffer 0.05 M pH 3.8–methanol–acetonitrile (87:10:3 v/v/v)). The flow rate was 1 ml/min. The separation was performed at ambient temperature and monitored at 235 nm. Linearity between and within day reproducibility were assessed. Interassay coefficients of variation were within the range 8.3–3.5% for cefpodoxime concentrations between 0.2 and 2 mM. The limit of quantification was 0.05 mM.

## 3. Results

In human duodenal washings we observe a significant hydrolysis of cefpodoxime-proxetil namely, 6.6 $\mu$M after 30 min and 11.04 after 1 h. Cefpodoxime-proxetil esterase activity (CPEA) in human is respectively 1.02 nmol/$\mu$g per 30 min and 1.5 nmol/$\mu$g per 60 min. CPEA found in the human is lower than the CPEA found in the rabbit.

Thus, the hydrolysis of cefpodoxime-proxetil by duodenal washings was significantly activated in the temperature range 4–50°C whereas its spontaneous hydrolysis at pH 7 remained insignificant (Fig. 1) as was found previously in the rabbit.

The characterization of the esterase activity in the human was achieved using different inhibitors (Table 2). Luminal activity was inhibited by 100 $\mu$M PMSF and by 100 $\mu$M eserine. Moreover, a complete inhibition was achieved using 1 mM $HgCl_2$.

These results are in accordance with our previous results (Crauste-Manciet et al., 1997) found in the rabbit intestinal washing.

Competition experiments were run with the drug ester cefuroxime-axetil using human intestinal washings (Fig. 2). No significant competition with cefpodoxime-proxetil hydrolysis was observed both in the rabbit and the human.

Competition with nutrients in the rabbit: no inhibition has been found with the two lipids tested (LCT and mixed LCT/MCT) but potent inhibitions were found with amino acids, vitamins and mixed trace elements. The cefpodoxime-proxetil esterase specific activity decreased with amino acids, trace elements and vitamins and is clearly related to their concentration (Table 3). For all tested dilutions of these nutrient mixtures, the inhibition rate of cefpodoxime-proxetil hydrolysis in intestinal washings was always significant when compared with the control (Table 3). A significant inhibition rate with amino acids is shown in Table 3a, with trace elements in Table 3b and vitamins in Table 3c.

Specific acetylcholinesterase activity measured at 37°C and pH 8 by the change in absorbance at 412 nm for 10 min was inhibited by the cefpodoxime-proxetil solution. The ratio between ab-

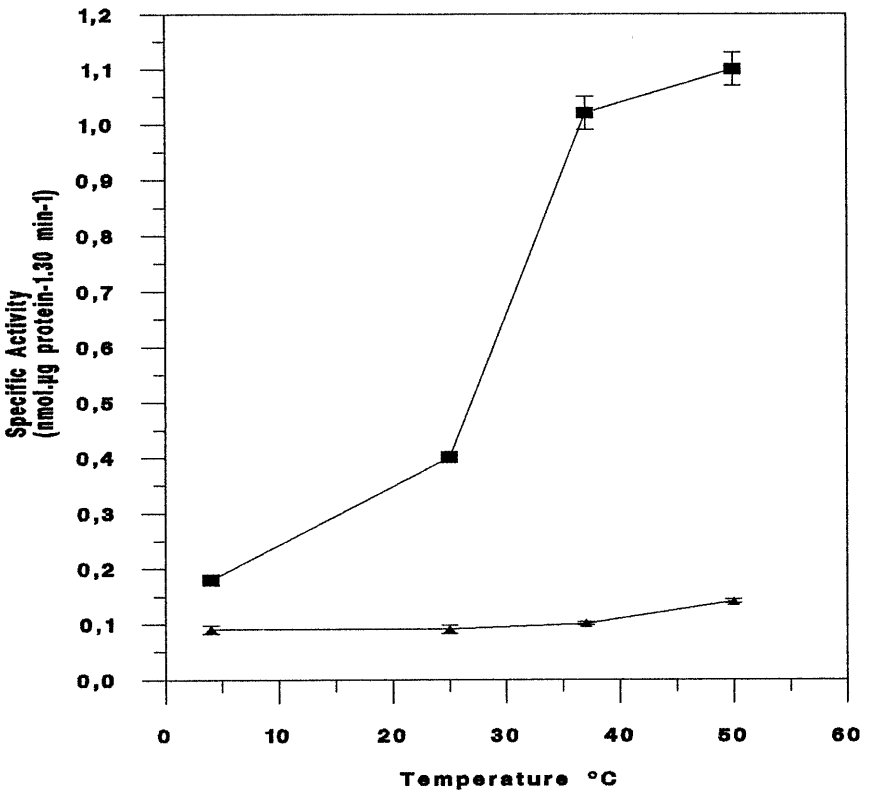


Fig. 1. Effect of temperature on the rate of hydrolysis of 100 $\mu$M cefpodoxime-proxetil in human duodenal washings (■) or in 10 mM Hepes and 300 mM mannitol pH 7 alone (▼). The specific activity was calculated from the amount of free cefpodoxime released in the incubation medium, the amount of protein present in the reaction mixture being 5 $\mu$g.

sorbance by minute and extinction factor of the DTNB anion was 3.65 $10^{-5}$ ($\pm$0.03 $10^{-5}$) mol/l per min without cefpodoxime-proxetil and 1.84 $10^{-5}$ ($\pm$0.1 $10^{-5}$) mol/l per min with cefpodoxime-proxetil. Results are mean $\pm$ S.D. of 3 observations. The inhibition rate of the acetylcholinesterase activity was 50.4% which suggests competition with the acetylthiocholine substrate of the acetylcholinesterase.

## 4. Discussion

Cefpodoxime-proxetil esterase activity found in human duodenal washings is in agreement with our previous results found in the rabbit (Crauste-Manciet et al., 1997). Hydrolysis is clearly related to an enzymatic activity since no spontaneous hydrolysis of the prodrug, even at temperatures as high as 50°C, was observed. Whereas, on the other hand, intestinal washing deesterification was clearly activated by increasing the temperature in the range 4–50°C.

Cefpodoxime-proxetil esterase activity was inhibited in the human both by PMSF and eserine, so that this activity can be classified as B-esterase according to Aldridge's classification (Aldridge, 1953) and a cholinesterase according to that of Walker and Mackness (Walker and Mackness, 1983).

Cholinesterases (ChEs) regroup acetylcholinesterases (AcChE, E.C. 3.1.1.7) and pseudocholinesterases or butyrylcholinesterases (BuChE, E.C. 3.1.1.8) can be distinguished from the other B-esterase (carboxylesterases) on the ground of their preference for choline esters and their inhibition by eserine (Walker, 1989).

Table 2
Distribution of cefpodoxime-proxetil esterase activity in human duodenal washings and the effect of esterase inhibitors: comparison of inhibition rates in the human and rabbit

| Inhibitors | Specific activity in the human (nmol/$\mu$g protein per 30 min) | Specific activity inhibition rate in the human (%) | Specific activity inhibition rate in the rabbit (Crauste-Manciet et al., 1997) (%) |
|---|---|---|---|
| Control | $1.02 \pm 0.03$ | 0 | 0 |
| PMSF (100 $\mu$M) | $0.28 \pm 0.02$* | 72.5 | 67.7 |
| Eserine (100 $\mu$M) | $0.35 \pm 0.02$* | 65.7 | 74 |
| $HgCl_2$ (1 mM) | $0.07 \pm 0.007$* | 93.1 | 100 |

Cefpodoxime esterase activity was measured from the release of free cefpodoxdime in the incubation buffer (pH 7.0). The amount of protein in the reaction mixture was 5 $\mu$g and the final concentration of cefpodoxime-proxetil was 100 $\mu$M.
* Mean $\pm$ S.D. of 6 observations; $p < 0.001$ from paired controls.

Cholinesterases and carboxylesterases are known to hydrolyse xenobiotic esters as well as natural esters (Augustinsson, 1961; Walker, 1989).

Aliphatic esters are hydrolyzed by the two types of ChEs (La Du and Snady, 1971; Shinkula and Yalkowski, 1975). This is in agreement and explains the hydrolysis of the cefpodoxime ester (aliphatic ester) of cefpodoxime by the ChEs.

Conversely, direct activity of cefpodoxime-proxetil on AcChE was shown by the 50% decrease in AcChE activity when added to the reaction media. The cefpodoxime ester could act as a substrate of ChEs and be a competitor for the specific acetylthiocholine substrate used. It could also be a ChEs inhibitor and be consequently hydrolyzed by AcChE. ChEs inhibition was previously found by this method with itopride (Iwanaga et al., 1994).

The hydrolysis mechanism for bambuterol was recently explained. It is assumed that bambuterol inhibits the esterase (BuChE) simultaneously with hydrolysis (Ekholm and Konschin, 1994). In the case of the cefpodoxime ester, the same mechanism could be implicated, but needs further investigation to be confirmed.

In the case of cefuroxime-axetil, which exhibits some structural similarities to cefpodoxime-proxetil, it did not interact with the cefpodoxime-proxetil hydrolysis by ChEs. These results are in agreement with findings of a carboxylesterase in rat intestinal washings which hydrolyze the cefuroxime-axetil (Campbell et al., 1987). Thus, different kinds of enzymes (ChEs, carboxylesterase) could be responsible for the hydrolysis of the same ester drug throughout the body. (Ali and Kaur, 1983; Billiar and Eik-Nes, 1965; Inoue et al., 1979b; La Du and Snady, 1971; Morikawa et al., 1979; Myers, 1982; White and Hope, 1984; Williams, 1985). All in all, our results found in the rabbit and also in the human seems to indicate that the enzyme involved in luminal washing hydrolysis of cefpodoxime-proxetil can be related to the ChEs group. This hydrolysis could partially explain the incomplete absorption of the prodrug ester because ChE hydrolysis released the parent acid, cefpodoxime, which cannot be absorbed by the intestinal wall. Moreover, the correlation found between animal and human results in vitro could be very useful for further prospective investigations of the potential risk of hydrolysis by esterase in the intestinal lumen of new prodrug esters.

Nutrient impact on cefpodoxime-proxetil hydrolysis in the rabbit is of interest in regard to the pharmacokinetic studies in the human. Pharmacokinetic studies performed in the human found an increase in the absorption when cefpodoxime-proxetil tablets where administered with food (Hughes et al., 1989; Borin and Forbes, 1995; Borin et al., 1995a,b) The main hypothesis for food impact was the reduced gastric emptying rate and the enhancement of drug dissolution. Our hypothesis is that the impact of food could also be related to the decrease in prodrug hydrolysis in the intestinal lumen by decreasing the rate of release of cefpodoxime free acid which cannot be absorbed by the intestinal wall.

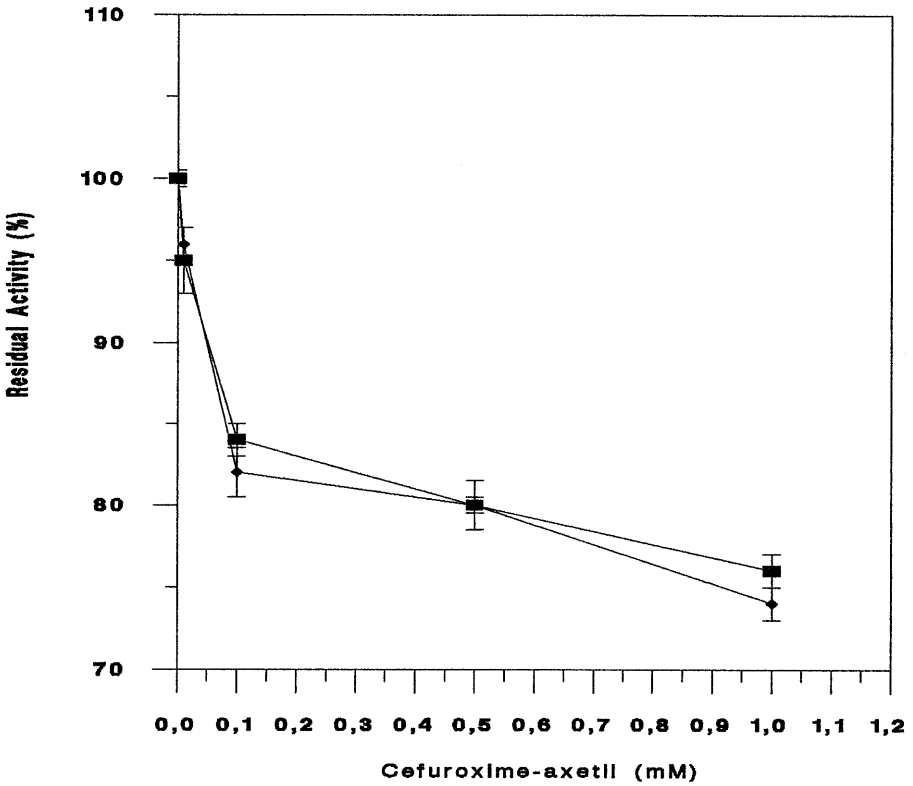


Fig. 2. Effect of cefuroxime-axetil competitor on the hydrolysis of cefpodoxime-proxetil in rabbit duodenal washings (■) and in human duodenal washings (◆). Cefuroxime-axetil was added at a concentration ranging from 0.01 to 1 mM to the reaction mixture together with 100 $\mu$M cefpodoxime-proxetil. The residual activity is the ratio between the activity measured in the presence of cefuroxime-axetil and the activity measured without cefuroxime-axetil. Results are mean $\pm$ S.D. of six observations.

This hypothesis can be supported by our investigation with the separate nutrients that we have tested. The lack of competition with cefpodoxime-proxetil hydrolysis involving lipids can be related to the fact that AcChEs did not hydrolyse triglycerides (La Du and Snady, 1971).

Otherwise, amino acids, trace elements and vitamins exhibit potent inhibition of the cefpodoxime-proxetil hydrolysis. This can be explained by the ChE inhibition mechanisms by cationic inhibitors (La Du and Snady, 1971).

Amino acid mixture esterase inhibition can be explained by the ChEs inhibition found with 3 amino acids, namely, glycine, L-glutamic acid and L-arginine (Bergmann et al., 1950). Both were present in the mixed amino acid solution used in our experiment and L-glutamic acid is the major amino acid in the Vamine® formulation.

The cefpodoxime-proxetil hydrolysis inhibition by trace elements can be related to the ChEs inhibition by several metal ions. Divalent ions inhibit ChEs activity more than monovalent ions. Zinc ions are inhibitors of the carboxylic acid group in the anionic active center of the ChEs. Cupric and nickel chelates of ethylene diamine were inhibitors of the ChEs through fixation of the metals on the enzyme and organoselenoates are irreversible ChEs inhibitors (Usdin, 1970). $Co^{2+}$, $Cd^{2+}$ and $Hg^{2+}$ were also recognized as inhibiting ChEs (Maruzek and Witkiewiecz, 1995). Fluoride ion, NaF and NaC1 strongly inhibit ChE enzymes. (Usdin, 1970; Martinval-maseda et al., 1995; Cimasoni, 1966).

Moreover, inhibition by vitamins can be related to the ChEs inhibition by thiamine and nicotinic acid (Stoytcheva and Zlatev, 1996).

Other antimicrobiological prodrug esters display a similar pharmacokinetic profile in the presence of low gastric pH and food: cefetamet-pivoxil (Blouin et al., 1990; Tam et al., 1990) and cefuroxime-axetil (Sommers et al., 1984; Finn et al., 1987; Ginsburg et al., 1985).

As ChEs, the carboxylesterase involved in the cefuroxime-axetil hydrolysis could also be inhibited by some nutrient components.

All in all, our results corroborate the idea that nutrients could inhibit ChEs activity and have a protecting effect on cefpodoxime-proxetil hydrolysis in the intestinal lumen. Moreover, our results can explain only partially the in vivo findings for the impact of food components—better solubilization and reduced gastric emptying rate with food cannot be ruled out.

Table 3
Effect of nutrients on cefpodoxime-proxetil hydrolysis in the rabbit

| Dilution factor | Specific activity (nmol/$\mu$g protein per 30 min) | Specific activity inhibition rate (%) |
|---|---|---|
| a. Amino acids mixture | | |
| Control | $4.15 \pm 0.14$ | 0 |
| 1 (undiluted) | $0.39 \pm 0.04$* | 90.6 |
| 0.5 | $1.44 \pm 0.05$* | 65.3 |
| 0.1 | $3.15 \pm 0.03$* | 24.1 |
| 0.01 | $3.73 \pm 0.14$* | 10.1 |
| b. Trace element mixture | | |
| Control | $4.15 \pm 0.14$ | 0 |
| 1 (undiluted) | $0.28 \pm 0.03$* | 93.3 |
| 0.5 | $0.52 \pm 0.03$* | 87.5 |
| 0.1 | $1.21 \pm 0.007$* | 70.9 |
| 0.01 | $3.15 \pm 0.03$* | 24.1 |
| c. Vitamin mixture | | |
| Control | $4.15 \pm 0.14$ | 0 |
| 1 (undiluted) | $0.36 \pm 0.07$* | 91.3 |
| 0.5 | $0.71 \pm 0.07$* | 82.9 |
| 0.01 | $1.83 \pm 0.07$* | 56.0 |

The different nutrient mixtures were added to the incubation medium with dilution factors 1 (undiluted) to 0.01 together with 100 $\mu$M cefpodoxime-proxetil. The specific activity inhibition rate is the difference between the residual activity measured in the presence of the nutrients (a, the amino acid mixture; b, the trace element mixture; c, the vitamin mixture) and the residual activity without any nutrients (100%).
* Mean $\pm$ S.D. of 6 observations; $p < 0.001$ from paired controls.

The role of food for solubilizing the prodrug was expected, because the increase in extent of cefpodoxime-proxetil absorption is greatest for tablets (and within tablet doses, is higher for higher doses), followed by the suspension and then, the solution (Borin and Forbes, 1995).

Similar findings have been reported for syrup and tablet formulations of cefetamet-pivoxil. When cefetamet-pivoxil is taken with a meal, bioavailability is increased by 25 to 30% for tablets and only 12% for the syrup (Tam et al., 1990; Ducharme et al., 1993).

Thus, solubility and lumen hydrolysis are two factors to be considered for cefpodoxime-proxetil absorption and probably for other ester cephalosporin prodrugs.

The rabbit model could be useful for a prospective investigation of the hydrolysis risks or the impact of food on ester prodrugs.

In conclusion, cefpodoxime-proxetil is hydrolyzed in human intestinal washings by ChEs enzymes. These findings partially explain its incomplete absorption. ChEs inhibitors could decrease the hydrolysis in the intestinal lumen (i.e. amino acids, metal ions and all quaternary compounds in general). These results could be very useful in protecting this prodrug from enzymatic hydrolysis. To improve cefpodoxime-proxetil bioavailability, it is necessary to find a protective formulation both to increase solubility and decrease enzymatic attack by ChEs in intestinal washings.

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