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Intestinal absorption of cefixime in rats[1]

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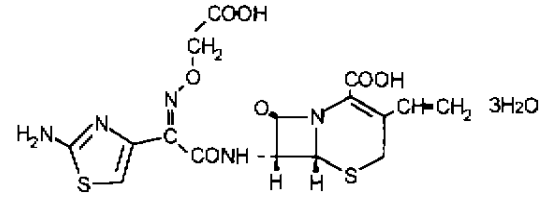
KEY WORDS cefixime; lactam antibiotics; peptides; intestinal absorption; calcium; hydrogen-ion concentration

ABSTRACT

AIM: To study the intestinal absorption characters of cefixime (Cef) and the factors affecting Cef absorption. **METHODS:** A rat intestine loop *in situ* technique was used to investigate the disappearance rate of Cef from the intestine. Cef concentration in the flux was measured by the reversed phase HPLC. **RESULTS:** Cef was mainly absorbed from the upper part of the intestine. Its disappearance rate was apparently pH-dependent [(5.8 ± 0.6) nmol·h^{-1}/(g wet tissue) at pH 7.4, (8.9 ± 1.4) nmol·h^{-1}/(g wet tissue) at pH 5.0, $P < 0.05$)]. The uptake rate of Cef was curvilinear at 0.01 - 0.5 mmol·L^{-1}. The values of apparent K_t, J_{max}, and K_d were 0.114 mmol, 78.41 nmol·h^{-1}/(g wet tissue), and 43.70 nmol·h^{-1}·mmol^{-1}/(g wet tissue), respectively. Sodium edetate markedly promoted the disappearance rate of Cef from the intestine. **CONCLUSION:** Cef was transported partly via carrier-mediated transport system and partly via the paracellular transport system.

INTRODUCTION

Cefixime (Cef) is an orally absorbed third generation cephalosporin with a broad spectrum of antibacterial activities. The absolute bioavailability of Cef was 40 % for 400 mg capsules, 48 % for 200 mg capsules in healthy volunteers[1]. Cef possesses a vinyl group in 3 position. The substitution at 3 position and the introduction of 2-aminothiazol-4-yl-(alpha-alkoximine) acetamide side chain at 7 position of the cephem nucleus results in an improved stability to β-lactamase enzymes and favorable oral absorption[1]. It has a bioavailability of about 50 % after oral administration[2]. The purpose of this research was to investigate intestinal absorption characters of Cef and to gain a better understanding of factors affecting Cef absorption.



Cefixime

MATERIALS AND METHODS

Instrument The pH of the solutions was measured using a pH-meter equipped with GST-125C and GST-152C combination electrodes (Model PHS-25, Shanghai Magnetic Instrument Manufacturer).

Materials Cef was obtained from Fujisawa Pharmaceutical Co, Osaka. All other chemicals were at least reagent grade

HPLC analysis The HPLC (Shimadzu LC-6A) was equipped with a UV detector

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(Shimadzu SPD-10A UV-VIS) set at 254 nm; separation was carried out using a 250 mm × 5 mm ID Shim-pack CLC ODS column with tetrabutylammonium phosphate (0.01 mol·L^{-1}): acetonitrile (700:300) mobile phases with a flow rate of 1.5 mL·min^{-1}. Peak areas, which were calculated by a programmable integrator (Shimadzu C-R3A Chromatopac), were used to measure Cef amounts.

Recovery rate was 102 % ± 3 % (n = 5 rats) for the flux buffer samples (recirculated in the intestine for 120 min) spiked with Cef 0.01 – 0.5 mmol·L^{-1}.

Perfusion and drug solutions Krebs-Ringer's solution and Ca^{2+}-free Krebs-Ringer's solution were used as Ca^{2+} medium and Ca^{2+}-free medium, respectively. Cef was dissolved in Krebs-Ringer's solution or Ca^{2+}-free Krebs-Ringer's solution. H_3PO_4 1.5 mol·L^{-1} or NaOH 1 mol·L^{-1} solution was employed to maintain the desired pH of the drug solutions. The ionic strength was maintained with NaCl.

Rats Sprague-Dawley rats (♂, 250 – 300 g) were supplied by the Animal Center of China Pharmaceutical University (Grade Ⅱ, Certificate № 97002). Rats were fasted for 12 h prior to the experiments. Rats were anesthetized with 20 % urethan solution (6 mL·kg^{-1}).

Intestine loop *in situ* technique The experiments were carried out by modifying the method [3]. The intestine was exposed by laparotomy. Glass cannulas were inserted through small slits at the intestine and tied to keep in position. The bile duct was ligated. Fifty mL of Cef solution, kept at 37 ℃, was recirculated through the intestine at a rate of 3 mL·min^{-1} using a peristaltic pump. All the concentrations of the drug in perfusate were corrected for water flux by reading the volume marks of the fine graduated perfusion reservoir at sampling.

Concentration-dependence of Cef uptake To examine the kinetics of Cef transported by the intestine, rates of drug uptake were measured at 0.01 – 0.5 mmol·L^{-1}, pH 6.5 after 30 min. The data were fitted by computer to a single Michaelis-Menten term plus a nonsaturable term:

$$J = (J_{max} \cdot S)/(K_t + S) + K_d \times S \quad (1)$$

where J was the uptake rate, S was the concentration of substrate in the medium, J_{max} was the maximal uptake rate, K_t was the Michaelis constant for saturable uptake, and K_d was the coefficient for nonsaturable uptake.

pH and site-dependency of the uptake rate The perfusion experiments were carried out as above. The effect of the flux buffer at pH 5.0 – 7.4 on the disappearance rate of Cef 0.01 mmol·L^{-1} was measured for 120 min.

For the experiment of the absorption site-dependence, 3 sections of the intestine: 1) duodenum and upper part of jejunum; 2) the lower part of jejunum; and 3) the ileum, and the colon were used. Cef solution was recirculated through each part of the intestine separately. The disappearance rate of Cef 0.01 mmol·L^{-1} was measured at pH 6.5 for 120 min.

Effect of Ca^{2+} level on Cef absorption The disappearance rates of Cef 0.02 mmol·L^{-1} were measured at pH 6.5 in the Ca^{2+}-free medium with 2 % sodium edetate and the Ca^{2+} medium for 120 min.

RESULTS

Cef was mainly absorbed from the upper part of the intestine, 15.2 % ± 1.2 % (n = 5 rats) of a 0.01 mmol·L^{-1} dose of Cef disappeared from the duodenum and the upper part of jejunum loop *vs* only 2.1 % ± 0.3 % (n = 5 rats) from the lower part of a jejunum, ileum and colon loop after 60 min ($P < 0.05$).

Cef disappearance rate increased when pH of the drug solution was lowered from 7.4 [(5.8 ± 0.6) nmol·h^{-1}/(g wet tissue)] to 5.0 [(8.9 ± 1.4) nmol·h^{-1}/(g wet tissue)] (n = 5

rats, $P < 0.05$).

Sodium edetate promoted the disappearance rate of Cef 0.02 mmol·L^{-1} from the intestine. The total disappearance amounts of Cef from the intestine with and without sodium edetate were (24.0 ± 2.2) and (12.1 ± 1.1) nmol·h^{-1}/(g wet tissue), respectively ($n = 5$ rats, $P < 0.05$).

The uptake rate for Cef at pH 6.5 as a function of the concentration of Cef was curvilinear at 0.01 – 0.5 mmol·L^{-1} (Fig 1).

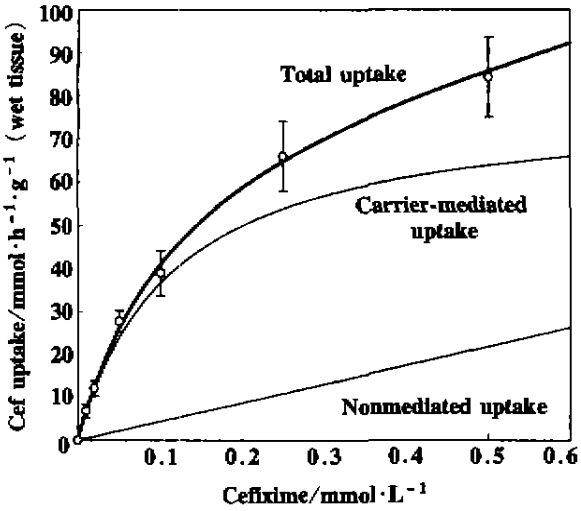

Fig 1. Concentration-dependence of cefixime uptake by rat intestinal loop *in situ* method. $n = 5$ rats in duplicate. $\bar{x} \pm s$.

The uptake rates were expressed by the equation 1 using nonlinear least squares regression analysis ($r = 0.9486$). The values of apparent K_t, J_{max}, and K_d were 0.114 mmol, 78.41 nmol·h^{-1}/(g wet tissue), and 43.70 nmol·h^{-1}·mmol^{-1}/(g wet tissue), respectively.

DISCUSSION

The present results demonstrated that Cef absorption was mainly restricted to the upper small intestine. The long-time gastric retention time in fed state conditions favored the drug absorption from the upper small intestine. Perhaps, this was why presence of food in the GI tract only decreased the rate of absorption of Cef but generally did not affect the extent of absorption of the drug[4]. Cef was transported, in part, via carrier-mediated transport system. β-lactam antibiotics shared a common transport system with peptides[5]. The uptake was stimulated by an inwardly directed H^+ gradient and was saturable. So, the percents of Cef absorbed after *po* 200 mg and 400 mg were similar[1]. The results for the saturable transport character of Cef were similar to those[5,6]. Cef was transported via the paracellular transport system. The presence of sodium acetate induced a marked stimulation of Cef uptake in accordance with the transport mechanism of the paracellular transport drugs. Sodium acetate, which is considered to increase intercellular penetration by chelated depletion of calcium and magnesium in regions of the tight junction, is a paracellular promoter[7]. The absorption of some β-lactam antibiotics, such as the cefmetazole, was enhanced by sodium acetate as a paracellular promoter[8].

In summary, the transport of Cef through the rat intestine may occur via the carrier-mediated peptide transport system and via the paracellular transport system. The upper small intestine is the main absorption area of Cef.

REFERENCES

1 Faulkner RD, Fernandez P, Lawrence G, Sia LL, Falkowski AJ, Weiss AI, *et al*.
Absolute bioavailability of cefixime in man.
J Clin Pharmacol 1988; 28: 700 – 6.

2 Montay G, Masala F, Roux YL, Liboux AL, Uhlrich J, Chassard D, *et al*.
Comparative bioavailability study of cefixime administered as tablets or aqueous solution.
Drugs 1991; 42 Suppl 4: 6 – 9.

3 James B, Lisa MT, Margaret EE.
Reevaluation of the absorption of carbenoxolone using an *in situ* rat intestinal technique.

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E-mail aps@server.shcnc.ac.cn Phn/Fax 86-21-6474-2629

J Pharm Sci 1990; 79: 411 – 4.

4 Brogden RN, Campolk-Richards DM. Cefixime, a review of its antibacterial activity, pharmacokinetic properties and therapeutic potential. Drugs 1989; 38: 524 – 50.

5 Akira T, Ikumi T, Hideki H, Tetsuya T. β-Lactam antibiotics and transport via the dipeptide carrier system across the intestinal brush-border membrane. Biochem Pharmacol 1987; 36: 565 – 7.

6 Akira T, Hideki H, Tetsuya T, Ikumi T, Emi N. Saturable uptake of cefixime, a new oral cephalosporin without an α-amimo group, by the rat intestine. J Pharm Pharmacol 1987; 39: 272 – 7.

7 Nishihata T, Nghiem BT, Yoshitomi H, Lee CS, Dillsaver M, Higuchi T, *et al*. Changes in the intestinal mucosal permeability caused by nonprotein thiol loss in rats. Pharm Res 1986; 3: 345 – 51.

8 Masaharu S, Masahiro H, Toshiharu H, Shoji A. Difference in the promotion mechanism of the colonic absorption of antipyrime, phenol red and cefmetazole. J Pharm Pharmacol 1986; 39: 118 – 23.

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头孢克肟在大鼠肠内的吸收[1]

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关键词 头孢克肟；内酰胺抗菌素；肽类；肠吸收；钙；氢离子浓度

目的：研究头孢克肟(Cef)的肠吸收特性及影响 Cef 吸收的因素. **方法**：采用一种改良的在体肠回流技术，对 Cef 从肠内消失速率进行研究. 用反相高压液相色谱法对回流液中 Cef 浓度进行分析. **结果**：Cef 主要从小肠的上部吸收，从肠中的消失速率有明显的 pH 依赖性. Cef 在 0.01 – 0.5 mmol·L^{-1}范围内的吸收速率为一曲线. 依地酸钠能够明显促进 Cef 的肠内消失速率. **结论**：Cef 部分是经载体转运的，且又具有明显的细胞外转运特征.

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