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Original Research Paper

The effect of cephalexin in influencing the pharmacokinetics of a novel drug – 5′-valyl-cytarabine hydrochloride

Xiaotong Song, Yinghua Sun, Chenyao Zhao, Zhonggui He *

Shenyang Pharmaceutical University, No. 103, Wenhua Road, Shenyang 110016, China

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ABSTRACT

The aim of this study is to investigate the pharmacokinetics of 5′-valyl-cytarabine hydrochloride (OPC) when co-administered with cephalexin, which are both the substrates of PepT1. The drugs were administered orally by gavage. Blood samples were collected from the orbital plexus of the rats after oral administration of drug solutions. A new high-performance liquid chromatographic method was validated and used for determination of the two drugs. Pharmacokinetic parameters were calculated using DAS 2.1.1 software with noncompartmental analysis. After oral administration of OPC and co-administration of OPC and cephalexin, there were significant differences in the main pharmacokinetic parameters. The main pharmacokinetic parameters for the OPC group and the co-administrative group were as follows: $AUC_{0\text{-}10}$ (18,168.7 ± 2561.4) ng·h/ml and (13,448.5 ± 2544.73) ng·h/ml, $AUC_{0\text{-}\infty}$ (18,683.1 ± 3066.5) ng·h/ml and (13,721.1 ± 2683.0) ng·h/ml, C_{max} (6654.8 ± 481.3) ng/ml and (4765.1 ± 928.9) ng/ml, respectively. The results showed that the bioavailability of OPC could be reduced when co-administered with cephalexin, suggesting that the efficacy of a novel drug might be reduced when it came to combination use of β-lactam antibiotics.

1. Introduction

Drug transporters are very important in the process of oral drug absorption, distribution, metabolism, and elimination. Two major uptake transporters are two solute carrier (SLC and SLCO) superfamilies [1]. There are two kinds of POT having transport activity. One is PepT1, which is mainly expressed in the small intestine and also in the proximal tubules of the kidney [2,3]. The other is PepT2, which is predominantly located in the kidney [4]. Cytarabine (1-β-D-arabinofuranosylcytosine) is used in approximately 70% of cases of acute myelogenous leukemia (AML) [5]. Combination using of cytarabine and interferon-alpha shows great efficiency in the treatment of chronic myeloid leukemia (CML) [6]. Cytarabine is also an alternative drug to many cancers (stomach cancer, pancreatic cancer, liver cancer, colon cancer, lung cancer, breast cancer, uterine cancer, etc.). It has a quite short half-life which necessitates the administrative way of continuous infusion to maintain therapeutic plasma level, which is not convenient and time-consuming.

* *Corresponding author.* Shenyang Pharmaceutical University, No. 103, Wenhua Road, Shenyang 110016, China. Fax: +86 24 23986321.
E-mail address: hezhgui_student@aliyun.com (Z. He).
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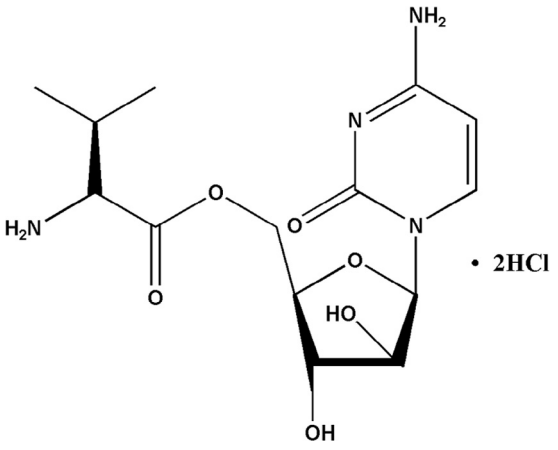

Fig. 1 – Structure of 5′-valyl-cytarabine hydrochloride.

5′-Valyl-cytarabine hydrochloride (see Fig. 1) is a novel 5′-amino acid ester prodrug of cytarabine. It is the substrate of PepT1, which increases the oral bioavailability of cytarabine. An *in vivo* pharmacokinetics study showed that the oral absolute bioavailability of rats increased 40% compared with that of cytarabine. Cytarabine could be released from the prodrug rapidly [7]. This improvement suggested that OPC might become a promising oral drug in dealing with AML, CML and stomach cancer, etc. A number of drugs have been reported as the substrates of PepT1, including β-lactam antibiotics, ACE-inhibitors, renin inhibitors, thrombin inhibitors, bestatin and prodrugs of acyclovir and ganciclovir [8–15].

Cytarabine is mainly used in the treatment of acute myelogenous leukemia and non-Hodgkin's lymphoma. It is also used with other chemotherapy agents when people suffered chronic myelogenous leukemia, multiple myeloma, Hodgkin's lymphoma and non-Hodgkin's lymphoma [16]. Therefore, cytarabine plays an important role in cancer chemotherapy. Patients are susceptible to infections due to a compromised immune system resulting from chemotherapy. Neutropenia and fever are very common life-threatening complications in cancer chemotherapy patients. Oral antibiotics can be an alternative approach for low risk cancer patients. To date, the best oral regimen is a combination of quinolone and amoxicillin/clavulanate [17]. Cephalexin is a kind of broad-spectrum, oral, antimicrobial agent. Cephalexin and amoxicillin are both β-lactam antibiotics, they share similar functional groups. Previously, the pharmacokinetic interaction between cephalexin and quinapril – a substrate of PepT1 – was investigated; the pharmacokinetic interaction between cephalexin and JBP485 – another substrate of PepT1 – was also studied. Cephalexin was chosen as a typical kind of β-lactam antibiotic for the study of the interaction between substrates of PepT1 [18,19].

Previously, the study of the absorption of OPC in the presence of cephalexin by using a single pass perfusion model was completed in our laboratory. The results showed that the absorption of OPC was greatly inhibited by cephalexin. However, the intraluminal environment is quite complicated and there are many differences between *in vivo* experiments and *in situ* single pass perfusion. Further study has to be carried out to elucidate the pharmacokinetic interaction in rats between OPC and cephalexin which are both substrates of PepT1. Pharmacokinetic interaction between the two drugs is of great importance to the clinical application of OPC.

2. Materials and methods

2.1. *Materials*

OPC was provided by Kunming Jida Pharmaceutical Co., Ltd. (Kunming, China) with a purity of 99.8%. Cytarabine was purchased from Langrb Technology Co., Ltd. (Beijing, China), with a purity of 99.9%. Cephalexin with a purity of 98% was purchased from HMC Chemical Technology Co., Ltd. (Beijing, China). Lamivudine with a purity of 99.7% was purchased from Longze Pharmaceutical Co., Ltd. (Shijiazhuang, China). Tetrahydrouridine was provided by Toronto Research Chemicals Inc. The rest of the chemicals were of analytical grade.

Male Sprague–Dawley (SD) rats weighing 220–250 g were purchased from the Experimental Animal Center (Shenyang Pharmaceutical University, Shenyang, China). The experimental protocol was evaluated and approved by the University Ethics Committee for the use of experimental animals and conformed to the Guide for Care and Use of Laboratory Animals.

2.2. *Preparation of solutions for oral administration*

The cephalexin solution was prepared by dissolving 125 mg cephalexin in 25 ml aqueous solution to obtain a concentration of 5 mg/ml. The OPC solution was prepared by dissolving 64 mg OPC in 25 ml aqueous solution to obtain a concentration of 1.5 mg/ml (calculated as cytarabine). The mixed solution of cephalexin and OPC was prepared by dissolving 125 mg cephalexin and 64 mg OPC in 25 ml aqueous solution.

2.3. *Preparation of standard solution*

Standard solutions of the two drugs at concentrations of 0.05, 0.1, 0.2, 0.25, 0.5, 1.0, 5.0, 8.0, 10.0 μg/ml for cytarabine and 0.2, 0.4, 0.8, 1.0, 2.0, 4.0, 20.0, 32.0, 40.0 μg/ml for cephalexin were prepared. The internal standard solution was prepared by dissolving 30 mg lamivudine in 100 ml distilled water to obtain a stock solution. 1 ml stock solution was diluted with water to obtain 100 ml solution at a concentration of 3 μg/ml.

2.4. *Collection and treatment of biological samples*

Serial blood samples (0.5 ml) were obtained from the orbital plexus at 5, 15, 30, 45 min, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 h after oral administration separately. The blood samples were centrifuged at 13,000 r/m for 10 min, plasma was then removed and stored at −80 °C until later analysis. During sampling, rats were anesthetized with ether. All samples were placed into heparinized tubes containing the deaminase inhibitor, tetrahydrouridine (0.1 mM). A 100 μl aliquot of internal standard solution and a 100 μl aliquot of distilled water were added to a 100 μl aliquot of plasma and vortex-mixed for 3 min. Then, a 0.8 ml aliquot of acetonitrile was added, vortex-mixed for 3 min, centrifuged at 13,000 r/m for 10 min, then the supernatant was transferred to a clean tube and dried under nitrogen

Table 1 – The elution gradients of HPLC analysis.

Time (min)	Phosphate buffer (%)	Methanol (%)
0	95	5
2	95	5
7	70	30
13	70	30
14	95	5
17	95	5

gas at 37 °C. The residue was dissolved in 100 μl distilled water, centrifuged for 10 min at 13,000 r/m, and 20 μl supernatant was injected into the HPLC column. The peak-area ratios of the biological sample to the internal standard were used to calculate drug concentrations at different time points.

2.5. *Chromatographic conditions*

HPLC analysis was carried out on a Waters liquid chromatography instrument equipped with a Waters 2489 UV/Visible Detector and e2695 Separations Module. A C_{18} column (ZORBAX SB-C_{18}, 4.6 mm × 250 mm, 5 μm, Agilent Technologies) was used; HPLC elution was carried out using phosphate buffer containing 0.005 M K_2HPO_4 and KH_2PO_4 and methanol. The elution gradients are listed in Table 1. Column temperature was 30 °C, flow rate was 1.0 ml/min, ultraviolet detection wavelength was 254 nm and injection volume was 20 μl.

2.6. *Methodology verification*

2.6.1. *Method specificity*

Under the chromatographic conditions described, there was no interference from the endogenous substances present in the plasma.

2.6.2. *Preparation of standard curves and quality control samples*

Different concentrations of standard solution were mixed with 100 μl aliquots of blank plasma to prepare biological sample solutions. The regression equation was obtained from the plot of the peak-area ratio of cephalexin or cytarabine to internal standard (A_s/A_i) as the *Y*-axis and the concentrations (C) as the *X*-axis. Cytarabine (0.1, 0.5, 8.0 μg/ml) and cephalexin (0.4, 2.0, 32 μg/ml) were added in blank plasma to prepare the low, medium and high levels of quality control (QC) samples. The spiked samples were then treated as the sample preparation procedure indicated in Section 2.4.

2.6.3. *Extraction recovery*

The extraction efficiency was determined by comparing the peak areas of extracted QC samples with peak areas of the standard solution and IS solution added to the blank plasma extract. The concentration of the IS solution was 3 μg/ml. Three concentration levels (0.1, 0.5, 8.0 μg/ml for cytarabine and 0.4, 2.0, 32 μg/ml for cephalexin) in rat plasma were studied in recovery experiments.

2.6.4. *Precision experiment*

The intra-day precision and inter-day precision were determined at the same three high, medium and low concentrations of QC samples. The intra-day precision was obtained from 6 replicates injected on the same day, while the inter-day precision was obtained from samples injected on 3 different days.

2.6.5. *Lower limit of quantification (LLOQ)*

The samples of LLOQ were made by using the method of preparing the lowest point of the standard curve with standard solution. The intra-day precision was obtained from 6 replicates injected on the same day. The accuracy was calculated by the mean deviation of all concentrations from the theoretical value.

2.6.6. *Stability test*

The stability of the plasma samples at the high, medium and low concentrations were examined after storing at room temperature for 12 h, after repeated freeze–thawing (3 times) and after storing at –80 °C for 14 d.

2.7. *Animal study*

Before the experiments, SD rats were fasted for 12 h with free access to water. They were then randomly divided into three groups, namely, OPC group after an oral administration at 15 mg/kg (calculated as cytarabine), cephalexin group after an oral administration at 50 mg/kg [18] cephalexin and combination group after an oral administration at 15 mg/kg (calculated as cytarabine) and 50 mg/kg cephalexin, with 6 rats per group. The drugs were administered orally by gavage. 0.5 ml blood samples were collected from the orbital plexus of the rats before and after oral administration of drug solutions, at time intervals of 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8 and 10 h. The rats were then sacrificed. The concentration of drugs in each sample was determined as described previously.

2.8. *Pharmacokinetics and statistical analysis*

The main pharmacokinetic parameters were calculated according to the DAS 2.1.1 software with non-compartmental analysis. The statistical differences were tested using Student *t* test at the $P < 0.05$ level.

3. Results and discussion

During cancer chemotherapies, combination usage of cytarabine with broad-spectrum antibiotics is very common. Drug–drug pharmacokinetic interaction is of great importance in guiding clinical use of drug dose. In this study, cephalexin's influence on the pharmacokinetics of OPC was investigated.

3.1. *Methodology verification*

3.1.1. *Specificity of the analytical method*

An example of a typical chromatogram is shown in Fig. 2. The peak shapes were very good and the three compounds were separated totally. Endogenous components in plasma did not cause any interference in the chromatogram.

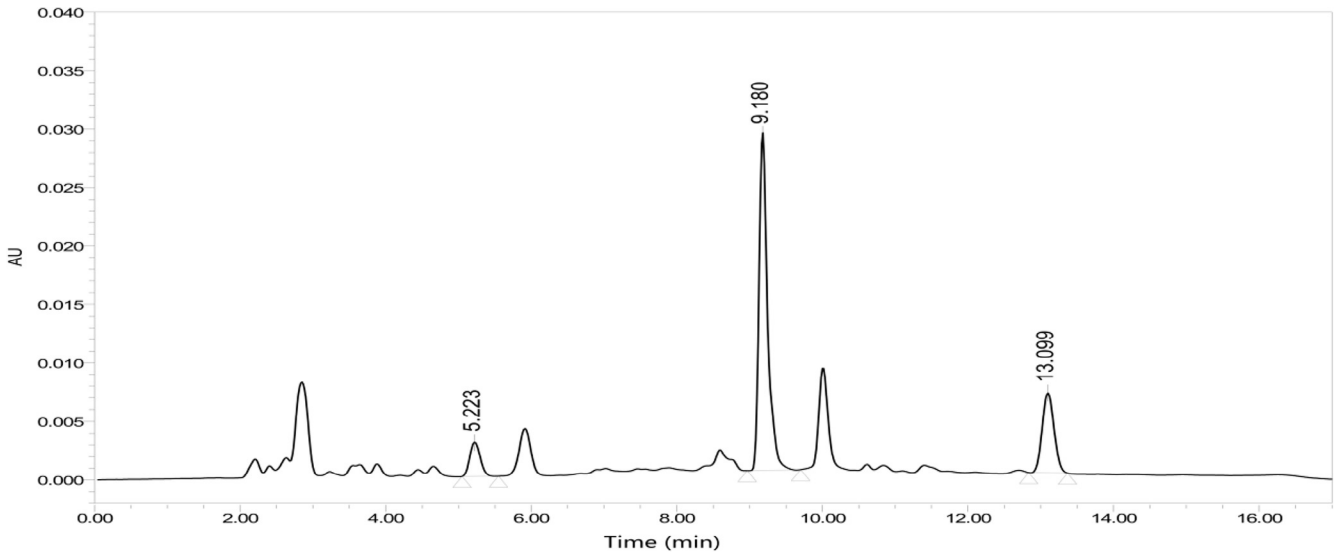

Fig. 2 – Typical chromatogram obtained from an extract of blank serum spiked with 1000 ng/ml cytarabine, 4000 ng/ml cephalexin and the IS; cytarabine, cephalexin and IS were eluted at 5.223, 13.099 and 9.180 min, respectively.

3.1.2. *Standard curves*

Using the internal standard method, the linear regression lines of the standard concentration (*C*) versus the peak area ratio (Y) were plotted, the linear range was 0.05–10 μg/ml for cytarabine and 0.2–40 μg/ml for cephalexin. The regression equations of cytarabine and cephalexin in rat plasma are $Y = 0.0002C–0.0033$, $r = 0.9999$ and $Y = 0.0001C–0.0173$, $r = 0.9999$.

3.1.3. *Lower limit of quantification (LLOQ)*

The LLOQ of cytarabine and cephalexin were 0.05 and 0.2 μg/ml, the RSD of intra-day precision were 7.3% and 2.4%. The RE of accuracy were –8.8% and –6.7% respectively.

3.1.4. *Recovery, precision and stability results*

The extraction recovery of each biological sample was more than 90%, which is shown in Table 2. The results of the precision tests are shown in Table 3. The intra-day precision and inter-day precision were less than 15%. After three freeze/thaw cycles, all samples were found to be stable with an accuracy of 15%. After sample preparation of nitrogen blowing, the samples at ambient temperature for 12 h were stable with an accuracy of 15% at three levels of QC samples. After 14 days storage in –80 °C, all samples were stable with accuracy less than 15%. The stability was good and the RSD was less than 5%. The results are shown in Table 4.

Table 2 – Recovery for the analysis of cytarabine and cephalexin in rat plasma ($n = 3$).

Recovery (%)	Cytarabine (ng/ml)			Cephalexin (ng/ml)		
	100	500	8,000	400	2,000	32,000
Mean (%)	94.6	100.4	92.9	93.2	96.2	95.6
SD (%)	3.4	3.1	0.2	3.0	0.3	0.1
RSD (%)	3.6	3.1	0.2	3.2	0.3	0.1

3.2. *Pharmacokinetic study*

Mean plasma concentration–time curves of cytarabine after oral administration of OPC (dose 15 mg/kg calculated as cytarabine) without and with cephalexin (dose 50 mg/kg) to SD rats (mean ± SD, $n = 6$) are shown in Fig. 3. Cephalexin (dose 50 mg/kg) after oral administration without and with OPC (dose 15 mg/kg calculated as cytarabine) to SD rats (mean ± SD, $n = 6$) are shown in Fig. 4. When the two drugs were administered orally in combination, the oral bioavailability and maximum concentration of OPC were significantly decreased compared with those for the control group. The area under the curve (AUC) of OPC was only 74% of those of the control group, the AUCs of the combination group ($AUC_{0\text{-}t}$ 13,448.5 ± 2544.7 ng·h/ml and $AUC_{0\text{-}\infty}$ 13,721.1 ± 2683.0 ng·h/ml) were significantly lower ($P < 0.05$) than OPC in the control group ($AUC_{0\text{-}t}$ 18,168.7 ± 2561.4 ng·h/ml and $AUC_{0\text{-}\infty}$ 18,683.1 ± 3066.5 ng·h/ml). The C_{max} of OPC was only 72% of those of the control group.

Table 3 – Precision and accuracy for the analysis of cytarabine and cephalexin in rat plasma ($n = 6$).

Analytes	Added concentration (ng/ml)	Found concentration (ng/ml)	Intra-day RSD (%)	Inter-day RSD (%)	RE (%)
Cytarabine	100	95.6	4.0	13.4	–4.4
	500	494.6	1.2	3.7	–1.1
	8,000	7,962.0	0.6	1.6	–0.5
Cephalexin	400	375.5	4.0	5.0	–6.1
	2,000	2,001.6	1.6	8.8	0.1
	32,000	31,726.5	1.7	12.8	–0.9

Table 4 – Stability of cytarabine and cephalexin in rat plasma under various storage conditions (n = 3).

Conditions	Analytes	Added Concentration (ng/ml)	Found Concentration (ng/ml)	SD (%)	RSD (%)	RE (%)
Three freeze/thaw cycles	Cytarabine	100	97.5	3.5	3.5	–2.5
		500	495.6	3.0	0.6	–0.9
		8,000	7,852.4	12.0	0.2	–1.8
	Cephalexin	400	392.6	6.6	1.7	–1.9
		2,000	2,083.2	5.2	0.2	4.2
		32,000	32,402.9	41.7	0.1	1.3
Room temperature for 12 h	Cytarabine	100	97.4	4.2	4.3	–2.6
		500	492.1	0.9	0.2	–1.6
		8,000	7,927.6	7.4	0.1	–0.9
	Cephalexin	400	394.5	7.2	1.8	–1.4
		2,000	2,038.8	12.7	0.6	1.9
		32,000	31,936.8	42.1	0.1	–0.2
Freezing for 14 d at –80 °C	Cytarabine	100	86.8	0.6	0.6	–13.2
		500	497.9	3.9	0.8	–0.4
		8,000	8,000.2	8.7	0.1	0.0
	Cephalexin	400	369.2	2.4	0.7	–7.7
		2,000	1,952.7	10.8	0.6	–2.4
		32,000	30,965.1	48.2	0.2	–3.2

The C_{max} of OPC (4765.1 ± 928.9 ng/ml) in the combination group was found to be significantly lower than that in the control group (6654.8 ± 481.3 ng/ml). t_{max} and $t_{1/2}$ of OPC in the co-administration group were 0.8 ± 0.2 h and 1.7 ± 0.7 h, whereas OPC in the control group has t_{max} and $t_{1/2}$ of 0.8 ± 0.1 h and 1.7 ± 0.8 h (Table 5). Cephalexin competed with OPC for the active site of Pept1, limiting the extent of absorption of OPC. The velocity of absorption was not changed remarkably, which might be due to Pept1 being not saturated. Most of the drugs were absorbed passively through oral administration. However, substrates of Pept1 were transported actively by an energy-dependent transporter. Pept1 with low affinity and high capacity was mainly located in the intestine, its expression decreased from the duodenum to the ileum. There were many substrates of Pept1, β-lactam antibiotics, ACE-inhibitors, renin inhibitors, thrombin inhibitors, bestatin and prodrugs of acyclovir and ganciclovir. OPC and cephalexin were both substrates of Pept1, they both had the same chemical structure of peptide. AUCs and C_{max} of cephalexin of the combination group were also lower than those of cephalexin with single administration. However, there were no significant differences between the pharmacokinetic parameters of cephalexin without and with interaction of OPC. Firstly, it was because of the high dosage of cephalexin compared with the quite low dosage of OPC. Secondly, cephalexin probably had higher affinity for Pept1 compared with OPC.

4. Conclusion

Decreased bioavailability of OPC was observed when co-administered with cephalexin, which can reduce the novel drug

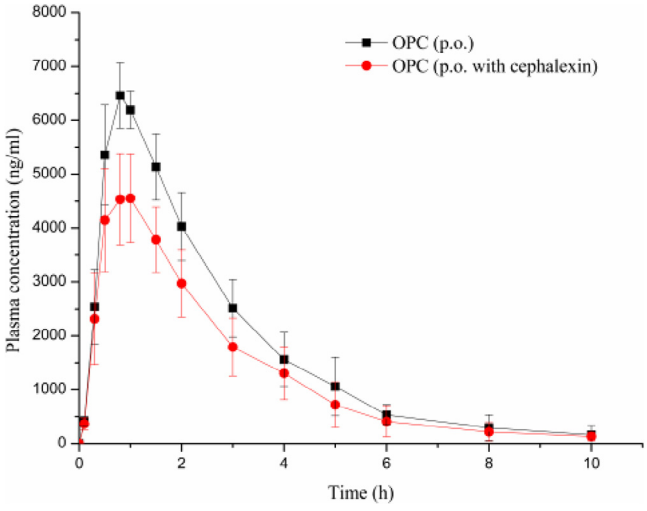

Fig. 3 – Mean plasma concentration–time curves of cytarabine after oral administration of OPC (dose 15 mg/kg calculated as cytarabine) without and with cephalexin (dose 50 mg/kg) to SD rats (mean ± SD, n = 6).

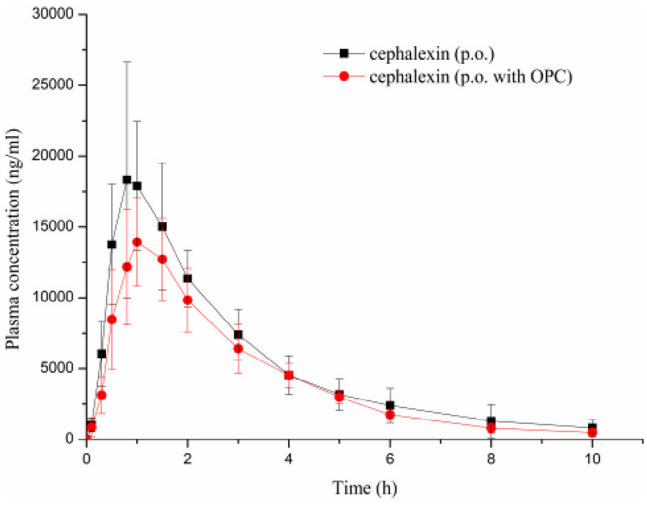

Fig. 4 – Mean plasma concentration–time curves of cephalexin (dose 50 mg/kg) after oral administration without and with OPC (dose 15 mg/kg calculated as cytarabine) to SD rats (mean ± SD, n = 6).

Table 5 – The main pharmacokinetic parameters of cephalexin after oral administration without and with OPC and the main pharmacokinetic parameters of OPC after oral administration of OPC without and with cephalexin to SD rats (mean ± SD, n = 6).

Parameters	OPC	OPC (p.o. with cephalexin)	cephalexin	Cephalexin (p.o. with OPC)
$AUC_{0\text{-}t}$ (ng·h/ml)	18,168.7 ± 2,561.4	13,448.5 ± 2,544.7	54,161.7 ± 13,505.4	43,206.3 ± 8,710.3
$AUC_{0\text{-}\infty}$ (ng·h/ml)	18,683.1 ± 3,066.5	13,721.1 ± 2,683.0	56,522.1 ± 15,966.6	44,421.3 ± 9,131.6
$t_{1/2}$ (h)	1.7 ± 0.8	1.7 ± 0.7	2.0 ± 0.7	1.7 ± 0.3
t_{max} (h)	0.8 ± 0.1	0.8 ± 0.2	1.1 ± 0.3	1.2 ± 0.3
C_{max} (ng/ml)	6,654.8 ± 481.3	4,765.1 ± 928.9	20,440.7 ± 7,501.6	14,808.8 ± 3,140.2

efficacy when it comes to clinical use. We should pay great attention to the combination usage of OPC and β-lactam antibiotics. Different dosages of OPC and β-lactam antibiotics in humans still need further study.

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