Efficacy of Emetic and United State Pharmacopoeia Ipecac Syrup in Prevention of Drug Absorption

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The efficacy of both the emetic syrup prepared in the previous report[1] and the United States Pharmacopoeia (USP) ipecac syrup concerning the prevention of drug absorption was investigated in 4 beagle dogs using a randomized and cross-over design. In order to control the intragastric pH of the beagle dogs, the administration of pentagastrin or hydrochloric acid (HCl)–glycine buffer (pH 1.5) was tested. The intragastric pH changed from 7.2 to 1.8 with the intramuscular administration of pentagastrin, but the primary emesis occurred more slowly. On the other hand, the HCl–glycine buffer (pH 1.5) gave the appropriate emesis. Therefore, the HCl–glycine buffer (pH 1.5) was used to control the intragastric pH of the beagle dogs.

Acetaminophen (AcA), salicylic acid (SA) and kanamycin (KM) as markers were administered orally after conditioning the intragastric pH at 1.5. The emetic syrup or the USP ipecac syrup was then administered. The recovery rate of AcA and KM from vomit was 42—65%. The emetic syrup and the USP ipecac syrup significantly reduced the absorption of AcA from the calculation of pharmacokinetic parameters compared to the control syrup. It was observed that the absorption of cephaeline (CP) in the emetic syrup was less than that of CP in the USP ipecac syrup.

Keywords cephaeline; emetic syrup; USP ipecac syrup; γ-cyclodextrin; pentagastrin; acute poisoning; intragastric pH; drug absorption

If a poison ingested can be removed or inactivated in the gastrointestinal tract before absorption, acute poisoning can be prevented or reduced. Therefore, emetics or charcoal, which can be administered immediately and easily by anyone, is a drug of first choice in an emergency. Gastric lavage and hemodialysis are other treatments, however, these can not be done immediately and easily because they need special techniques and instruments.

Families having children under five years old have often used ipecac syrup, which is more effective than gastric lavage,[2] as a first-aid medicine when their children have accidentally ingested harmful substances. However, ipecac has not been used in Japan as an emetic, but rather as an expectorant and an amebacide. There is no adequate emetic in Japan, and ipecac syrup has been strongly requested from a place in acute medicine. Therefore, our study was to develop a better emetic than the United States Pharmacopoeia (USP) ipecac syrup for the purpose of meeting this need.

This paper presents a comparison of the prevention of drug absorption between emetic syrup and USP ipecac syrup investigated by the analysis of the concentrations of acetaminophen (AcA) and salicylic acid (SA) in vomit and serum and kanamycin (KM) in vomit. AcA and acetylsalicylic acid (AS) are widely used for influenza. Therefore, many acute poisonings have occurred from accidental ingestion. SA, instead of AS, was selected as a marker drug in this study since AS was hydrolyzed to SA easily in the serum, liver and kidneys. Since the absorption of KM is very little in post oral,[3] KM is suitable as a comparative drug for the determination of recovery from the vomit. The absorption characteristic of cephaeline (CP) in emetic syrup and USP ipecac syrup is also discussed.

Experimental

Animals Male beagle dogs, weighing 10.0—11.5 kg, were used. They were fed on commercial food and water and were fasted for 24 h before the experiment, but were allowed free access to water.

Materials CP was isolated from powdered ipecac and purified according to the previous report. It was identified by thin layer chromatography (TLC), electron ionization-mass spectroscopy (EI-MS) and proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy with an authentic sample.

γ-Cyclodextrin (γ-CyD) was purchased from Nihon Shokuhin Kako Co. and recrystallized from water. Sonde, pentagastrin and KM syrup were purchased from Argyle Co., Ltd. (Tokyo, Japan), I.C.I. Pharm. Co., Ltd. (Osaka, Japan) and Banyu Pharm. Co., Ltd. (Tokyo, Japan), respectively. All other chemicals and solvents used were of analytical reagent grade.

Preparation of Emetic Syrup According to the content of CP in the USP ipecac syrup, CP hydrochloride (89 mg) was dissolved in a phosphate buffer (pH 4) solution containing γ-CyD (3.6×10^{-2} M), and glycerin and syrup simplex were added similarly to the USP ipecac syrup.[4] The preparation of a control syrup was done according to that of emetic syrup, except for the addition of CP.

Preparation of Marker Syrup Drugs and their doses are shown in Table I. AcA (2700 mg) and SA (675 mg) were dissolved with an adequate volume of HCl–glycine buffer (pH 1.5). The solution obtained was filled up to 300 ml with the HCl–glycine buffer after the addition of KM syrup (30 ml). In order to delay the gastric emptying of drugs, the 400 ml of JP syrup simplex was added to include a sucrose concentration of 50% according to Kato's report[5] to the above solution.

Emetic Experiment The schedule of the emetic experiment is shown in Fig. 1. After fasting for 24 h, a sonde was inserted into the stomach of each beagle dog while standing without an anesthetic. In order to control their intragastric pH at 1.5—2.5, pentagastrin (6 mg/kg) was administered intramuscularly or the HCl–glycine buffer solution (pH 1.5; 100 ml) was injected into the stomach of each beagle dog through the sonde. After 10 min, 50 ml of the marker syrup was injected into the stomach through the sonde, and the remaining marker syrup in the sonde was completely washed with the HCl–glycine buffer solution (25 ml) and injected again. After 10 min, the USP ipecac syrup (20 ml) or the emetic syrup (20 ml) was injected into the stomach through the sonde, and the remaining emetic in the sonde was completely washed with the phosphate buffer solution (pH 4; 20 ml) and injected. The sonde was taken off the stomach. Eight blood samples were collected from each for the analysis of AcA and SA

TABLE I. Preparation of Marker Syrup

Salicylic acid	675 mg
Acetaminophen	2700 mg
Kanamycin syrup (50 mg/ml)	30 ml
HCl–glycine buffer (pH 1.5)	300 ml
+ JP syrup simplex	400 ml
Total	700 ml

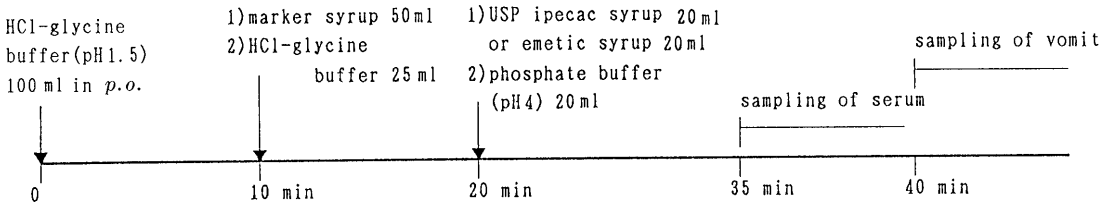

Fig. 1. Schedule of Emetic Experiment

during 0—8 h, and for that of CP during 0—24 h after the administration of the emetics. These samples were centrifuged at 3000 rpm for 10 min to obtain the serum sample, and stored in a refrigerator at −10 °C until analysis. The vomits collected during 20—65 min after the administration of the emetics were stored in a refrigerator at 5 °C. The cross-over method was used with an interval of two weeks.

Quantitative Analysis of Drugs in Serum and Vomit Serum concentrations of drugs were determined by the following methods. The concentrations of AcA and SA in the serum and the vomit and KM in the vomit were determined by fluorescence polarization immunoassay (FPIA) by a TDX analyzer (Abbott Laboratories, Chicago).

The concentrations of CP in the serum and the vomit were determined using a Shimadzu HPLC (model LC-3A) equipped with a Shimadzu fluorescence spectromonitor (model RF-510LCA). The column was prepacked TSK gel ODS-80TM (5 μm, 15 cm × 46 mm) and performed under the following conditions; injection volume, 100 μl; mobile phase, 10 mM sodium-1-heptanesulfonate solution adjusted to pH 4 with glacial acetic acid–methanol (46 : 54, v/v); flow rate, 1 ml/min; monitoring, excitation wavelength (285 nm) and emission wavelength (316 nm).

Two hundred and fifty microliter and 500 μl of 10% NH_4OH solution were added to the vomit (250 μl) and the serum (500 μl), respectively. Each solution was mixed together for 5 min, and ether (4 ml) was added. The individual ether layer (1 ml from vomit and 3 ml from serum) was evaporated *in vacuo* at 25 °C. The residue obtained from vomit was dissolved in 0.01% HCl solution (10 ml). The internal standard solution (acrinol 4 mg/ml; 50 μl) was mixed with the above sample solution (1 ml). The residue obtained from serum was dissolved in 0.01% HCl solution (200 μl), and the internal standard solution (acrinol 200 μg/ml; 50 μl) was added. Individual sample solutions (100 μl) were injected into high performance liquid chromatography (HPLC).

Determination of Absorption The area under the serum drug concentration–time curve during 0—8 h (AUC_{0-8h}) after the administration of the emetic syrup or USP ipecac syrup was calculated following the trapezoidal rule.

Results and Discussion

Administration of Pentagastrin The beagle dogs used as a pre-clinical experimental model have been usually classified into two groups, *i.e.* high acidic (under 3.0 of pH) and low acidic (over 5.0 of pH) groups according to their intragastric pHs.[6] Since the absorption of medicines easily changes due to intragastric pH, the administration of pentagastrin or the administration of HCl–glycine buffer (pH 1.5) was studied in order to maintain the intragastric pH of the beagle dogs at 1.5—2.5, similar to that of humans.

The intragastric pH of the beagle dog indicated 7.2 before the treatment of pentagastrin, but immediately changed to a strong acidity (pH 1.8) after the administration of pentagastrin. This state continued for about 80 min. These results showed a good agreement with the former study (Yamada *et al.*).[7] These beagle dogs controlled the intragastric pH at 1.8, however, needed more than two hours for the first emesis. It is known that the emetic effect occurred by the ipecac depends on both the indirect effect to the chemoreceptor trigger zone (CTZ) due to irritation of the intragastric wall and a direct effect to the CTZ due to absorption.[8] However, the long interval for emesis in this study will result from a direct effect to the CTZ, since the transmission of the irritation from the intragastric wall to the CTZ may be hindered by pentagastrin. Therefore, it is concluded that the beagle dogs controlling intragastric pH with pentagastrin can not be used for emetic experiments of ipecac.

TABLE II. Preparation of Emetic Syrup

CP·HCl	89 mg[a]
γ-CyD in phosphate buffer (3.6×10^{-2} M/l, pH 4)	25 ml
Glycerin	8.3 ml
Syrup simplex	66.7 ml
Total	100 ml

a) According to the CP content in USP ipecac syrup.

Administration of HCl–Glycine Buffer For the purpose of controlling the intragastric pH of the beagle dog, HCl–glycine buffer (pH 1.5) was supplemented. The pHs of vomits obtained from the beagle dogs showed 1.8—2.6. Futhermore, the primary emesis of these beagle dogs was faster compared to the administration of pentagastrin. Therefore, it is confirmed that the intragastric pH can be kept constantly by this method during the emetic experiment.

Preparation of Emetic Syrup USP ipecac syrup has some problems as follows. 1) Since the extract from ipecac is directly used, the contents of EM and CP are very variable. 2) EM and CP are known to decompose thermally and photochemically to various products such as emetamine, *O*-methylpsychotrine and psychotrine, which may significantly alter the pharmacological effect of ipecac. 3) The heart-injury-effect of EM is the most dangerous in the various side effects of ipecac.[9] 4) The emetic action of EM is half as strong as that of CP.[10]

Therefore, emetic syrup was prepared in this study. Since this syrup does not include EM, it can avoid the heart-injury-side effect. Since this syrup consists of CP and γ-CyD, it is possible to control the emetic effect by changing the content of CP.

Table II shows the preparation method of emetic syrup. The content of CP in this study was adjusted to that of CP contained in the USP ipecac syrup (100 ml). However, it is well known that CP is a fragile compound with respect to high temperature and light. CyDs have been extensively utilized[11] to improve various physico- and bio-pharmaceutical properties such as chemical instability, poor dissolution characteristics, and low bioavailability of drugs by the formation of the inclusion complex. In the previous paper,[1] it was confirmed that an acidic medium (pH 3—4) promoted the stability of CP and γ- and dimethyl-β-CyDs (DM-β-CyD) inhibited the thermo- and photo-degradation of CP. In this study, γ-CyD was used as the stabilizer of CP

in the emetic syrup, since DM-β-CyD had a severe local irritative effect. The high content of γ-CyD (3.6×10^{-2} M) was used to prevent the absorption of CP as much as possible.

Drug Contents in Vomit Table III shows the drug content in vomit. The content of SA recovered from the vomit was lowest in three marker drugs, since SA was a typical drug absorbed from the stomach easily.[12] Therefore, other suitable and additional treatments are necessary for the poisoning due to the acidic drugs. On the other hand, it is well known that the maximum serum concentration (C_{max}) of AcA is achieved during 20—60 min in humans.[12] The recovery of AcA (42—50%) was nearly equal to that of KM (52—66%), which was absorbed very little in post oral.[3] Though CP was also easily absorbed,[13] the content of CP recovered from vomit was almost the same as that of AcA. Therefore, it was suggested that the absorptions of AcA and CP may be prevented by the stimulation of emesis. The recovery rates of four drugs from vomit were not significantly different between the emetic syrup and the USP ipecac syrup. Thus, it was concluded that the detoxification of emetic syrup is equivalent to that of USP ipecac syrup.

Serum Concentration of AcA and SA Figures 2 and 3 show the serum drug concentration–time curves of AcA and SA after oral administration of the combination of the marker syrup and emetic syrup or the combination of the marker syrup and USP ipecac syrup using beagle dogs. The AUC_{0-8h} calculated by the trapezoidal rule and the C_{max} are shown in Table IV. The emetic syrup and the USP ipecac syrup gave the C_{max} value of 2.54±0.87 and 2.25±0.97 μg/ml (mean±S.E.M.) for AcA, respectively. When the AUC_{0-8h} value of the control syrup was 100% for AcA, those of emetic syrup and USP ipecac syrup were 42.2% and 41.3% for AcA, respectively. Therefore, there was a statistically significant difference in the AUC_{0-8h} value on the absorption of AcA between the administration of either the emetic syrup or the USP ipecac syrup and the administration of the control syrup ($p<0.05$). The emetic syrup and the USP ipecac syrup gave the C_{max} value of 14.42±2.38 and 11.84±1.97 μg/ml (mean±S.E.M.) for SA, respectively. When AUC_{0-8h} of the control syrup was 100% for SA, those of emetic syrup and USP ipecac syrup were 87.5% and 68.5% for SA, respectively. Therefore, there was no significant difference in the AUC_{0-8h} value on the absorption of SA between the administration of either the emetic syrup or the USP ipecac syrup and the administration of the control syrup. The AUC_{0-8h} values of AcA and SA were related to the recovery rates of AcA and SA in vomit.

Serum Concentration of CP Figure 4 shows the serum drug concentration–time curve of CP after oral administrations of a combination of marker syrup and emetic syrup

TABLE III. The Recoveries of AcA, SA, KM and CP from Vomits after Oral Administration of USP Ipecac Syrup and Emetic Syrup to 4 Beagle Dogs

Emetic	Recovery (%)			
	AcA mean± S.E.M.	SA mean± S.E.M.	KM mean± S.E.M.	CP mean± S.E.M.
USP ipecac syrup	42.2±4.4	17.5±1.8	52.1±4.8	41.7±4.5
Emetic syrup	50.3±6.2	13.1±5.4	65.7±10.4	41.7±9.5

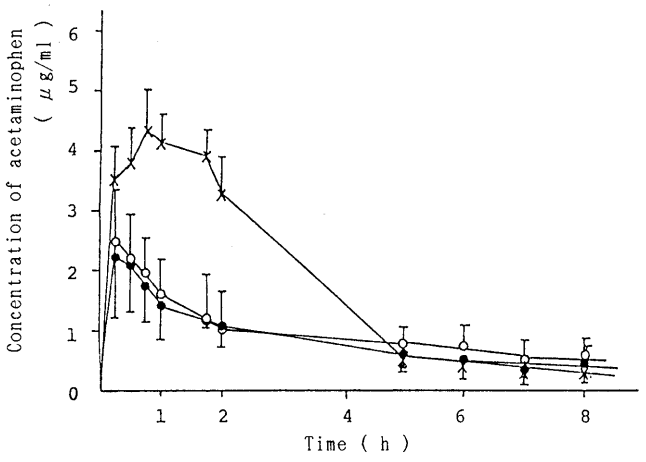

Fig. 2. Mean Serum Levels of AcA Following the Oral Administration of USP Ipecac Syrup and Emetic Syrup to 4 Beagle Dogs

●, USP ipecac syrup; ○, emetic syrup; ×, control syrup.

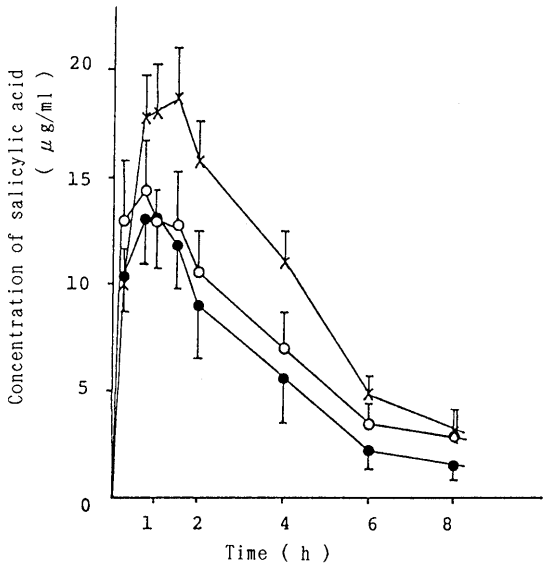

Fig. 3. Mean Serum Levels of SA Following the Oral Administration of USP Ipecac Syrup and Emetic Syrup to 4 Beagle Dogs

●, USP ipecac syrup; ○, emetic syrup; ×, control syrup.

TABLE IV. Bioavailability Parameters of AcA and SA after Oral Administrations of USP Ipecac Syrup and Emetic Syrup to 4 Beagle Dogs

	C_{max} (μg/ml) mean±S.E.M. (%)	AUC_{0-8h} (μg/ml·h) mean±S.E.M. (%)
AcA		
Control syrup	4.72±0.54 (100)	13.33±1.08 (100)
USP ipecac syrup	2.25±0.97[a] (47.7)	5.51±2.22[a] (41.3)
Emetic syrup	2.54±0.87[a] (53.8)	5.62±2.76[a] (42.2)
SA		
Control syrup	18.67±2.34 (100)	73.85±6.35 (100)
USP ipecac syrup	11.84±1.97[b] (63.4)	50.62±13.14[b] (68.5)
Emetic syrup	14.42±2.38[b] (77.2)	64.62±7.77[b] (87.5)

a) Student's *t*-test (control *vs.* USP ipecac syrup or emetic syrup), $p<0.05$.
b) Not significant.

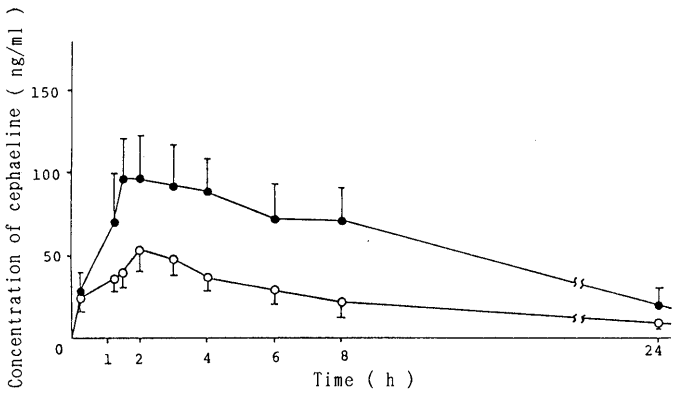

Fig. 4. Mean Serum Levels of CP Following the Oral Administration of USP Ipecac Syrup and Emetic Syrup to 4 Beagle Dogs

●, USP ipecac syrup; ○, emetic syrup.

TABLE V. Bioavailability Parameters of CP after Oral Administrations of USP Ipecac Syrup and Emetic Syrup to 4 Beagle Dogs

Emetic	C_{max} (ng/ml) mean±S.E.M.	AUC_{0-8h} (ng/ml·h) mean±S.E.M.
USP ipecac syrup	96.38±23.05	617.85±147.42
Emetic syrup	53.57±13.07	288.77± 61.60

or the combination of marker syrup and USP ipecac syrup to the beagle dogs. The AUC_{0-8h} calculated by the trapezoidal rule, and the C_{max} are shown in Table V.

The C_{max} value of USP ipecac syrup (96.38±23.05 ng/ml) was about twice compared with that of emetic syrup (53.57±13.07 ng/ml). The emetic syrup and the USP ipecac syrup gave the AUC_{0-8h} values of 288.77±61.60 and 617.85±147.42 ng/ml·h (mean±S.E.M.) for CP, respectively. There was no significant difference in AUC_{0-8h} value between the emetic syrup and the USP ipecac syrup. However, the administration of emetic syrup tends to somehow inhibit the absorption of CP compared to that of USP ipecac syrup.

USP ipecac syrup consists of the ethanol extract of ipecac, glycerin and syrup simplex. On the contrary, the emetic syrup prepared in this study includes a high content of γ-CyD as a stabilizer except for CP and syrup simplex. The CyD complexes must dissociate before absorption, since only the free form of the drug can permeate the lipid barrier of the intragastric tract. If the CyD concentration is sufficiently high, the equilibrium is shifted greatly toward complexation and the absorption is considerably hindered.[14] Therefore, the γ-CyD added into the emetic syrup as a stabilizer may inhibit the absorption of CP because of including the high content of γ-CyD.

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