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Biotransformation of the ipecac alkaloids cephaeline and emetine from ipecac syrup in rats

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SUMMARY

The metabolism of cephaeline and emetine, which are the primary active components of ipecac syrup, were investigated in rats. Cephaeline-6'-O-glucuronide was found to be a biliary metabolite of cephaeline. Cephaeline (6'-O-demethylemetine) and 9-O-demethylemetine were observed to be enzyme-hydrolyzed biliary metabolites of emetine. Cephaeline was conjugated to glucuronide, while emetine was demethylated to cephaeline and 9-O-demethylemetine, and may be conjugated to glucuronides afterwards. Urine, feces and bile were collected from rats within 48 hours following the administration of ipecac syrup containing tritium (^3H) - labeled cephaeline or emetine. Metabolites were separated and quantified by thin layer chromatography (TLC) or high-performance liquid chromatography (HPLC). Biliary and urinary excretion rates of ^3H-cephaeline were 57.5% and 16.5% of the dose, respectively. Cephaeline-6'-O-glucuronide was comprised 79.5% of biliary radioactivity and 84.3% of urinary radioactivity. Unchanged cephaeline was detected in 42.4% of the dose in feces. Biliary excretion rate of ^3H-emetine was 6.9% of the dose. Emetine, cephaeline and 9-O-demethylemetine comprised 5.8%, 43.2% and 13.6% in hydrolyzed bile, respectively. There were no emetine-derived metabolites in urine or feces. The occurrence of unchanged emetine was 6.8% and 19.7% of the dose in urine and feces, respectively.

INTRODUCTION

Ipecac syrup is an emetic agent prepared from the extract of *Cephaelis ipecacuanha* (Broterol) A. Richard or *Cephaelis acuminata* Karsten by Tsumura Co., Ltd. as an emergency medicine for swallowing accidents in Japan. The primary active ingredients of ipecac syrup are believed to be the isoquinoline-type alkaloids, cephaeline and emetine[1]. However, despite the widely accepted use of ipecac in emergency medical applications in the US and other countries, the detailed metabolic fates of the ipecac alkaloids cephaeline and emetine remain unclear.

The objective of the present study was to investigate cephaeline and emetine metabolites in rats.

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We have previously synthesized tritium (^{3}H)-labeled cephaeline and emetine and examined absorption, distribution and excretion of these compounds in rats[2]. Those findings indicated that the half-life ($t_{1/2}$) of ^{3}H-emetine was longer than that of ^{3}H-cephaelin, and ^{3}H-emetine remained in tissues for a long term. Moreover, in administration of ipecac syrup containing ^{3}H-cephaeline, we demonstrated that approximately 90% of the absorbed radioactivity was excreted in bile up to 48 hours following its administration. The main route of excretion was shown to be in bile. Therefore, metabolites of cephaeline were isolated from bile and purified. Additionally, the main route of excretion of ^{3}H-emetine was also suggested in bile. However, the biliary clearance of ^{3}H-emetine was substantially smaller in comparison to that of ^{3}H-cephaeline. The administration of ipecac syrup containing ^{3}H-emetine resulted in the excretion of 12.5% of the radioactivity dosage in bile up to 48 hours after its administration. Consequently, biliary metabolites which are small quantities were examined by LC-MS-MS analysis. Emetine possesses four methoxyl groups. Thus, a demethylated form is expected as a metabolite. In this study, deuterium-labeled emetine was synthesized from cephaeline (derived from demethylation of the 6' position of emetine) as a tracer in order to ascertain the position of demethylation of emetine.

Materials and Methods

Chemicals

Cephaeline (mol wt 466) was isolated from Cephaelis ipecacuanha (Broterol) A. Richard or Cephaelis acuminata Karsten and purified by Tsumura Co., Ltd.[3] Emetine (mol wt 480) was purchased from Fluka Chemie AG (Buchs, Swizerland). Tritium (^{3}H)-labeled cephaeline dihydrochloride (specific radioactivity, 555 MBq/mg, radiochemical purity, 98% or more) and ^{3}H-emetine dihydrochloride (specific radioactivity, 327 MBq/mg, radiochemical purity, 98% or more) were synthesized at Chemsyn Science Laboratories (Lenexa, KS, USA). 9-O-demethylemetine and 10-O-demethylemetine were synthesized as described by Fujii et al.[4-6] These structures are shown in Fig.1. Ipecac syrup (content ratio of cephaeline, 0.783 mg/mL, and of emetine, 0.468 mg/mL) was prepared according to the Japanese Pharmacopeia Thirteenth Edition by Tsumura Co., Ltd.

Reagents and materials

DIAION HP-20 was purchased from Mitsubishi Kasei Industry Co., Ltd. (Tokyo, Japan). Cation exchange resin (Amberlite IRB-120B) was obtained from Organo Co., Ltd. (Tokyo, Japan). Sephadex LH-20 was acquired from Pharmacia Biotech K.K. (Uppsala, Sweden) and Toyopearl HW-40 obtained was from Mitsubishi Chemical Industry Co., Ltd. (Tokyo, Japan). Silica gel products, Kieselgel 60 (70-230 mesh, Art. 7734) and TLC plate Kieselgel 60 F254 (Art. 5714, 5715, 5515), were purchased from Merck (Darmstadt, Germany). β-glucuronidase (Type H-1 from Helix pomentia) was purchased from Sigma Chemical Co. (St. Louis, MO, USA). 2-(2-ethoxyethoxy)ethan(ol-*d*), diazald and ethyl-d_5 alcohol-*d* were purchased from Aldrich Chemical Company Inc. (Milwaukee, WI, USA).

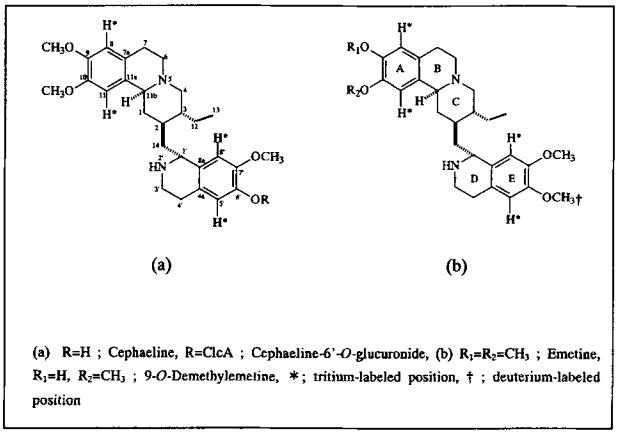
Synthesis of deuterium-labeled emetine

Diazomethane-d_2 diethylether solution was synthesized from sodium deuteroxide 40 wt% deuterated water, 2-(2-ethoxyethoxy) ethan (ol-*d*), diazald and ethyl-d_5 alcohol-d according to Aldrich Technical Information Bulletin Number AL-180. One gram of cephaeline was dissolved in 10 mL of tetrahydrofuran. The resulting solution was then mixed with 1 mL of ethyl-d_5-alcohol-d and refluxed. Diazomethane-d_2 diethylether solution was gradually added to the mixed solution at room temperature and agitated overnight.

During silica gel column chromatography (Kieselgel 60, 70-230 mesh), the reactive solution was purified by elution with a solvent mixture of cyclohexane-chloroform-diethylamine (5:4:1 v/v/v). 6'-Deuterium-labeled emetine (0.4227 g) was obtained (Fig. 1) with a collection yield of 41%. Deuterium-labeled emetine was analyzed by FAB-MS and FD-MS.

Animals

Eight-week-old Sprague-Dawley SPF male rats (obtained from Charles River Japan Inc.,Tokyo, Japan) were used. The rats were given water and food pellets (CF-2, Japan



(a) R=H ; Cephaeline, R=ClcA ; Cephaeline-6'-*O*-glucuronide, (b) R_1=R_2=CH_3 ; Emetine, R_1=H, R_2=CH_3 ; 9-*O*-Demethylemetine, *; tritium-labeled position, † ; deuterium-labeled position

Fig. 1 : Chemical structures of cephaeline, emetine and its metabolites.

Crea Japan Inc., Tokyo, Japan.) ad libitum. Prior to this study, the rats were acclimated for 7-12 days under the following conditions: temperature, 23 ± 2 °C; humidity, 55 ± 15%; and lighting cycle, 12 hours. Protocols of animal studies were approved by the Animal Care Committee of Tsumura & Co., Ltd.

Radio-TLC analysis of biliary, urinary and fecal metabolite of ^{3}H-cephaeline in rats

Fifteen MBq/0.5 mL/kg of ipecac syrup containing ^{3}H-cephaeline was orally administered to three rats. Urine, feces and bile were collected at intervals up to 48 hours after administration for analysis of metabolites by TLC. A specific volume of urine and bile samples was applied to a TLC plate. Fecal samples were homogenized with water. Aliquots of homogenate were centrifuged at 1600 g for 10 minutes in order to remove the supernatant. The residues were then ultrasonicated with ethanol for 30 minutes. Following centrifugation, the supernatant was utilized for analysis. Solvent systems employed were chloroform-methanol-water (5:5:1 v/v/v) or cyclohexane-chloroform-diethylamine (5:4:1 v/v/v) using a BAS-TR2040 imaging plate (20 x 20 cm, Fuji Photo Film Co., Ltd., Tokyo, Japan) overnight or longer. A BAS-2000 bioimaging analyzer (Fuji Photo Film Co., Ltd.) was used for analysis.

Radio-HPLC analysis of biliary, urinary and fecal metabolite of ^{3}H-emetine in rats

Fifteen MBq/0.5 mL/kg of ipecac syrup containing ^{3}H-emetine was orally administered to three rats. Urine, feces and bile were collected at intervals up to 48 hours after administration for analysis of metabolites by HPLC radiochromatography. Intact samples of bile and urine, in addition to samples obtained by enzyme hydrolysis as described below, were used for analysis. These intact samples were mixed with acetic acid buffer (0.1 mol/L, pH 5.5) and β-glucuronidase (Type H-1). These mixtures were then refluxed and incubated at 37°C for 10 hours. The mixtures were then titrated with hydrochloric acid until approximately pH 2 was attained, defatted with diethylether and treated with ammonia. Subsequently, pH was adjusted to approximately 10 and samples were extracted with diethylether and utilized as enzyme hydrolysis samples. Fecal samples were homogenized with water. Aliquots of homogenate were centrifuged at 1600 g for 10 minutes in order to remove the supernatant. The residues were then ultrasonicated with ethanol for 30 minutes. Following centrifugation, a portion of the supernatant was hydrolyzed by β-glucuronidase by the same method as described above and utilized for analysis. For HPLC, a Gilson HPLC system (programmable pump Model 305, 306, programmable UV detector, Model 116, data processing RAMONA) was employed. Samples were eluted on a Waters Symmetry C18 column (5μm, 4.6 x 150 mm) in 16% acetonitrile buffer containing 0.1% trifluoroacetic acid. The column was maintained at room temperature. Run times were typically 15 minutes and the solvent rate of flow was 1 mL/min. Secondly, a linear gradient was run for 30 minutes in order to equilibrate the column in 100% acetonitrile containing 0.1% trifluoroacetic acid. In addition, these samples were eluted with 100% acetonitrile containing 0.1% trifluoroacetic acid for 15 minutes. The elution was fractionated at 30-second intervals. A portion of the elution was measured for radioactivity.

Isolation of biliary metabolite of cephaeline in rats

Cephaeline dihydrochloride was administered to 110 rats undergoing bile duct cannulation at a dose of 10 mg/kg in order to isolate and purify biliary cephaeline metabolites. Bile samples were mixed with an equivalent volume of water and chromatographed on DIAION HP-20, eluted with water, 40% methanol, 60% methanol and methanol, successively. The 60% methanol eluate was rechromatographed on Amberlite IR-120B (H form) eluted with water, water-aqueous ammonia (4:1 v/v) successively, to give metabolite fraction. The metabolite fraction was rechromatographed on DIAION HP-20, Sephadex LH-20 and Toyopearl HW-40, eluted with water-methanol respectively to afford CM1.

LC-MS-MS analysis of biliary metabolite of emetine in rats

Fifteen mg/kg of deuterium-labeled emetine was administered orally to five rats in order to investigate emetine metabolites. Bile was collected at intervals up to 24 hours following administration. These intact samples were hydrolyzed by β-glucuronidase using the same method as described above. The samples were extracted with ether and used for LC-MS-MS analysis. LC-MS-MS analysis was conducted on a Waters 2690 HPLC system (Waters Co., Milford, MA, USA) coupled to a Finnigan TSQ7000 tandem quadrupole mass spectrometer (Finnigan MAT, San Jose, CA, USA). The column used was a Waters Symmetry C18 column (5 μm, 4.6 x 75 mm, Waters) maintained at 50°C. The mobile phase was a 13% acetonitrile solution containing 0.1% trifluoroacetic acid,

flowing at 0.5 mL/min. The HPLC eluent was introduced into the ionizing source using a turbo ionspray interface field at 250°C. The electron multiplier voltage was maintained at 1.2 kV. The nebulizer gas was ultrapure nitrogen set at 70 psi. The mass spectrometer was configured in the positive ion electrospray mode. MS-MS was carried out utilizing nitrogen as the collision gas. The collision energy was maintained at 40 eV.

Measurement of spectra

Magnetic resonance spectra (^{1}H-NMR, ^{13}C-NMR, NOESY) were measured using tetramethylsilane as the internal standard on BRUKER AM-500 (^{1}H: 500. 14 MHz, ^{13}C: 125.76 MHz, Bruker Inc., Billerica, MA, USA) or JEOL EM-400 (^{1}H: 399. 78 MHz, ^{13}C: 100. 53 MHz, Japan Electron Co., Ltd., Tokyo, Japan) instruments. Infrared absorption spectra were measured using an FTS-60A device (Bio-Rad Laboratories, Billerica, MA, USA). HR-FAB-MS, FAB-MS and FD-MS were measured using a KRATOS CONCEPT 32 1H spectrometer (Kratos Analytical Ltd., Chestnut Ridge, NY, USA). EI-MS was performed on a KRATOS CONCEPT 32 1S spectrometer (Kratos Analytical Ltd.).

Measurement of radioactivity

Each biological sample was mixed with scintillation fluid (Hyonicflow, Packard Co., Ltd., Meriden, CT, USA) after dissolution in SOLUEN-350 (Packard Co., Ltd.). Each analytical sample was mixed directly with scintillation fluid. Radioactivity was measured using a liquid scintillation counter (TRI-CARB, 2000CA, Packard). Counting efficiency was calculated by the external standard method.

Results

Radio-TLC analysis of biliary, urinary and fecal metabolite from ^{3}H-cephaeline in rats

The radioactivity of ^{3}H-cephaeline was excreted at a total of nearly 100% of the dose in bile, urine and feces within 48 hours following administration. These biological samples were analyzed by TLC (Fig.2). CM1, which is an unknown metabolite, was detected in urine and biliary samples. Unchanged cephaeline was detected in fecal samples. Biliary and urinary excretion rates of radioactivity were 57.5% and 16.5% of the dose, respectively. CM1 comprised 79.5% of biliary radioactivity and 84.3% of urinary radioactivity. Cephaeline comprised 42.4% of the dose in feces.

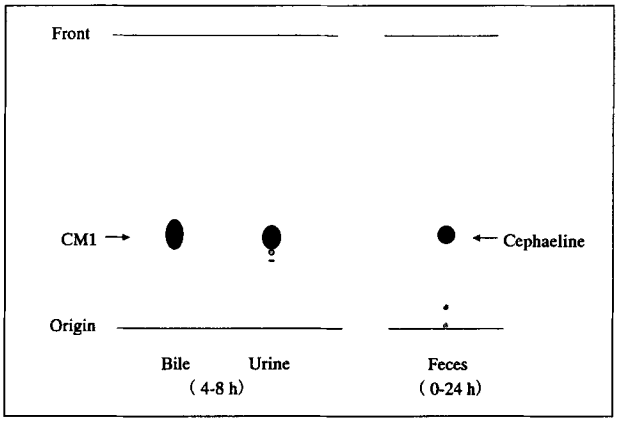


Fig. 2: Typical TLC patterns in the autoradiography of bile, urine and feces after a single oral administration of 0.5 mL/kg of ipecac syrup containing tritium-labeled cephaeline to rats Solvent; bile and urine ; chloroform-methanol-water (5:5:1 v/v/v), feces ; cyclohexane-chloroform-diethylamine (5:4:1 v/v/v).

Radio-HPLC analysis of biliary, urinary and fecal metabolite from ^{3}H-emetine in rats

The radioactivity of ^{3}H-emetine was excreted of a total of approximately 33% of the dose in urine, feces and bile within 48 hours following administration. These hydrolyzed samples were analyzed by HPLC (Fig.3). Biliary excretion rate of radioactivity was determined at 6.9% of the dose. Emetine comprised 5.8% of biliary radioactivity. EM1 and EM2, which are unknown metabolites were comprised 43.2% and 13.6% of biliary radioactivity, respectively. Moreover, the excretion of radioactivity in hydrolyzed samples of urine and feces was determined at 6.8% and 19.7% of the dose, respectively. There were no metabolites detected in these hydrolyzed samples; however, the unchanged emetine was detected. Additionally, in intact samples of bile, urine and feces, we did not detect the demethylated metabolites of emetine (data not shown).

Identification of biliary metabolite of cephaeline in rats

CM1 was obtained as a white powder. The molecular formula of CM1 was established as $C_{34}H_{46}N_2O_{10}$ on the basis of HR-FAB-MS spectrum, which showed that CM1 was a glucuronic acid conjugate of cephaeline. In the EI-MS spectrum, the presence of ion fragments at m/z 244 and m/z 191 suggested that CM1 had two methoxy groups in the A ring[7] (Fig.4). The anomeric proton of glucuronic

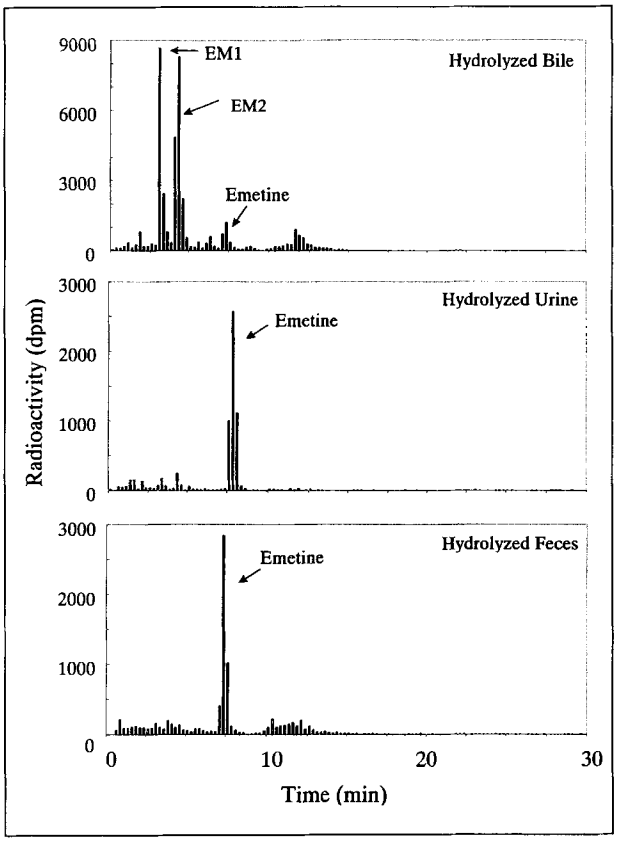


Fig. 3: Typical HPLC profiles of unchanged emetine and its metabolites in hydrolyzed samples of bile (0-24h), urine (0-24h) and feces (0-48h) after a single oral administration of 0.5 mL/kg of ipecac syrup containing tritium-labeled emetine to rats.

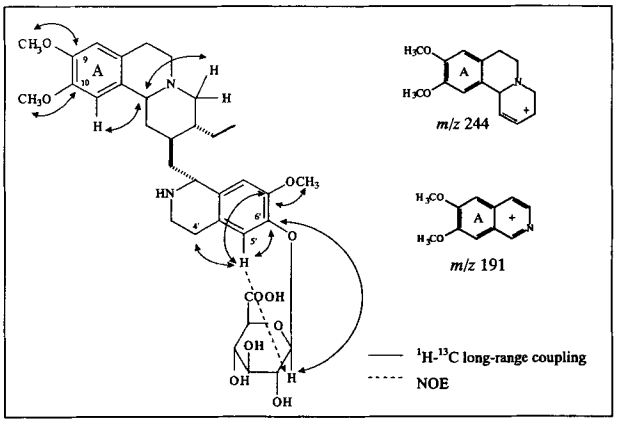


Fig. 4: Long-range ^{1}H-^{13}C coupling. NOE Shift correlation spectrum in methanol-d_4 and EI-MS spectrum of CM1.

acid moiety showed HMBC correlation to the 6' carbon. In the NOESY spectrum, the anomeric proton indicated the NOE interaction to the 5' proton. These results indicated that the glucuronide group was connected to the 6' hydroxy group (Fig. 4). Based on these data, CM1 was determinated to be cephaeline-6'-O-glucuronide. Data on various spectra for CM1 are shown in Table I.

Identification of biliary metabolite of emetine in rats

Main peaks on total ion chromatogram (TIC) were noted at retention time (t_R) 7'58", 10'17" and 20'00" (Fig.5). The peak at t_R 7'58" demonstrated m/z 467. This peak was indicative of demethylation at the C6'

Table I: Spectral data of CM1 isolated form rat bile after a single oral administration of cephaeline

Item	Spectral data
HR-FAB-MS (positive mode)	m/z: 643.3238 (Calcd for $C_{34}H_{47}N_2O_{10}$ $[M+H]^+$ 643.3231)
EI-MS	m/z: 466, 272, 244, 191, 190, 178
IRν_{max}^{KBr} cm^{-1}	3428 (br, OH), 2922 (C-H), 1606 (C=O), 1514, 1412, 1256
^{1}H-NMR (d in CD_3OD)*	0.94 (3H, t, *J*=7.5 Hz, H-13), 1.16 (1H, m, H-12), 1.26 (1H, br q, *J*=11 Hz, H-1), 1.44 (1H, br, H-3), 1.68 (2H, m, H-2 and H-14), 1.73 (1H, m, H-12), 2.10 (1H, br t, *J*=12 Hz, H-14), 2.19 (1H, br t, *J*=12 Hz, H-4), 2.58 (1H, m, H-6), 2.75 (2H, m, H-1 and H-7), 2.81 (1H, dt, *J*=5.6 and 11 Hz, H-4'), 2.92 (1H, m, H-4'), 3.04 ~ 3.15 (3H, m, H-3', H-6 and H-7), 3.14 (1H, dd, *J*=4 and 12 Hz, H-4), 3.27 (1H, br d, *J*=11 Hz, H-11b), 3.30 (m, H-3', overlapping with signals of solvent), 3.48 ~ 3.55 (3H, m, GlcA-2 ~ GlcA-4), 3.75 (1H, br d, *J*=9 Hz, GlcA-5), 3.80, 3.82, 3.83 (each 3H, s, OCH_3), 4.29 (1H, br d, *J*=11 Hz, H-1'), 4.96 (1H, br d, *J*=7 Hz, GlcA-1), 6.69 (1H, s, H-8 or H-8'), 6.70 (1H, s, H-8 or H-8'), 6.98 (1H, s, H-5'), 7.03 (1H, s, H-11).
^{13}C-NMR (d in CD_3OD)*	11.6 (q, C-13), 24.4 (t, C-12), 27.8 (t, C-4'), 29.5 (t, C-7), 36.9 (t, C-1), 37.8 (d, C-2). 40.2 (t, C-14), 41.2 (t, C-3'), 42.4 (d, C-3), 53.3 (t, C-6), 53.5 (d, C-1'), 56.4, 57.0 and 57.5 (each q, OCH_3), 62.1 (t, C-4), 63.8 (d, C-11b), 73.5, 74.8 and 77.8 (each d, GlcA-2 ~ Glc-4), 76.5 (d, GlcA-5), 102.5 (d, GlcA-1), 111.5 (d, C-11), 111.9 (d, C-8 or C-8'), 113.3 (d, C-8 or C-8'), 118.0 (d, C-5')|, 127.3 (s, C-4' a or C-8' a), 128.1 (s, C-7a or C-11a), 130.9 (s, C-7a or C-11a), 131.5 (s, C-8' a or C-4' a), 147.1 (s. C-6'), 149.0 (s, C-9 or C-10), 149.7 (s, C-10 or C-9), 149.4 (s, C-7'), 176.4 (br s, GlcA-6)
*: The CD_3OD signals were regarded as the reference (d_H = 3.30, d_c = 49.0).	

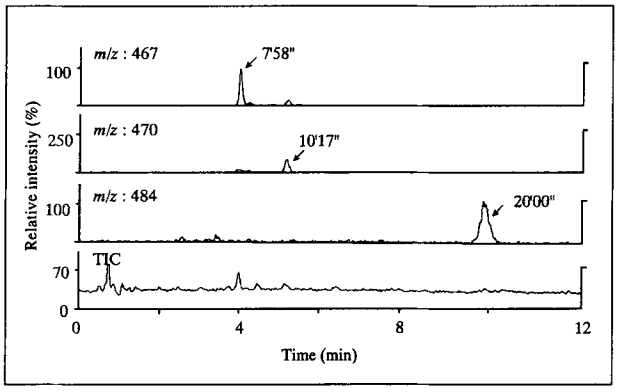


Fig. 5 : Mass chromatograms (LC-MS) for the $[M+M]^+$ ions of the biliary metabolites of deuterium-labeled emetine in rats.

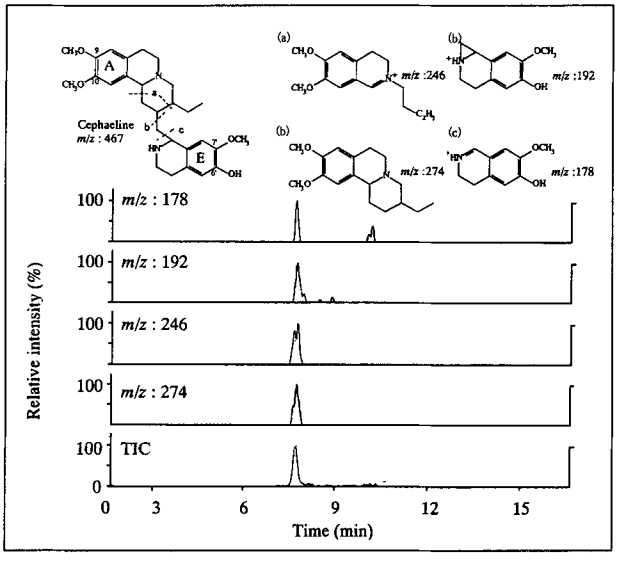


Fig. 6 : Mass chromatograms (LC-MS-MS) for the parent ion (m/z 467, $[M+M]^+$ of the biliary metabolites of deuterium-labeled emetine in rats.

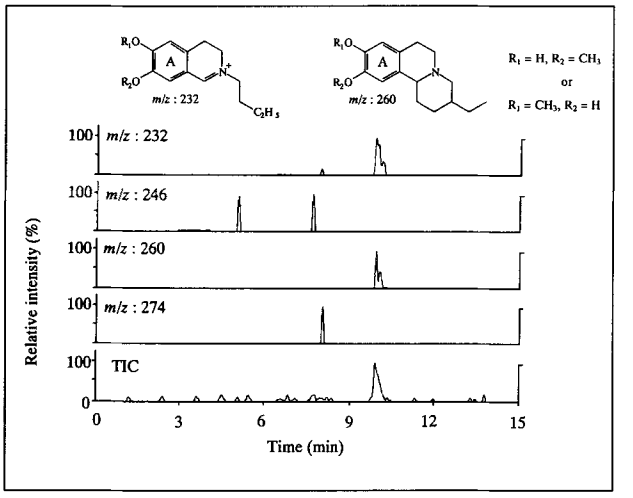


Fig. 7: Mass chromatograms (LC-MS-MS) for the parent ion (m/z 470, $[M+M]^+$ of the biliary metabolites of deuterium-labeled emetine in rats.

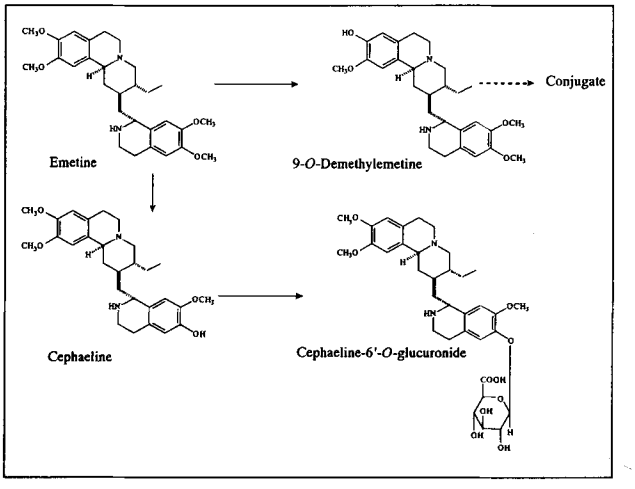


Fig. 8 : Metabolic pathway of cephaeline and emetine in rats.

position, evident when deuterium-labeled emetine (m/z 484) was converted to cephaeline (6'-O-demethylemetine). MS-MS analysis was performed on samples exhibiting a parent ion of m/z 467. Daughter ions (m/z 178, 192, 246, 274) were detected, as demonstrated in cephaeline standards (Fig.6). Consequently, EM1 was identified as cephaeline.

The peak occurring at t_R 10'17" displayed an m/z value of 470, suggesting the presence of a mono-demethyl compound characterized by the loss of a methoxyl group other than the deuterated moiety. This metabolite was tentatively designated as EM2. For MS-MS analysis, m/z 232 and m/z 260 were detected as daughter ions in the peak at t_R 10'17". However, neither m/z 246 nor m/z 274 was detected (Fig.7). Consequently, the demethylation position for EM2 may be either the C9 or C10 position. The standard samples of these two metabolites were synthesized and retention times were confirmed by HPLC. The retention time of EM2 was consistent with 9-O-demethylemetine. Therefore, EM2 was identified as 9-O-demethylemetine.

Based on the peak at t_R 20'00", retention time and mass spectrum were consistent with those of deuterium-labeled emetine standards. As a result, this peak was identified as deuterium-labeled emetine.

Discussion

This study is the first attempt to identify the metabolic fate of the ipecac alkaloids, cephaeline and emetine. The

findings confirmed that cephaeline was conjugated to glucuronide, while emetine was demethylated to cephaeline and 9-O-demethylemetine, and may be conjugated to glucuronides afterwards (Fig.8).

In our previous report, we studied the absorption, distribution and excretion of ^{3}H-cephaeline and ^{3}H-emetine in rats[2]. The findings indicated that the tissue distribution of ^{3}H-emetine was greater than that of ^{3}H-cephaeline. Furthermore, the biliary clearance of ^{3}H-emetine into the main excretion route was smaller than that for ^{3}H-cephaeline despite similar absorption levels for both compounds. We also found differences in the metabolic pathways of cephaeline and emetine. Cephaeline is rapidly converted to a highly polar metabolite by phase II metabolic reaction as a result of its hydroxyl groups. Subsequently, it is excreted primarily in bile. On the other hand, emetine undergoes demethylation to cephaeline and 9-O-demethylemetine and is excreted primarily in bile following conjugation. The differences in the metabolic processes of cephaeline and emetine appear to be a result of the demethylation mechanism of the latter compound. Peeples et al.[8] reported that little demethylation reaction was confirmed by in vitro incubation of emetine with microsomal suspension and NADPH. Moreover, this report also suggested that the affinity between emetine and cytochrome P450 is weak because the Ks value was 34 mmol/L. Consequently, this rate-determining step of metabolic process of emetine seems to be the primary cause of the small biliary clearance.

In emergency medical practice, ipecac syrup has long been employed due to its clinical efficacy and safety. However, a few reports have described intoxication related to misuse of ipecac extract or syrup preparation[9,10]. Ipecac alkaloids have been shown to cause cardiac toxicity in humans[11]. Emetine is a direct myotoxin which inhibits protein synthesis and disrupts mitochondrial oxidative phosphorylation[12]. Emetine has also been shown to cause cardiac toxicity in experimental animals[13,14]. Moreover, studies using mammalian heart indicate that cephaeline is a cardiotoxin with a potency rivaling that of emetine at large intravenous doses[15,16]. Cephaeline may also cause cardiac toxicity in humans. However, a report on the cardiotoxicity of cephaeline by oral administration has shown it to be lesser than that of emetine. The reason for decreased cephaeline cardiotoxicity may be attributed to its more rapid detoxification by conjugation reaction.

This study provides substantial findings on the biotransformation of ipeca alcaloid, compound that are very useful remedies in emergency medecine.

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