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Demethylation metabolism of roxithromycin in humans and rats[1]

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KEY WORDS roxithromycin; metabolism; macrolide antibiotics; liquid chromatography; mass spectrum analysis

ABSTRACT

AIM: To investigate the demethylated metabolites of roxithromycin (RXM) in humans and rats, and to study the antibiotic activity of these metabolites *in vitro*. **METHODS**: The demethylated metabolites of RXM in humans and in rats were identified by liquid chromatography-mass spectrometry (LC-MS), and the *in vitro* antibiotic activities of them against three standard strains were also studied compared with those of the parent drug and some other metabolites of RXM. **RESULTS**: *O*-Demethylation of RXM was one of the main metabolic routes of RXM in humans, whereas *N*-demethylation metabolism was more predominant in rats. *O*-Demethyl-RXM appeared to be equally effective with RXM. **CONCLUTION**: The *O*-demethyl-RXM was an active metabolite in humans, and there were some species differences in RXM demethylation metabolism between humans and rats.

INTRODUCTION

Erythromycin A (EM-A) has been used as one of the most effective macrolide antibiotics for the past three decades. In recent years, many derivatives of EM-A have been synthesized to improve antimicrobial activities and pharmacokinetics and also to reduce toxicities. Roxithromycin (RXM) is commercially available as (*E*)-erythromycin-9-[*O*-(2-methoxyethoxy) methyl] oxime and has more potency than its *Z*-isomer. It is frequently used as an orally administered antibacterial macrolide structurally related to EM-A, and *in vitro* activities of RXM are comparable or superior to those of EM-A. Furthermore, RXM exhibits excellent antimicrobial activities *in vivo*, because of its outstanding stability in acidic conditions and superior pharmacokinetic properties[1-3].

A few investigations in animals and in humans have reported that after oral administration of RXM, four metabolites have been identified in urine and feces[4-6]. These are erythromycin-oxime (ERY-oxime), a descladinose derivative (to which a sugar residue of RXM is lost), and *N*-mono- and *N*-di-demethylated derivatives of RXM. The biotransformation of RXM is poorly understood and this is due in part to difficulties that have been encountered in establishing a sensitive and specific assay for RXM and its metabolites. Because of lack of a strong chromophore, development of a suitable analytical method for metabolic studies using high-performance liquid chromatography (HPLC) with ultraviolet or fluorescence detection is not practical. Reported thin-layer chromatography methods[4-6] had low specificity and sensitivity, and HPLC with electrochemical detection[7] could not respond to those metabolites which have low electrochemical activity. Thus, although the pharmacokinetic properties of RXM have been investigated, many questions remain as to its fate after administration. The metabolism of RXM in humans has been thoroughly investigated in our laboratory using a specific and sensitive liquid chromatography-multistage mass spectrometry (LC/MS^n) assay technique[8]. A total of 15 metabolites of RXM were identified in humans as descladinose-RXM (M1), erythromycin-oxime (M2), *N*-, *O*-, and *N*,*O*-di-demethylated derivatives of RXM (M3, M4, and M6), and *N*-mono- and *N*-di-demethylated derivatives of erythromycin-oxime (M5 and M7), as well as the (*Z*)-isomers (M8 - M15) of RXM and metabolites M1 - M7, respectively, and 10 of them were produced *via* demethylation of RXM and its primary metabolites. The metabolites of RXM were only found in trace amount in plasma, but a considerable amount in urine and especially

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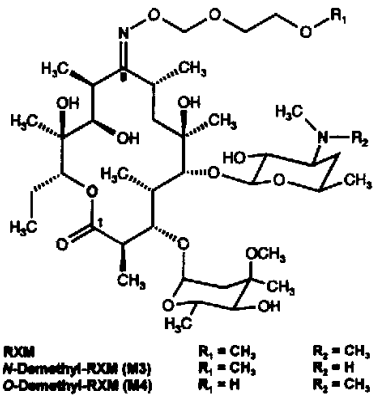
in bile were detected.

O-Demethyl-RXM was a new metabolite found in humans. To gain further insight into the demethylation metabolism of RXM, we examined the *N*- and *O*-demethylated biotransformation of RXM after oral administration in humans and in rats. The chemical structures are given below. Furthermore, we investigated the antimicrobial activities of the new discovered metabolite *O*-demethyl-RXM compared with the parent drug and five other metabolites of RXM.



Structures of RXM and two demethylated metabolites

MATERIALS AND METHODS

Chemicals and reagents RXM tablets (150 mg tablet) were supplied by Aim Pharmaceutical Inc (Shenyang, China). RXM and (*E*)-ERY-oxime reference substances were supplied by Huatai Drug Research Institute (Shenyang, China). (*E*)-*N*-demethyl roxithromycin (RU44981) was obtained from Hoechst-Marion-Roussel (Romainvill Cedex, France). (*E*)-*O*-demethyl roxithromycin was sythesized at the Department of Pharmaceutical Chemistry, Shenyang Pharmaceutical University (Shenyang, China). (*E*)-Descladinose derivatives of RXM, (*Z*)-RXM, and (*Z*)-ERY-oxime were synthesized using the published procedures[1] as described in the precursor work[8]. The internal standard (clarithromycin) was obtained from the Pharmaceutical Inspection Institute of Harbin, China.

Methanol and acetonitrile were of HPLC grade; water was double distilled in our laboratory. All other chemicals were of analytical grade or better and commercially obtained.

The *Micrococcus luteus* CMCC(B) 28991, *Bacillus subtilis* CMCC(B) 63501, and *Bacillus pumilus* CMCC (B) 63202 strains were supplied by Department of Microbiology, Shenyang Pharmaceutical University, Shenyang, China.

Liquid chromatographic system The LC system (Shimadzu Corp, Kyoto, Japan) consisted of a Shimadzu 10AD pump equipped with a 7125 Rheodyne injector. Samples were analyzed on a Kromasil ODS column (particle size 5 μm, 20 cm × 4.6 mm ID, Hi-Tech Scientific Instrument Corp, Tianjin, China). The mobile phase consisted of acetonitrile-methanol-ammonium acetate 10 mmol·L^{-1} (200:40:140, v/v/v). The flow rate was isocratic 0.4 mL·min^{-1}.

Ion trap mass spectrometer set-up The Finnigan LCQ ion trap mass spectrometer (Finnigan Mat, San Jose, CA) with electrospray interface (ESI) was calibrated according to the manufacturer's specifications. The instrument was operated in the positive ESI mode directly coupled to an HPLC system *via* a Finnigan API source. It was operated in positive ion MS/MS mode. The ESI source settings were as described in our previous study[8]. Under these conditions, authentic standards of RXM, (*E*)-*O*-demethyl-RXM, and (*E*)-*N*-demethyl-RXM were characterized by a retention time (±1.0 min) and molecular ion ($[M+H]^+$) of 11.5 min (*m/z* 837), 9.3 min (*m/z* 823; $[M+H]^+$-14), and 7.6 min (*m/z* 823; $[M+H]^+$-14), respectively. Data were collected and analyzed by the Navigator software (version 1.2, Finnigan).

Bacteria and *in vitro* antimicrobial activity The *Micrococcus luteus* CMCC(B)28991, *Bacillus subtilis* CMCC(B) 63501, and *Bacillus pumilus* CMCC(B) 63202 strains used were maintained in agar plates and subcultured every 3 weeks. The MIC were determined by an agar dilution method, using sensitivity test agar plates containing a series of 2-fold dilutions of sample. Overnight cultures in sensitivity test broth were used for precultures of tested strains. An incolum of 1×10^5 cfu was applied to the agar with a replicate inoculating device. Broth dilution was performed with an inoculum of 1×10^8 cfu·L^{-1}. Incubation took place at 37 ℃ for 24 h. The MIC was defined as the lowest concentration of drug that inhibited any visible growth.

Subjects and dosing procedure

Urinary studies Five healthy volunteers aged 21 to 26 a and weighing 45 to 75 kg (3 males and 2 females) participated in this study. Subjects were judged to be in good health based on a medical history, physical examination, and laboratory profiles that were performed within

2 weeks prior to the study. Subjects fasted, except for water, for 12 h prior to drug administration. Each subject was given an oral 150 mg dose of RXM tablets. Urine samples were collected before drug administration (blank urine) and during 0 – 3, 3 – 12, 12 – 24, and 24 – 36 h intervals post drug intake. Urine volumes were recorded, and 10-mL aliquots were stored at – 30 ℃ until analysis.

Biliary excretion studies Three patients (2 males and 1 female) aged 16 to 66 a and weighing 40 to 70 kg participated in this study. All were nonsmokers with normal renal function as assessed by serum creatinine levels and none had severe hepatic disease as assessed by clinical symptoms and conventional laboratory tests. All patients had undergone cholecystectomy because of symptomatic choledococholecystolithiasis. Bile was collected *via* a T-tube which was left *in situ* for at least 7 d following surgical intervention. No medications or ethanol consumption were allowed for 48 h prior to or during the study period. Each patient received a single oral dose of RXM (150 mg tablet) in the morning together with 100 mL plain water after an overnight fast. Bile samples were collected *via* the T-tube before drug administration (blank sample) and during 0 – 1.5, 1.5 – 5, and 5 – 10 h intervals following drug intake. The volume of each sample was duly recorded. All samples were kept at – 30 ℃ until analysis.

Animals Male Wistar rats (300 g ± 30 g, Grade Ⅱ, Certificate No 033) were purchased from Department of Experimental Animals, Shenyang Pharmaceutical University. Animals were quarantined for a minimum of 7 d before treatment and maintained on a 12-h light/dark cycle. Animals were fed food and water *ad lib*.

Urinary studies A group of five male Wistar rats were housed individually in stainless steel metabolic cages. The animals were dosed by gavage a 20 mg·kg^{-1} dose of RXM. Urine samples were collected from animals for 2 d at 0 – 1, 1 – 3, 3 – 5, 5 – 7, 7 – 9, 9 – 12, 12 – 24, and 24 – 36 h, and the volumes were recorded. All of the samples were stored at – 30 ℃ until analysis.

Biliary excretion studies Another group of five male Wistar rats were implanted with a PE-10 cannula into the common bile-duct under anesthesia by ethyl ether, and then allowed to recover for 2 h before drug administration. The animals were orally administered a 20 mg·kg^{-1} dose of RXM. The dose was prepared by dissolving RXM in the mixture of ethanol and distilled water (1:5) at a concentration of 5 g·L^{-1}. All rats were fed at 3 h after the dose. Bile samples were collected at 0 – 4, 4 – 8, and 8 – 12 h after the dose. The volumes of bile samples were recorded, and all of the samples were stored at – 30 ℃ until analysis.

Pretreatment of biological samples for LC-MS analysis A 0.2 mL portion of urine or bile samples were added in a glass tube, to which was added 50 μL of IS (5 mg·L^{-1} in methanol) and 100 μL of sodium carbonate 0.1 mol·L^{-1} followed by 2 mL of fresh distilled diethyl ether. Samples were vortexed vigorously for 3 min and afterwards centrifuged for 10 min at 2000 × *g*. The organic layer was transferred into a conical test tube and evaporated to dryness under a stream of nitrogen at 25 ℃. The residue was dissolved in 100 μL of the HPLC mobile phase and an aliquot of 20 μL was injected onto the chromatographic system.

Analytical methods Calibration curves, from 0.05 to 5.00 mg·L^{-1}, were established, using weighted ($w = 1/c$) linear least-squares regression analyses, from RXM/IS peak height ratios *vs* various concentrations of RXM in drug-free urine and bile samples to which aliquots of standard RXM had been added. In the case of (*E*)-*O*-demethylated and (*E*)-*N*-demethylated metabolites of RXM, the calibration curves also involve 0.05 – 5.00 mg·L^{-1} ranges.

RESULTS

Characterization of (*E*)-*O*-demethyl RXM The molecular formula of synthesized (*E*)-*O*-demethyl RXM was determined from LC-MS and ^{13}C NMR spectra, indicating a loss of one methyl group from RXM[8]. The ^{1}H NMR spectrum of (*E*)-*O*-demethyl RXM was almost similar to that of RXM except for a lack of a *O*-methyl group at the 19-position of RXM. It was proved identical to the metabolite M4 by LC-MS.

Quantification and analytical variables Under the LC-MS conditions described above, full scan LC-MS-MS chromatograms for analysis of RXM and the demethylated metabolites showed the LC separation and the! mass resolution obtained for the two demethylated metabolites Fig 1. No endogenous interfering peaks were found in bile and urine according to the chromatograms. For the linear regression of RXM, an r^2 value of 0.994 and 0.993 were obtained in bile and urine, respectively; r^2 values between 0.981 to 0.996 were obtained for the linear regression of (*E*)-*O*- and *N*-demethyl-RXM in urine and bile, respectively. The lower limit of quanti-

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tation for RXM and the two metabolites were all 0.05 mg $\cdot L^{-1}$. Analytical reproducibility (per cent coefficient of variation) values for intra- and interday assay variations were below 11.4 % in urine and bile.

Excretion of RXM and its demethylated metabolites RXM was rapidly and extensively metabolized in both humans and rats. Characterization of the urinary demethylated metabolites of RXM was performed by urine samples to LC-MS analysis, as described in Materials and Methods. The cumulative curves for RXM and its demethylated metabolites excreted into urine of human and rat are illustrated in Fig 2. The metabolites excreted in bile are similar to those in urine. The only apparent difference between the two fluids was that the concentration of the parent drug in urine was predominant, while the metabolites in bile were at much greater level. Fractions of the orally administered dose excreted in human urine as RXM and (*E*)-*N*-demethyl-RXM were comparable with those reported previously. McLean *et al*[6] using HPLC and TLC analysis investigated four healthy subjects and found that approximately half of the radioactivity (56 %) collected in urine was due to RXM (about 4 % of dose), with 2 % was (*E*)-*N*-demethyl-RXM. This means the amount of (*E*)-*N*-demethyl-RXM is only 3.6 % of the parent drug. Esumi *et al*[4] using the similar method studied the metabolism of RXM in rats, and found (*E*)-*N*-demethylated metabolite was approximately 7 % of the parent drug in the urine. Interesting in our experiment, we found that after 150 mg oral dose of RXM to healthy subjects, approximately 9 % of dose in the urine were RXM, whereas different with the reported results, (*E*)-*N*-demethyl-RXM only presented in no more than 0.4 % of the parent drug. Additionally, the metabolite (*E*)-*O*-demethyl-RXM was about 5 % of the parent drug excreted in the urine. Contrast to the results in humans, the amount of (*E*)-*N*-demethyl-RXM was more than 5 % of RXM in rat urine, which was similar to the previous report, while (*E*)-*O*-demethyl-RXM was only present in trace amount. Characterization of the biliary excretion of (*E*)-*O*-demethyl-RXM and (*E*)-*N*-demethyl-RXM were also different in humans and in rats. In human bile, the cumulative excretion of (*E*)-*O*-demethyl-RXM over 10 h was more than 14 % of the parent drug, whereas (*E*)-*N*-demethylated metabolite existed in trace amount and were not determined; in rat bile, the cumulative excretion of (*E*)-*O*-demethyl-RXM over 12 h was less than 8 % of parent drug, whereas the (*E*)-*N*-demethylated metabolite was about 1.6-fold greater than RXM. The secondary metabolites which endue di-demethylated or isomerized metabolic pathway were present in a relative small amount and not reported here.

Antibiotic activity The *in vitro* antibiotic activities of (*E*)-*O*-demethyl-RXM against three standard strains are shown in Tab 1. (*E*)-*O*-demethyl-RXM was equal to or 2-fold more active than the parent drug (RXM), while (*E*)-*N*-demethyl RXM was much less active compared with RXM. The two isomers of metabolite ERY-oxime were also equal to or more active than RXM. Both (*E*)-*O*-demethyl RXM and (*E*)-*N*-demethyl RXM possess antibiotic activity *in vitro*, and will attribute to the contribution of these compounds to the overall therapeutic effect of RXM.

DISCUSSION

In our present study, we demonstrated that one of the primary metabolic routes of RXM in humans and in rats was an oxidative pathway leading to demethylated metabolites or metabolites resulting from further demethylation of the primary metabolites. Demethylation occurs primarily at the *N*-methyl group of desosamine moeity or the *O*-methyl group of oxime alkylether side chain. In contrast with the previous reports[5,6] that described *N*-demethylation as the major metabolic pathway of RXM in Caucasians and Japanese, we have proved that *O*-demethyl-RXM is one of the main metabolites in Chinese subjects, whereas *N*-demethylation of RXM was present only in trace amounts. It appears that the identification of the demethyl metabolites in humans with the thin-layer chromatography method may have been incorrect, which can be explained easily by the fact that the analytical methods used in earlier investigations were clearly less specific than ours and presumably failed to differentiate between the two geometrical isomers of *N*-demethylate and *O*-demethylate RXM. However, consistent with the reports[4,9] that described *N*-demethyl RXM as the major metabolite in rats, we have demonstrated that it is indeed the main metabolite in rats according to experiments we have done. It is obvious that some species difference occurs between humans and rats.

As the microlide antibiotics have polyfunctional structures, various types of metabolism have been reported. Concerning the metabolism of EM-A, *N*-demethylation, cleavage of cladinose moiety, and the formation of 6,9;9,12-spiroketal have been reported[10]. However, these metabolisms cause the inactivation of EM-A. In this study, we demonstrated that *O*-demethyl \ IRXM

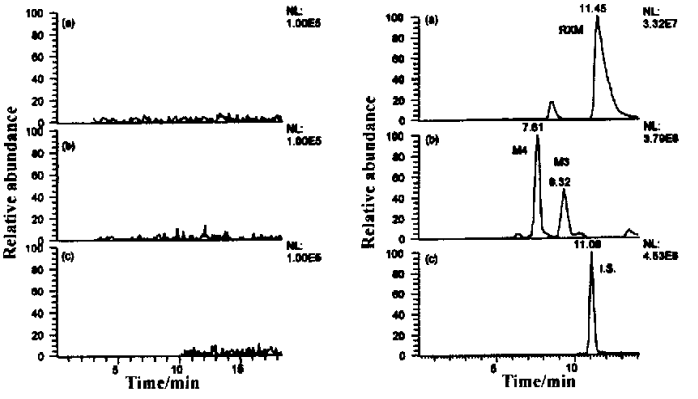

Fig 1. Representative LC-MS-MS chromatograms of RXM and its (*E*)-*N*-demethylated (M3) and (*E*)-*O*-demethylated (M4) metabolites in human blank urine (left column), and urine sample after oral administration of RXM (150 mg) to a healthy subject (right column). Panels a to c were the product ion mass chromatograms of *m/z* 837, 823, and 748 (IS), respectively.

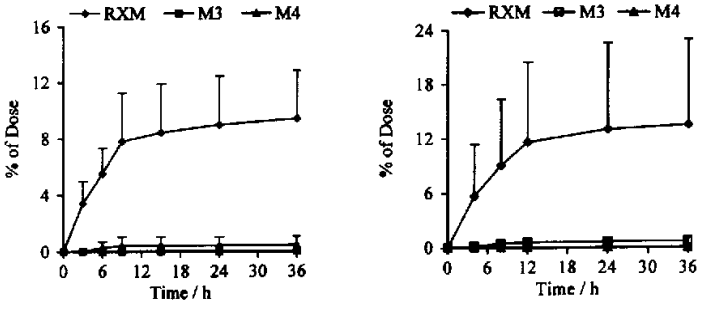

Fig 2. Urinary cumulative excretion of RXM and its demethylated metabolites after oral administration of RXM to humans (150 mg, left) and male rats (20 mg·kg^{-1}, right). $n=5$. $\bar{x} \pm s$.

Tab 1. Antimicrobial activities of metabolites of RXM.

Compound		Micrococcus luteus	Bacillus subtilis MIC/mg·L^{-1}	Bacillus pumilus
(*E*)-RXM		0.016	0.125	0.125
(*Z*)-RXM	(M8)	0.031	0.5	0.5
(*E*)-*O*-Demethyl-RXM	(M4)	0.016	0.062	0.125
(*E*)-*N*-Demethyl-RXM	(M3)	0.125	2	2
(*E*)-ERY	(M2)	0.008	0.125	0.125
(*Z*)-ERY	(M10)	0.004	0.062	0.25
(*E*)-Descladinose-RXM	(M1)	64	512	>512

was an active metabolite of RXM. From the viewpoint of antimicrobial activity, the metabolite *O*-demethyl-RXM was equal to or 2-fold more than RXM *in vitro*. Because of the formation of *O*-demethyl-RXM in significant quantity in human and the excellent antimicrobial activities, this metabolite gives distinctive features to RXM.

This study indicates the importance of demethylation metabolism in the biliary and urinary excretion of RXM in humans and rats. This finding might also be of clinical relevance because CYP3A catalyses demethylation[11], and *O*-demethyl-RXM is proved an active metabolite. Therefore, formation of mono- or di-demethylated

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metabolites might be increased by various therapeutic CYP3A inducers, for example phenytoin and rifampicin[12,13], although RXM itself does not induce CYP3A. Furthermore, demethylation of roxithromycin might play a role in the pharmacokinetic and metabolic interaction of drugs[14,15].

In conclusion, the results of previous studies, together with the finding presented here, indicate that *O*-demethylation of RXM play an important role in the biotransformation of RXM in humans, resulting an active metabolite. There are some species differences exist in RXM demethylation metabolism between humans and rats.

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关键词 罗红霉素；代谢；大环内酯抗菌素；液相色谱法；质量光谱分析

目的：研究罗红霉素在人体和大鼠体内的去甲基化代谢途径，并研究去甲基罗红霉素的体外抗菌活性。**方法**：采用 LC-MS 方法测定了罗红霉素在人体和大鼠体内的去甲基代谢产物；并用二倍稀释法，选择三种生物检测实验标准菌株，测定了罗红霉素、去甲基代谢产物以及其他几种主要代谢产物的体外抗菌活性。**结果**：罗红霉素在人体内主要经历 *O*-去甲基化代谢，而在大鼠体内主要经历 *N*-去甲基化代谢。代谢物 *O*-去甲基罗红霉素具有与母体药相当的体外抗菌活性。**结论**：*O*-去甲基罗红霉素是罗红霉素在人体内的活性代谢产物，罗红霉素在人与大鼠体内的去甲基化产物具有种属差异。

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