

# A Preliminary Study to Predict the Ingested Dose of Doxylamine from its Plasma Concentration in the Korean Patients with Doxylamine Intoxication

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## Abstract

**Background:** Doxylamine succinate, over-the-counter antihistamine, is commonly used as a nighttime sleep-aid and is world-wide ingested in overdoses when one attempts a suicide because of its easy accessibility. The objective of this study was aimed to find out models to predict the ingested amount of doxylamine from its blood concentrations of thirty Korean patients with doxylamine intoxication.

**Method:** Thirty patients who were admitted to two emergency centers through Jul, 2006 to Jul, 2008 due to doxylamine overdose were recruited. In all patients, demographic information and clinical variables, arrival time to the hospital after doxylamine overdose, amount of doxylamine ingested, and vomiting were evaluated.

**Results:** Of these thirty patients, average ingestion amount of doxylamine was 750 mg (range, 200~2500 mg). The mean arrival time to the hospital after the doxylamine ingestion was 4.5 h (range, <1.0~24 h) and its mean blood level at arrival time was 3.15 µg/mL (range, 0.64~11.31 µg/mL). Ingested doxylamine dose was predicted by determining the coefficient of plasma drug concentration using stepwise regression analysis. The linear regression formula calculated was:  $y=241.769(x)+217.117$  ( $y$ =ingested doxylamine dose,  $x$ =its plasma concentration,  $p=0.001$ ).

**Conclusion:** Close clinical observation, laboratory follow-up and analysis of blood doxylamine concentration were required for patients, who intoxicated doxylamine and admitted emergency department, to estimate ingested dose and time of doxylamine, and to prevent the clinical toxicity. We suggested that recommended sampling time for analysis of plasma doxylamine concentration was 1~3 h after the ingestion, and its plasma level at the arrival time was a statistically significant factor to predict the ingested dose of doxylamine in the 30 Korean patients with doxylamine intoxication.

**Keywords:** Doxylamine intoxication; Plasma concentration; Prediction model for dose of ingestion

## Introduction

The H-1 histamine antagonist doxylamine (Figure 1) is an over-the-counter drug widely used in the management of insomnia. Doxylamine has antihistaminic, sedative, and anticholinergic properties [1,2] and increases the potential not only for suicidal ingestion world-wide by adults, but also for inadvertent ingestion by children, probably because of their accessibility [3,4]. In Korea, doxylamine overdose accounts for 25% of visits due to drug intoxication in urban emergency departments [5]. This drug is relatively safe, but is known to cause rhabdomyolysis that is a potentially life-threatening complication of drug abuse, including doxylamine overdose [6]. In Korea, it has been reported that the incidence of rhabdomyolysis in patients with doxylamine overdose is highly ranged from 32% to 77% [7,8], which can be progressed to Acute Renal Failure (ARF). Hence, prediction, early detection and treatment of rhabdomyolysis are necessary to minimize the risk of kidney damage [9-11]. If it is treated promptly, patients can be usually

recovered completely from rhabdomyolysis, and kidney damages can be prevented [3]. Therefore, the early detection of high risks for developing rhabdomyolysis following doxylamine ingestion is very important to encounter the complications of doxylamine in the patients with doxylamine intoxication.

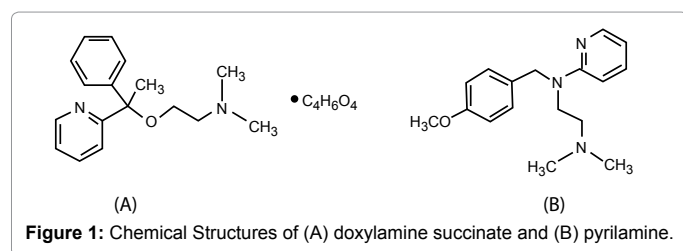
The fact that rhabdomyolysis could be the most serious complication of doxylamine overdose was firstly described in 1983 [2]. Although several factors which may contribute to the development of rhabdomyolysis or rhabdomyolysis-related ARF in doxylamine overdose have been defined [12-17]; its mechanism has not been fully elucidated. There have been a few studies conducted on the risk factors for the development of doxylamine-induced rhabdomyolysis except for a few reports of rhabdomyolysis or rhabdomyolysis-related ARF after doxylamine overdose [4,10,18,19].

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Even if there is no direct correlation between ingested amount of doxylamine, its plasma level, and the clinical manifestations [1,4], initial serum creatinine level and arterial pH showed a significant association with rhabdomyolysis in bivariate analysis [6]. Until now, there were no guidelines for the discharge of patients from hospitals. Discharges depend on the doctor's decision, but drug-induced complications may occur after discharge. Therefore, accurate information for plasma doxylamine levels, ingested amount and time may be helpful in prevention or management of doxylamine-induced rhabdomyolysis or rhabdomyolysis-induced ARF, and also in making decisions for discharge time of the patients from the hospital.

Because of the emergency situations of drug overdose and the hectic environment of the hospital, patients become very stressful physically and psychologically. Patients tend to be vulnerable, and it is difficult to obtain the accurate information of the amount and time of doxylamine ingestion directly from the patients without the help of their friends and family.

In this study, we conducted a preliminary study in order to identify plasma doxylamine levels and ingested amounts of doxylamine patterns, and to find out models to predict the ingested amount of doxylamine by its blood concentrations at arrival time to hospital after ingestion of doxylamine in 30 patients with doxylamine intoxication who admitted through the emergency departments in 2 hospitals in Korea.

## Methods and Materials

Patients with doxylamine overdose, who were admitted to Hanyang University Medical Center and Sahmyook Medical Center between Jul. 2006 and Jul. 2008 were recruited for this prospective study. This study was approved by the Institutional Review Board (IRB) of Hanyang University Medical Centre, Seoul, Korea and was carried out in accordance with the Declaration of Helsinki of the World Medical Association. Patients who concurrently ingested other drugs along with doxylamine, other than alcohol, were excluded according to inclusion criteria (Table 1). Patients were also excluded if they had evidences of myocardial ischemia, cerebrovascular accidents, or other

conditions according to exclusion criteria (Table 1). In all patients, the amount of doxylamine ingested, concomitant alcohol ingestion, and time elapsed before primary detoxification were checked on admission, and the presenting symptoms or signs were recorded according to Emergency Room Drug Information note (ER-DI Note) (Table 2). The amount of doxylamine ingested was determined from the number of tablets (25 mg/tablet). In all patients, general detoxification such as activated charcoal treatment or gastric lavage was performed, and intravenous hydration along with blood sampling for routine blood tests and analysis of blood doxylamine concentration were begun immediately at the point of admission into the hospital.

The plasma concentrations of doxylamine were determined using HPLC-UV method [20]. Pylamine (Figure 1) was used as an Internal Standard (IS). Calibration standards for doxylamine are prepared by adding each 0.05, 0.5, 1.0, 5.0, 10.0 µg of drug to consecutive tubes. Drug-free control plasma is added to each of the calibration tubes. Briefly, a 1.0 mL of human plasma in polypropylene tube was added with 0.1 mL of pylamine (IS, 100 µg/mL in mobile phase). After sample preparation such as protein precipitation and centrifugation, upper organic phase was removed and evaporated by nitrogen gas at 40°C on the heat plate. The residue was reconstituted with 10% methanol and vortexed for 20 sec. A volume of 80 µL of the reconstituted was injected into HPLC-UV system. The analytical separation was performed on the Capcell-Pak C18 MG column (4.6×150 mm, 5 µm, Shiseido Co, Ltd. Japan) and maintained at 30°C. The mobile phase consisted of acetonitrile and 0.005 M 1-hepatane sulphonic acid (v/v, 35/65, pH 3.0) with 1% phosphoric acid and pumped 0.8 mL/min. Drug ingested dose was predicted by determination coefficient of plasma drug concentration and arrival time to hospital after ingestion, using multiple stepwise regression analysis. The data collected before  $T_{max}$  (3 h) of doxylamine succinate were statistically analyzed using SPSS version 18.0 at  $p < 0.05$ .

## Results

### Patients

Thirty patients (M/F 11/19, age 29.3 years) were enrolled in this

Inclusion criteria	Exclusion criteria
1) Age >15 years. 2) Suspicion of doxylamine succinate intoxication (confirmation of doxylamine succinate ingestion by patients or caregivers or by remaining drugs). 3) first visit after drug ingestion without any treatment for drug ingestion by other clinics	1) Cannot confirm doxylamine intoxication. 2) Ingestion of other drug with doxylamine. 3) Noncompliance to blood sampling for analysis of doxylamine.

Table 1: Inclusion and exclusion criteria.

Notice as follows: 1. Try best to find out the name of toxicant that patient intoxicated. 2. If patient is consciousness, gather information about the type and the amount of drug. 3. If patient loses consciousness or unable to provide information, ask patient's guardian to detect rest of package of drug, prescription or drug from intoxicated place. 4. Investigate acquaintances and check hospital or pharmacy that patient used to go and if there is remained drug, identify it from web site which provides information about drugs such as www.druginfo.co.kr, etc., by using formulation identification menu. 5. Conservative treatment must be performed even though drug is not certain and if identification of drug is done, appropriate treatment should be continued.
Drug Name:
2. Amount of ingestion:
3. Dose of ingestion: [ ] mg/kg Toxic dose: Consult toxic dose (poison index) on online or text
4. Time interval from intake to lavage:
5. Prehospital vomiting:
6. Verify for intentional, incidental, or accidental drug intoxication:
7. Lavage finding:
8. Dosage of activated charcoal:
9. Verify type and amount of coingested drug or no congestion:

Table 2: ER Drug Information Note.

study. The mean age of male and female were 32.1 and 27.9 years, respectively, and highest incidence age group was the twenties in both genders, and the incidence of female was higher than that of male in all age groups (Table 3).

### Analytical method

The analytical method was evaluated in terms of extraction efficiency, interference, linearity, and precision. The peaks observed for doxylamine and pyrilamine were well separated from any naturally occurred plasma constituents or any metabolites of the drug. Under the described conditions, the retention time for doxylamine was 4.9 min and for pyrilamine was 8.5 min. With the blank plasma, when the standard doxylamine was eliminated from the assay, no peaks absorbing at 210 nm that had the same retention time as doxylamine were observed (Figure 2-I). The relationship between doxylamine concentrations and peak area ratios (SD/IS, doxylamine/pyrilamine) was linear at least from 0.05 to 10.0 µg/mL. Calibration curves were shown good linearity ( $Y=0.1342 \cdot X-0.0042$ ,  $R^2=0.999$ ,  $Y=SD/IS$  ratio,  $X=concentration$ ) and correlation coefficient was always greater than 0.999 (Figure 2-II). Relative standard deviation (RSD, %) calculated by doing five replicated analyses of known standards (0.05, 0.5, 1.0, 5.0, 10.0 µg/mL) were below 12.3% with LLOQ of 0.05 µg/mL.

### Characteristics for distribution of amount of doxylamine and its blood concentration in 30 patients

The range of ingested dose of doxylamine was from 200 to 2,500 mg and arrival time to hospital after ingestion was variable from within 1 h to 24 h. The most frequent arrival time after ingestion was within 3 h and the mean arrival time was 4.5 h. Two patients of current study had no information about the ingested amount of doxylamine. Mean amount of doxylamine ingested and blood concentrations were 750 mg and 3.15 µg/mL, respectively (Table 4).

### Statistical models for factors predicting amount of doxylamine ingested according to blood doxylamine levels by stepwise regression analysis

After drug administration by oral route, blood concentrations were increased gradually to the peak level until time to maximal concentration ( $T_{max}$ ) and then decreased gradually to zero until infinity. Therefore, we used blood doxylamine concentrations within  $T_{max}$  (3 h) of 24 patients out of thirty to make statistical models for prediction of ingested amount of doxylamine by multiple stepwise regression analysis in this study. We used two factors such as arrival time to hospital after ingestion and blood doxylamine level for predicting ingested amount of doxylamine. Among these two factors, plasma doxylamine level was statistically significant and acceptable to predict amount of doxylamine ingested in 24 patients ( $p<0.01$ , table 5). Figure 3 illustrated the linear relationship between doxylamine dose and plasma drug levels in the patients who arrived at hospital within  $T_{max}$  (3 h) after overdose ( $R^2=0.445$ ). The correlation coefficient for dose and blood drug concentration in the

Subjects Age(years)	Gender		Total	%
	Male	Female		
15 ~ 19	0	3	3	10.0
20 ~ 29	7	8	15	50.0
30 ~ 39	3	5	8	26.6
40 ~ 49	1	1	2	6.7
50 ~ 59	0	2	2	6.7
Total	11	19	30	100.0

Table 3: Baseline age distribution in patients with doxylamine intoxication.

Patients No.	Plasma concentration at arrival time (µg/mL)	Arrival time after ingestion (h)	Dose of ingestion (mg)
1	0.10	?	?
2~10	0.65~5.72	<1	250~1750
11~13	1.47~6.69	1	200~2500
14	2.92	1.5	1250
15~22	0.16~5.71	2	200~2250
23	1.14	2.5	500
24~25	1.24~2.22	3	750~1500
26	2.66	4	500
27	1.96	7	1250
28	10.84	8	2500
29	0.64	18	?
30	11.31	24	2500
Mean ± s.d.	3.15 ± 2.69	3.16 ± 5.13	736 ± 719

Table 4: Dose of doxylamine ingested and arrival time after intoxication and plasma doxylamine concentration in 30 patients with doxylamine intoxication.

Model	coefficient		Beta	t	p-value
	B	S.E.			
Model 1 (constant)	3.864	287.965		0.013	0.989
Plasma drug concentration (µg/mL)	249.648	60.654	0.690	4.116	0.001**
Arrival time (h) after ingestion	129.140	125.236	0.173	1.031	0.315
$R^2=0.475$ , Adjusted $R^2=0.420$ , $R=0.689$ , $F=8.604$ , $p=0.002$					
Model 2 (constant)	217.117	200.706		1.082	0.292
Plasma drug Concentration (µg/mL)	241.769	60.266	0.668	4.012	0.001***

$R^2=0.446$ , Adjusted  $R^2=0.418$ ,  $R=0.668$ ,  $F=16.094$ ,  $p=0.001$

\* Dependent variable: Drug intake dose (mg)

\*\* Model 1: Drug intake dose =  $249.648 \times \text{Plasma drug level} + 129.140 \times \text{Blood sampling time} + 3.864$  ( $p=0.001$ ,  $p=0.315$ )

\*\*\* Model 2: Drug intake dose =  $241.769 \times \text{Plasma drug level} + 217.117$  ( $p=0.001$ )

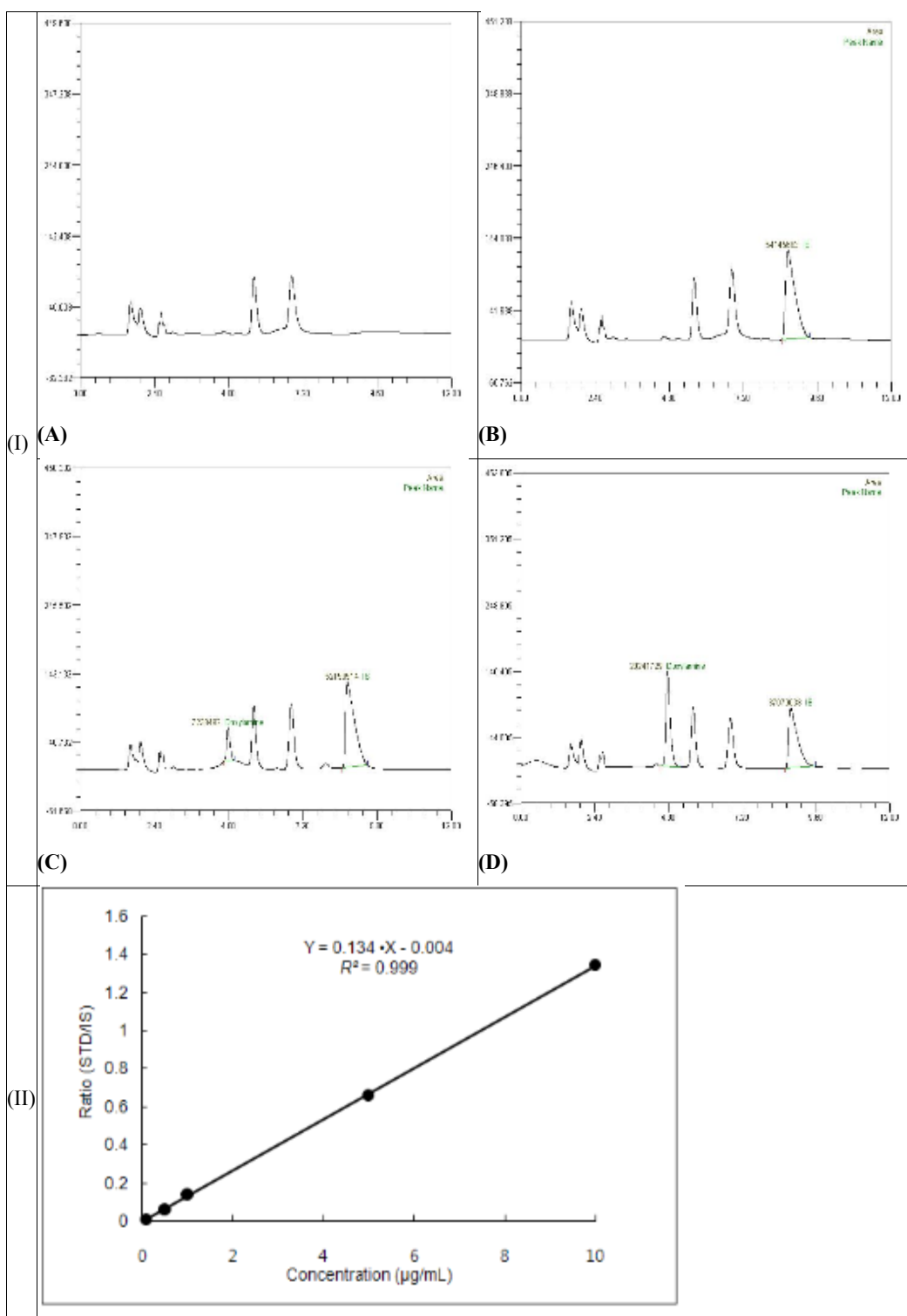
Table 5: Model for predicting Dose of doxylamine ingested by regression analysis.

Model 2 was 0.668 ( $p=0.001$ ). The linear regression formula calculated from dose and blood drug concentration was:  $y=241.769(x)+217.117$  ( $y$ =dose of ingestion,  $x$ =blood drug concentration,  $p=0.001$ ). A linear regression plot was established by drug intake and the significantly predictable factor (Table 5, figure 3).

### Discussion

Doxylamine succinate was the most commonly used antiemetic for nausea and vomiting of pregnancy, and the only one approved by FDA until its voluntary withdrawal from market in 1983, after a large series of lawsuits due to allegation of teratogenicity including fetal heart and limb reduction defects [21-24]. Doxylamine succinate 25~50 mg is more than effective as a sedative than 100 mg of secobarbital [25], and it is often used as a hypnotic antihistamine at bedtime [26]. Doxylamine succinate is well absorbed after oral administration of a single dose of 25 mg in 16 healthy male volunteers and reaches a peak level of 99 ng/mL within 2~3 h after dose, the elimination half-life was 10.1 h [27,28]. The majority of the dose (60%) is excreted unchanged in the urine and remainder is metabolized through various metabolic pathways [1,29].

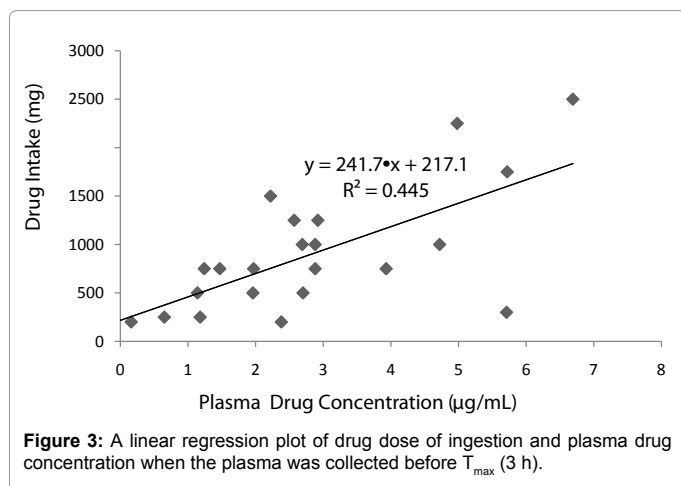
Because the lethal dosage of doxylamine in human is 25~250 mg/kg body weight and the dosage required to induce sleep can be as low as 6.25 mg, but doxylamine is usually effective in the dosage of up to 25 mg which is generally safe to healthy adults [30]. This drug is relatively safe, but is known to induce rhabdomyolysis that was firstly reported in 1983 [2], and Koppel et al. [1] described complications including rhabdomyolysis in 1987. It has been reported that the incidence of rhabdomyolysis induced by doxylamine overdose was 5~57% and that could result in ARF. Fortunately, patients can be usually recovered completely from rhabdomyolysis, if it is recognized



**Figure 2:** (I) Chromatograms of (A) a blank plasma, (B) a blank plasma spiked with 100 µg/mL of pyrillamine, (C) a blank plasma spiked with 1 µg/mL of doxylamine and 100 µg/mL of pyrillamine, and (D) a plasma sample from a subject taken 2 h after 300 mg of doxylamine ingestion and repressed as 5.71 µg/mL in blood doxylamine concentration. (II) Calibration curve showing good linear relation of plasma doxylamine concentration (0.05~10 µg/mL) to peak area ratio of doxylamine versus internal standard.

and treated promptly so that serious complications such as ARF can be prevented [31]. Most patients with drug intoxication ingested usually multiple drugs, and in the death case with doxylamine overdose, the

postmortem blood concentration was 0.7~12 µg/mL [32-34] which greatly exceeds the therapeutic range of approximately 0.05~0.15 µg/mL of doxylamine. The blood doxylamine concentration of the



overdose death case was 1.2 µg/mL presented by Siek and Dunn [33] and 12 µg/mL by Bayley et al. [34]. However, these concentrations appear to be low, since they indicate a lethal dosage less than 1000 mg. The most common manifestations of antihistamine overdose including doxylamine succinate are related to their anticholinergic effects that include variable levels of CNS depression, hallucinations, convulsions, tachycardia, arrhythmias, mydriasis, hyperthermia, skin flushing, rhabdomyolysis and hypotension [12]. Even if the anticholinergic manifestations of doxylamine overdose may be depended on the amount of doxylamine ingested, it could not be suggested that the blood doxylamine concentrations is related to complications of doxylamine overdose, because no blood doxylamine concentration happens in some patients with doxylamine overdose [10].

Nowadays, there are no guidelines for discharge of patients from the hospital and the discharges depend on the decision of doctor's, but complications of doxylamine intoxication are possible to occur to late period after discharge. Therefore, accurate information for plasma doxylamine levels, such as amount of drug ingested and ingested time may be helpful in prevention or management of late-onset complications such as rhabdomyolysis or ARF, and also in finding appropriate time of discharge of patients from the hospital. Although no correlation has been observed among the ingested dose, serum doxylamine levels and the extent of muscle injury [4], ingested amount and blood doxylamine levels may be very important information to manage the patients with doxylamine intoxication in various emergency situations successfully. This study has some limitations in that there is no information regarding the ingested amount of drug in two patients, and in five patients the arrival time to hospital was over 4 h after the ingestion of doxylamine. Further study is needed for blood concentration and critical clinical toxicity after ingestion of high dose of doxylamine in large scale of patients in emergency situations.

## Conclusion

The arrival time at hospital after ingestion was within 3 h and mean arrival time was 4.5 h. Mean amount of doxylamine ingested and its blood concentrations were 750 mg (200~2,500 mg) and 3.15 µg/mL, respectively. We analyzed statistical models for prediction of ingested amount of drug by multiple stepwise regression analysis using two factors such as arrival time to hospital after ingestion and blood doxylamine levels at the arrival times in this study. In conclusion, plasma doxylamine level at the arrival time to the hospital was statistically significant factor to predict amount of doxylamine ingested in 23 patients.

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