

## PHARMACOKINETIC STUDY OF DEXTROMETHORPHAN WITH URINARY EXCRETION

Heesun CHUNG, Wonkyung YANG, Hwakyung CHOI, Wontack JIN, Sihnyoung SIHN, Youngchan YOO

*National Institute of Scientific Investigation, Seoul, Korea*

**ABSTRACT:** Because the abuse of Dextromethorphan, a non-narcotic antitussive agent, is very common and characteristic in Korea, the metabolic phenotype of dextromethorphan is studied to understand the disposition of the drug in the Korean population. Firstly, the pharmacokinetic study with urinary excretion in man was performed to obtain the urinary excretion rate constant (K) of the unchanged drug and elimination half-life ( $t_{1/2}$ ) of the drug. Secondly, the pharmacokinetics of dextromethorphan in rat was studied. After a single 30 mg dextromethorphan oral administration to volunteers, dextromethorphan and free dextrophan concentrations in urine were measured using solid-phase extraction by GC and GC/MS. Urine was collected every 2 h for 8 h, 3–4 times in 24 h and then every 12 h for 72 h. The excretion rate constant of dextromethorphan was 0.056/h. The elimination half-life of dextromethorphan in the body was 6.58 h. Urinary recovery of dextromethorphan ranged from 0.23–0.55% in five subjects over 24 h. The metabolic ratio of free dextrophan to dextromethorphan varied between subjects. The ratio between dextrophan/dextromethorphan ranged from 1.6 to 37.3. The plasma concentration of dextromethorphan was determined in five rats after administration of 10 mg/kg of dextromethorphan intravenously. The first order elimination rate constant of dextromethorphan by two compartment model was 0.036 and the value of Vd (l/kg) was 0.66.

**KEY WORDS:** Dextromethorphan; Urinary excretion; Pharmacokinetics.

*Problems of Forensic Sciences, vol. XLIII, 2000, 57–61*

*Received 9 September 1999; accepted 16 May 2000*

### INTRODUCTION

The abuse of dextromethorphan, non-narcotic antitussive agent, is very common and characteristic in Korea. In addition to the abuse of controlled drug such as methamphetamine and cannabis, there has been a growing tendency for the abuse of common medicines among young people in Korea. Even though the portion of these non-controlled drug represented only 10% of the total abuse picture, the seriousness of this abuse is related to how easily these medicines can be obtained. Among non-controlled medicines, the abuse of dextromethorphan is most serious. In this study, the metabolic phenotype of dextromethorphan was studied to understand the disposition of drug in Korean population. Firstly, the pharmacokinetic study with urinary excretion in man was performed to obtain the urinary excretion rate constant (K) of the unchanged

drug and elimination half-life ( $t_{1/2}$ ) of the drug. Secondly, the toxicokinetics of dextromethorphan in rat was studied.

## MATERIAL AND METHODS

### Chemicals

Dextromethorphan-HBr was supplied by Sigma Company. The tablet of dextromethorphan-HBr was provided by Roche Company. Clean Screen ZSDAU columns were supplied by Worldwide Monitoring Corporation. All other chemicals and solvents were of analytical grade. The standard stock solution of dextromethorphan was 1 mg/ml in ethanol. Working standards were prepared by dilution with ethanol.

### Animal study

Male Sprague Dawley rats weighing about 200 g were administered i.p. dextromethorphan 10, 20 and 40 mg/kg. Pharmacokinetic study of dextromethorphan was performed with 1.5 and 10 mg/kg of dose in rat.

### Human volunteers

Five healthy human, male volunteers (age 28–41) were fasted overnight for 12 h before and 4 h after dosing. Each volunteer received an oral dose of 30 mg dextromethorphan-HBr in an aqueous solution.

### Sample collection

Man: Urine samples were collected every 2 h for 8 h, 3–4 times in 24 h and then every 12 h for 72 h. Samples were collected and stored at  $-20^{\circ}\text{C}$  until use.

Rat: Blood from eye vein was collected 15, 30 min, 1, 2, 4, 6 h. Rat was housed in a metabolic cage and urine was collected every 24 h until 72 h. For kinetics study, blood was collected 1, 5, 10, 15, 30, 45, 60, 90, 120, 180, 240 and 360 min after drug administration from femoral vein.

### Sample preparation

Sample was extracted with Clean Screen ZSDAU column. Columns were preconditioned with 3 ml methanol, followed by 3 ml of water and 1 ml of phosphate buffer (pH 6.0). Then the 1 ml urine and 3 ml of phosphate buffer (pH 6.0) were applied onto column. The columns were washed with 3 ml deionized water, and acidified by passing through 1 ml of 1.0 M acetic acid. Then the columns were dried with 3 ml of methanol. To each column, 3 ml of dichloromethane: isopropanol: ammonia water (78 : 20 : 2) was added and eluted completely. The eluates was evaporated under a nitrogen

stream after adding 30  $\mu$ l of 0.1% HCl in methanol. The was reconstituted with ethanol and injected into GC and GC/MS.

### Equipment

A Varian model Star 3400 gas chromatograph equipped with TSD (thermionic specific detector) and Star data system was used. The GC conditions were as follows: A DB-5 capillary column (30 m x 0.53 mm, J&W) was used. The temperature was programmed from 120°C to 260°C at 20°C/min: the injection port temperature was 270°C; and the detector temperature was 280°C. The carrier gas, helium had a flow rate of 7 ml/min.

HP 5972 MSD was used to identify the drug and metabolite. The MS conditions were as follows: A HP-5 MS column (30 m x 0.32 mm, J&W) was used. The column temperature was programmed from 160°C to 190°C at 10°C/min and then to 260°C at 3°C/min; the ionization energy was 70 eV; the tranferline temperature was 270°C; and the EM voltage was 1600 V.

Calibration curve over the range of 1, 5, 10, 20  $\mu$ g/ml for rat urine and 0.1, 0.2, 0.5 and 2  $\mu$ g/ml for human urine were determined.

## RESULTS

Fig. 1. Cumulative amount of dextromethorphan in urine collected for 24 h.

The excretion rate constant of dextromerhophan was 0.056/h and the elimination half-life's of dextromethorphan in human was 6.58 h. Urinary recovery of dextromethorphan ranged from 0.23–0.55% in five subjects during 24 h (Figure 1).

The metabolic ratio of free dextrophan to dextromethorphan varied between subjects with the ratio of 0.12–37.3, indicating all volunteers are extensive metabolizer. The level of excreted dextrophan was higher in woman than man, incurring sex differences in dextromethorphan treatment (Table I).

TABLE I. CUMULATIVE AMOUNT OF DEXTROMETHORPHAN IN URINE COLLECTED FOR 24 H.

Free			Total		
Volunteers		Abusers	Volunteers		Abusers
Male	Female		Male	Female	
7.10±10.16 (0.74–34.29)	10.74±7.41 (2.6–23.0)	2.67±3.32 (0.4–11.8)	198.96±157.46 (16.44–440.02)	338.0±350.35 (62.9–955.4)	45.83±55.99* (9.8–198.4)

Values are mean ± SE.

\* Significantly different from Volunteers ( $p < 0.05$ ).

Male (n = 8); urine was collected around 8 h after drug administration.

Female (n = 5); urine was collected around 8 h after drug administration.

Abusers (n = 10); collection time for urine was unknown.

### Comparison of dextrophan/dextromethorphan from volunteers vs. drug abusers

The plasma concentration of dextromethorphan was determined in five rats after administration of 10 mg/kg of dextromethorphan intravenously. The first order elimination rate constant of dextromethorphan by two compartment model was 0.036 and the value of Vd (l/kg) was 0.66, AUC was 435.7 ng/min/μl, C<sub>max</sub> was 15.3 ng/μl and mean retention time was about 2.6 h (Table II).

TABLE II. PHARMACOKINETIC PARAMETERS OF DEXTROMETHORPHAN IN RAT PLASMA CALCULATED BY WINNONLIN PROGRAM

Parameters	C <sub>max</sub>	AUC	t <sub>1/2</sub>	Cl <sub>tot</sub>	MRT
Mean	15.29	435.7	19.75	4.59	155.42
Std	0.69	118.06	5.51	1.25	75.07

### References:

1. Bochner F., Somogyi A. A., Chen Z. R., Dextromethorphan metabolism in rat interstrain differences and the fate of individually administered oxidative metabolites, *Xenobiotica* 1994, vol. 24, pp. 543–552.
2. Brands B., Sproule B., Marshman J. [eds.], Drug and drug abuse: A reference text, Addiction Research Foundation, Ontario 1998, pp. 571–572.

3. Mortimer O., Lindstrom B., Laurell H., Bergman U., Rane A., Dextromethorphan: polymorphic serum pattern of the O demethylated and didemethylated metabolites in man, *British Journal of Clinical Pharmacology* 1989, vol. 27, 223–227.
4. Nagai N., Takashi K., Fumiyo K., Mika I., Raito S., Yukihiisa S., Hideo S., Akihiro O., Hiroyasu O., Pharmacokinetics and polymorphic oxidation of dextromethorphan in a Japanese population, *Biopharmaceutics & Drug Disposition* 1996, vol. 17, pp. 421–433.
5. Vetticaden S. J., Cabana B. E., Prasad V. K., Purich E. D., Jonkman J. H. J., de Zeeuw R., Ball L. A., Leeson L. J., Braun R. L., Phenotypic differences in dextromethorphan metabolism, *Pharmaceutical Research* 1989, vol. 6.
6. Silvasti M., Karttunen P., Tukiainen H., Kokkonen P., Hanninen U., Nykanen S., Pharmacokinetics of dextromethorphan and dextrophan: a single dose comparison of three preparations in human volunteers, *International Journal of Clinical Pharmacology: Therapy and Toxicology* 1987, vol. 25, pp. 493–497.