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Pharmacokinetics of Dextromethorphan and Metabolites in Humans: Influence of the CYP2D6 Phenotype and Quinidine Inhibition

MORDECAI SCHADEL, MD,[1] DAFANG WU, PHD,[1,2] S. VICTORIA OTTON, PHD,[1,2] WERNER KALOW, MD,[2] AND EDWARD M. SELLERS, MD, PHD[1,2]

[1] *Clinical Research and Treatment Institute of the Addiction Research Foundation, and*
[2] *Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada*

Dextromethorphan is primarily metabolized to dextrorphan by cytochrome P450 2D6 (CYP2D6), a genetically polymorphic enzyme in humans. Dextrorphan is an active metabolite that produces phencyclidine-like behavioral effects in animals and exhibits anticonvulsant and neuroprotective properties in a variety of experimental models. In these studies, we examined the effects of CYP2D6 phenotype and quinidine inhibition on the pharmacokinetics of dextromethorphan and its metabolites in humans. After a single oral dose of dextromethorphan HBr (30 mg), the major metabolites in the plasma of extensive metabolizers (N = 5) were conjugated dextrorphan and conjugated 3-hydroxymorphinan. Free dextrorphan concentrations were about 100-fold less than the conjugated dextrorphan, and dextromethorphan was not detectable. Pretreatment of these subjects with 100 mg of quinidine, a selective inhibitor of CYP2D6, significantly suppressed the formation of dextrorphan and elevated the concentrations of dextromethorphan ($t_{1/2}$, 16.4 hours). In poor metabolizers (N = 4) given the same dose, dextromethorphan was the major component in the plasma with a $t_{1/2}$ of 29.5 hours. Present at concentrations 5- to 10-fold less were conjugated dextrorphan and the other two metabolites. Urinary recovery studies indicated that the inhibition by quinidine was reversible and that the elimination of dextromethorphan primarily depends on CYP2D6 activity rather than renal elimination. These data demonstrated that the CYP2D6 phenotype and the concurrent administration of quinidine significantly affect the disposition of dextromethorphan and the formation of the active metabolite dextrorphan and are important factors to be considered in studies of the pharmacologic and behavioral effects of dextromethorphan. (J Clin Psychopharmacol 1995;15:263–269)

DEXTROMETHORPHAN is a drug that has been widely used for its antitussive properties for more than 30 years. Earlier studies[1,2] indicated that dextromethorphan doses as high as 240 mg do not produce classic opiate effects associated with levorotatory morphinans, e.g., analgesia, euphoria, respiratory depression, and morphine-like abuse liability. However, sporadic abuse of dextromethorphan has been reported over the last decades.[3–9] The mechanism of dextromethorphan abuse is unknown, but abusers experience drug effects similar to those of phencyclidine (PCP): dissociative symptoms such as hallucinations and perceptual alterations, along with physiologic manifestations such as dilated pupils, tachycardia, and hypertension. As shown in Figure 1, dextromethorphan is primarily metabolized either by O-demethylation to dextrorphan or to a lesser extent by N-demethylation to 3-methoxymorphinan. Both of the metabolites are further demethylated to 3-hydroxymorphinan. Although the pharmacology of 3-methoxymorphinan and 3-hydroxymorphinan is largely unknown, dextrorphan is an active metabolite that produces PCP-like behavioral effects in a variety of animal models, whereas dextromethorphan itself does not exhibit the same actions.[10–13] Consistent with these observations, it has been reported that dextrorphan but not dextromethorphan binds with high affinity to PCP receptor-binding sites in rat brain preparations.[14,15] Thus, the metabolic conversion of dextromethorphan to dextrorphan may be an important determinant in its abuse liability in humans.

Despite the side effects. clinical interest in dextromethorphan continues because dextromethorphan has

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Address requests for reprints to: Edward M. Sellers, MD, PhD, Addiction Research Foundation, 33 Russell Street. Toronto, Ontario, Canada M5S 2S1.

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been recently found to produce neuroprotective and anticonvulsant activities in a variety of experimental models.[16] These new findings have prompted a number of clinical trials in which dextromethorphan was tested for the treatment of chronic neurologic disorders such as Huntington's disease[17] and Parkinson's disease.[18, 19] However, many studies indicate that the major metabolite dextrorphan also has anticonvulsant and neuroprotective properties of high potence[15, 20, 21]; whether the metabolic formation of dextrorphan contributes to the actions of dextromethorphan remains to be determined. Because the metabolism of dextromethorphan into dextrorphan is catalyzed by cytochrome P450 2D6 (abbreviated as CYP2D6[22]), a genetically polymorphic drug-metabolizing enzyme in humans,[23] this may cause significant interindividual variations in the pharmacologic actions of dextromethorphan. In addition, the activity of CYP2D6 can be potently inhibited by many clinically used drugs,[24] and drug interactions may further complicate the clinical use of dextromethorphan as a novel therapeutic agent. Therefore, these studies were designed to examine the influence of CYP2D6 phenotype and quinidine inhibition on the pharmacokinetics of dextromethorphan and metabolites in human subjects.

Subjects and Methods

Subjects

Five extensive metabolizers (EMs) and four poor metabolizers (PMs) were recruited from a population of over 200 phenotyped healthy volunteers living in the Toronto area by the use of dextromethorphan as the probe drug and the subsequent analysis of urinary concentrations of dextromethorphan and its metabolite dextrorphan.[25] All subjects reported predominantly white ancestry. The phenotypes were confirmed by genotype analysis by the method of allele-specific polymerase chain reaction (PCR) described by Heim and Meyer.[26] Briefly, a venous blood sample (10 ml) was obtained from each subject, and total genomic DNA was prepared from peripheral leukocytes. PCR amplification was conducted by the use of primers designed to detect the presence of either D6-A and D6-B mutations or the normal wild-type sequence (D6-wt) at these sites. The clinical characteristics of these subjects are given in Table 1.

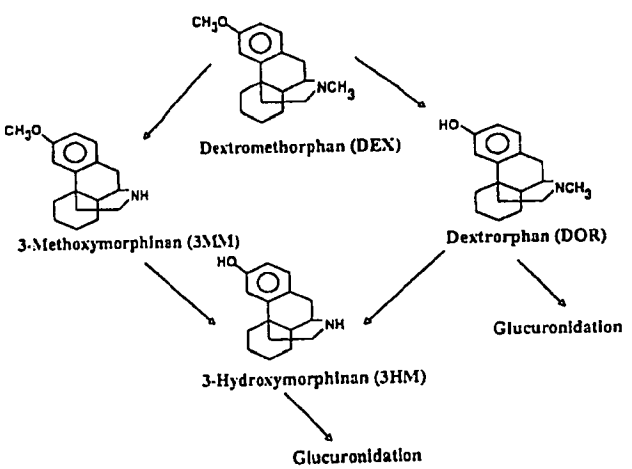

FIG. 1. The metabolic pathways of dextromethorphan in humans.

Study design

The research protocol was approved by the Human Subjects Review Committee of the Addiction Research Foundation, and informed written consent was obtained from the participants. The subjects had taken no drugs for 1 week before testing (as confirmed by urine drug screening on the study day). They arrived at the study unit after an overnight fast. Juice was available all morning, and a light lunch was provided at 12:00 p.m. There were two sessions for the EMs. During the first session, they ingested a single dose (30 mg) of dextromethorphan HBr with 100 ml of water at 8:00 a.m. and blood samples (7 ml) were taken into glass tubes containing EDTA as the anticoagulant at 0, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours postdose. Plasma was separated by centrifugation within 2 hours after collection and stored at −20°. Subjects emptied their bladder before dosing and made total urine collections every 4 hours for the first 12 hours and then every 12 hours for 3 days. Urine volume was measured, and an aliquot (10 ml) was stored at −20°. For the second session, the EM subjects received a single oral dose (100 mg) of quinidine sulfate at bedtime and 30 mg of dextromethorphan HBr the next morning (about 12 hours later). Blood and urine samples were collected in the same time schedule as the first session except that one more blood sample was taken, at 48 hours postdose. There was at least 1 week between sessions. PM subjects were tested in one session only with the ingestion of a single dose of 30 mg of dextromethorphan HBr. Blood and urine samples were collected in the same schedule as for the EMs, including a 48-hour postdose blood sample.

Drugs and chemicals

Dextromethorphan HBr (30 mg) Cough-Caps were supplied by SmithKline-Beecham Pharma, (Oakville, Ontario, Canada). Quinidine sulfate tablets (200 mg) were obtained from the Drug Trading Co. Ltd. (Ontario, Canada). The tablets were halved to 100 mg and prepared in gelatin capsules by the pharmacy of the Addiction Research Foundation of Ontario. The chemicals

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TABLE 1. Clinical characteristics of human subjects[a]

Subject	Age (yr)/Sex	Phenotype	ODMR	PCR Genotype
201	28/F	EM	0.00331	D6-wt/D6-B
202	26/M	EM	0.00129	D6-wt/D6-wt
203	31/F	EM	0.00096	D6-wt/D6-wt
305	25/F	EM	0.00085	D6-wt/D6-wt
303	22/F	EM	0.00025	not available
102	35/M	PM	2.344	D6-B/D6-B
103	46/M	PM	2.239	D6-A/D6-B
302	22/F	PM	4.786	D6-A/D6-A
304	27/F	PM	2.754	D6-B/D6-B

[a] EM, extensive metabolizer; PM, poor metabolizer; ODMR, O-demethylation metabolic ratio; PCR, polymerase chain reaction.

used as reference compounds for the high-performance liquid chromatography (HPLC) assay were dextromethorphan HBr (Sigma, St. Louis, MO), levallorphan tartrate as internal standard, dextrorphan tartrate, 3-methoxymorphinan, and 3-hydroxymorphinan (Hoffmann-La Roche, Nutley, NJ). β-Glucuronidase (type H-1, containing sulfatase) was purchased from Sigma. All other chemicals were of analytical reagent grade.

HPLC assay

Dextromethorphan, dextrorphan, 3-methoxymorphinan, and 3-hydroxymorphinan in plasma and urine were measured by a modification of the method of Chen and coworkers.[27] Briefly, an aliquot of alkalinized plasma or urine was extracted with a mixture of ether, chloroform, and 2-propanol (20:9:1, v/v/v) and back-extracted into 200 µl of 0.01 N HCl for the assay of free dextrorphan and free 3-hydroxymorphinan. Aliquots of the same samples were adjusted to pH 5.0, incubated with β-glucuronidase for deconjugation, and subsequently taken through the same extraction procedure in order to measure the total concentrations of the metabolites and unchanged dextromethorphan. The conjugated dextrorphan and 3-hydroxymorphinan were calculated by the subtraction of free metabolite from the total concentrations. The extracted samples were separated on a 150 × 4.6 mm, 5-µm phenyl column (Chromatography Sciences Co., Montreal, Canada) by the use of a Hewlett-Packard 1050 HPLC (Hewlett-Packard Co, Palo Alto, California). The mobile phase was 10 mM monobasic potassium phosphate buffer containing 1 mM heptanesulfonic acid (adjusted to pH 3.8): acetonitrile: methanol (70:25:5, v/v/v). The eluate was monitored by a fluorescence detector (Spectroflow 980; Applied Biosystems, Ramsey, NJ) with the excitation and emission wavelengths set at 195 and 280 nm, respectively. The recoveries of dextromethorphan, dextrorphan, 3-methoxymorphinan, 3-hydroxymorphinan, and the internal standard (levallorphan) were 87, 95, 81, 70, and 92.3%, respectively). The sensitivity of the assay was 2.5 pmol/ml for all compounds in both plasma and urine. The coefficients of variation within-days (N = 8) were 5.1, 12, 10.9, and 4.6%, and between-days (N = 6) were 11.7, 7.8, 15.9, and 13.4% for dextromethorphan, dextrorphan, 3-methoxymorphinan, and 3-hydroxymorphinan, respectively. Quinidine did not give any interfering peaks under the assay conditions.

Data analysis

The pharmacokinetic parameters for dextromethorphan and its metabolites in humans were calculated from plasma concentration-time data by the use of conventional model independent methods. Maximal concentration (C_{max}) and time to reach maximal concentration (T_{max}) were taken from the observed data. The total area under the curve (AUC) was measured from the observed data by the use of linear trapezoidal approximation and extrapolated to infinity (PHARM/PCS, R.J. Tallarida and R.B. Murray, 1984). The elimination half-life ($t_{½}$) was calculated from the equation $t_{½} = (\ln 2)/k_e$, where the apparent elimination rate constant (k_e) value was obtained from the regression of postpeak drug concentrations in plasma versus time. The apparent total clearance of dextromethorphan was calculated as dose/AUC, where dose was the administered dose of 22 mg of dextromethorphan free base. The renal clearance of dextromethorphan was calculated as the amount of dextromethorphan excreted unchanged in the collection interval divided by the AUC of dextromethorphan over the same period. The urinary recoveries of dextromethorphan and its metabolites were calculated as the molar amount excreted and were expressed as a percentage of the dextromethorphan dose. The means of every measurement for the three groups, e.g., EMs, PMs, and EMs+QD (EMs treated with quinidine), were calculated, and comparisons for each parameter between groups were computed by the use of the Mann-Whitney tests (PHARM/PCS). Values of $p < 0.05$ were considered statistically significant.

Results

The plasma profiles of dextromethorphan and its me-

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tabolites in the three groups of subjects are shown in Figure 2. The pharmacokinetic parameters for dextromethorphan are summarized in Table 2. Dextromethorphan was detectable in plasma samples from three of the five EM subjects, but the levels were so close to the limits of detection that pharmacokinetic parameters could not be estimated reliably. The major compounds in the plasma of EM subjects (Figure 2, top panel) were conjugated dextrorphan and conjugated 3-hydroxymorphinan. Free dextrorphan was detectable during the first 10 hours, whereas the N-demethylated metabolite 3-methoxymorphinan was undetectable at all times. The ingestion of quinidine sulfate (100 mg) 12 hours before the same dose of dextromethorphan (Figure 2, middle panel) delayed the occurrence and

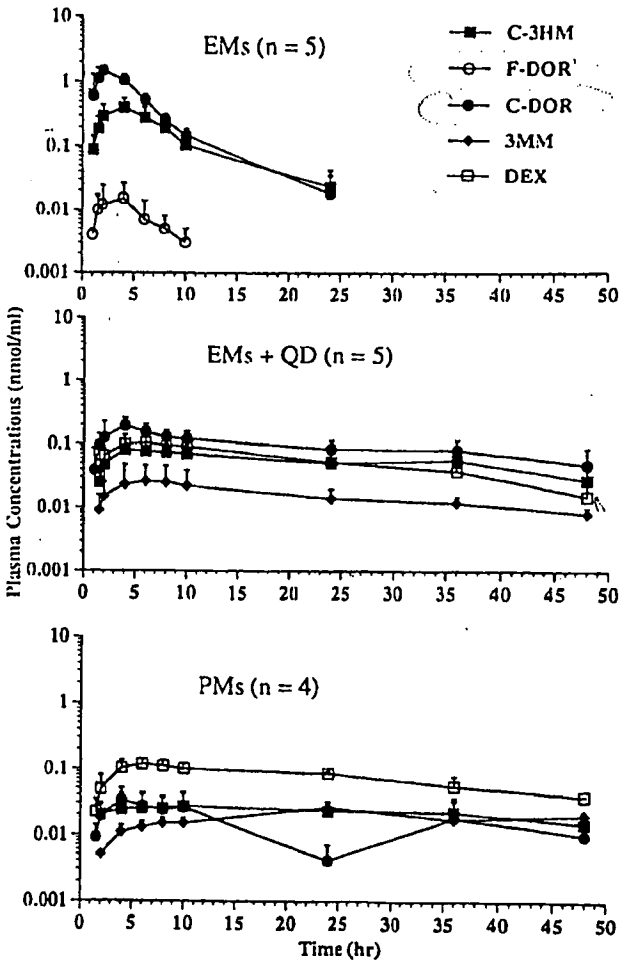

FIG. 2. Plasma profiles of dextromethorphan and its metabolites in five EMs with and without pretreatment with quinidine sulfate (100 mg) and four PMs after an oral dose of dextromethorphan HBr (30 mg). Data are expressed as mean ± SD. C-3HM, conjugated 3-hydroxymorphinan; F-DOR, free dextrorphan; C-DOR, conjugated dextrorphan; 3MM, 3-methoxymorphinan; DEX, dextromethorphan.

decreased the value of the C_{max} of conjugated dextrorphan (from 1.5 nmol/ml at 2 hours to 0.2 nmol/ml at 4 hours) and conjugated 3-hydroxymorphinan (from 0.54 nmol/ml at 2.5 hours to 0.08 nmol/ml at 4 hours). The $t_{1/2}$ of dextrorphan was increased from 2.25 to 12.11 hours. Dextromethorphan was present at levels similar to those of conjugated dextrorphan and 3-hydroxymorphinan. 3-Methoxymorphinan levels were approximately 10-fold less. The levels of all compounds decreased in parallel. By contrast, dextromethorphan was the major compound in the plasma of PM subjects (Figure 2, bottom panel) and its $t_{1/2}$ was almost two times longer than in EMs pretreated with quinidine (29.5 ± 8.4 vs. 16.4 ± 3.7 hours; $p < 0.05$). Conjugated dextrorphan and conjugated 3-hydroxymorphinan declined roughly in parallel with dextromethorphan. Their C_{max} and T_{max} values were: 0.03 nmol/ml at 4 hours and 0.03 nmol/ml over 6 to 10 hours, respectively. 3-Methoxymorphinan levels peaked at 0.03 nmol/ml 24 hours postdosing.

Figure 3 compares the AUC values for dextromethorphan metabolites in the three groups of subjects. The AUC values for conjugated dextrorphan and conjugated 3-hydroxymorphinan were significantly lower in PMs than in EMs, whereas the AUC values of 3-methoxymorphinan were higher. The AUC of conjugated dextrorphan was decreased significantly by the pretreatment of EMs with quinidine.

The urinary recoveries of dextromethorphan and its metabolites are presented in Table 3, and the cumulative recoveries from two representative subjects are plotted in Figure 4. In the urine of the EM subject, 55% of the dextromethorphan dose was recovered in the 12 hours after dosing, with conjugated dextrorphan being the major metabolite. In the PM subject, however, the total recovery was only 26% after 72 hours and unchanged dextromethorphan was the major excretion product. Pretreatment of the EM subject with 100 mg of quinidine sulfate slowed the recovery rate of all compounds, but the total recovery was unchanged. Unchanged dextromethorphan was excreted in amounts similar to those in PMs.

Discussion

Although dextromethorphan is one of the most widely used probe drugs for CYP2D6 phenotyping, a procedure in which urinary concentrations of dextromethorphan and dextrorphan are analyzed after the administration of dextromethorphan for the calculation of metabolic ratios, there are only a few studies of the effect of CYP2D6 phenotype on the time course of this drug and its metabolites in the plasma. Vetticaden and associates[28] reported phenotypic differences in the con-

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TABLE 2. Pharmacokinetic parameters of dextromethorphan in humans[a]

Subject No.	AUC (nmol/h per ml)	C_{max} (nmol/ml)	T_{max} (hour)	$t_{1/2}$ (hour)	CL_T (ml/min)	CL_R (ml/min)
EMs pretreated with QD (N = 5)						
201	3.87	0.15	6.25	14.9	349	68
202	1.42	0.05	4.25	17.0	951	165
203	2.15	0.07	8	11.1	628	46
303	3.23	0.13	2	18.3	418	51
305	5.77	0.16	8	20.8	234	25
Mean ± SD	3.29 ± 1.68	0.11 ± 0.05	5.7 ± 2.6	16.4 ± 3.7	516 ± 282	71.0 ± 54.7
PMs (N = 4)						
102	4.64	0.11	6	25.0	291	34
103	3.52	0.09	6	27.9	384	75
302	4.98	0.15	4	23.3	271	26
304	8.78	0.15	6	41.7	154	28
Mean ± SD	5.48 ± 2.29	0.12 ± 0.03	5.5 ± 1.0	29.5 ± 8.4	275 ± 95	40.8 ± 23.1
Mann-Whitney test	NS	NS	NS	$p < 0.05$	NS	NS

[a] A single dose of dextromethorphan HBr (30 mg) was given orally to five EMs and four PMs. The parameters in EMs without pretreatment with quinidine were not available because dextromethorphan was undetectable in most of the plasma samples. AUC, area under the curve; C_{max}, maximal concentration; T_{max}, time to reach maximal concentration; $t_{1/2}$, half-life; CL_T, total clearance; CL_R, renal clearance; EM, extensive metabolizer; QD, quinidine; PM, poor metabolizer; SD, standard deviation; NS, not significant.

centrations of dextromethorphan, total dextrorphan, and total 3-hydroxymorphinan in plasma after a single dose or multiple doses of dextromethorphan in a controlled-release formulation to 11 EMs and 1 PM. Recently, Chen and coworkers[27] presented the plasma profiles of dextromethorphan and its three metabolites in one EM and one PM subject, but no pharmacokinetic analysis was conducted. The results of analyses of a single blood sample collected after the administration of dextromethorphan to EMs and PMs have also been reported by other groups.[29,30] Consistent with these previous observations, we found that conjugated dextrorphan was the major metabolite in the plasma of EMs after a single dextromethorphan dose. The concentrations of total dextrorphan in plasma peaked earlier and were 50-fold higher in EMs compared with PMs and EMs pretreated with quinidine. Unconjugated dextrorphan was detected only in the plasma of EMs. By contrast, unchanged dextromethorphan was undetectable in the plasma of EMs but was the major compound in the plasma of PMs and was present at similar levels in plasma in the EMs after pretreatment with quinidine.

The T_{max} and C_{max} are major determinants of a drug's behavioral pharmacology.[31] Therefore, the first-pass metabolism of dextromethorphan to dextrorphan may be important in the abuse liability of this drug, although the rapid and extensive conjugation of dextrorphan may modulate its effect. There are no reports of central nervous system activity of the glucuronidated forms of dextrorphan or 3-hydroxymorphinan, probably because of their limited access to the brain. Similarly, we are aware of no literature describing the pharmacology of 3-methoxymorphinan, a metabolite that occurs in the plasma of PMs but not EMs.

The plasma half-life of dextromethorphan was longer in PMs (29.5 hours) than in EMs pretreated with quinidine (16.4 hours). Furthermore, dextromethorphan was not detectable in EMs without pretreatment with quini-

TABLE 3. Comparison of urinary output (72 hours) of dextromethorphan and its metabolites in human subjects receiving 30 mg of dextromethorphan HBr orally[a]

Subjects	Urinary Recovery (% of the dose) ± SD						
	F-3HM	C-3HM	F-DOR	C-DOR	3MM	DEX	Total Recovery
EMs (N = 5)	0.67 ± 0.25	15.7 ± 6.1	1.34 ± 1.13	37.6 ± 11.7	0.01 ± 0.21	0.19 ± 0.21	55.5 ± 17.6
EMs + QD (N = 5)	2.09 ± 0.44	14.0 ± 2.7	1.37 ± 0.43	24.9 ± 3.9	1.61 ± 0.87	10.4 ± 5.1	54.4 ± 5.7
PMs (N = 4)	0.70 ± 0.63	4.1 ± 2.3	0.47 ± 0.38	5.1 ± 2.6	4.72 ± 2.57	11.1 ± 3.0	26.2 ± 7.7
EMs vs. EMs+QD	$p < 0.05$	NS	NS	NS	NS	$p < 0.05$	NS
EMs vs. PMs	NS	$p < 0.05$	NS	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$
EMs+QD vs. PMs	$p < 0.05$	$p < 0.05$	NS	$p < 0.05$	$p < 0.05$	NS	$p < 0.05$

[a] SD, standard deviation; F-3HM, free 3-hydroxymorphinan; C-3HM, conjugated 3-hydroxymorphinan; F-DOR, free dextrorphan; C-DOR, conjugated dextrorphan; 3MM, 3-methoxymorphinan; DEX, dextromethorphan; EM, extensive metabolizer; QD, quinidine; PM, poor metabolizer; NS, not significant.

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dine, and the conjugated dextrorphan and conjugated 3-hydroxymorphinan decreased rapidly in the plasma and were eliminated in 24 hours after the administration of dextromethorphan to EMs. These results suggest that dextromethorphan and its metabolites will accumulate in PMs after multiple doses, whereas the accumulation will be less in EMs. Similarly, the concurrent administration of potent inhibitors of CYP2D6 such as quinidine and fluoxetine,[32] both of which are widely used medications, would significantly slow down the elimination of dextromethorphan and its metabolites in EM patients. This factor should be taken into consideration when dextromethorphan is applied as a therapeutic agent for the treatment of chronic neurologic disorders, such as Huntington's disease[17] and Parkinson's disease.[18, 19]

In these studies, 55% of the dose of dextromethorphan was recovered (primarily as dextrorphan and 3-hydroxymorphinan conjugates(within the first 12 hours after the administration to EMs, but after quinidine pretreatment, the same cumulative recovery was attained only after 72 hours. The likely explanation is the gradual return of CYP2D6 activity over the 3 days after the administration of quinidine.[33] In PM subjects, the total recovery was only 26% of the dose, primarily as unchanged dextromethorphan, after 72 hours of collection. These data clearly indicate that (1) the elimination of dextromethorphan primarily depends on the CYP2D6 activity rather than on renal excretion; (2) the metabolites of dextromethorphan are eliminated mainly through urinary excretion; and (3) in addition to the urinary excretion, a considerable proportion of dextromethorphan and its metabolites may be eliminated through bile excretion. The enterohepatic cycle may contribute to the long half-lives of dextromethorphan and its metabolites in PMs and EMs pretreated with quinidine.

Although the total recoveries of conjugated dextrorphan and 3-hydroxymorphinan were four- to seven-fold higher in EMs than in PMs, the output of free dextrorphan and 3-hydroxymorphinan was not significantly different between the two groups (Table 3). This finding is consistent with the observations of Vetticaden and associates,[23] who speculated that PMs may also exhibit impaired glucuronidation capacity. However, this notion is not supported by a recent study[34] in which there is no CYP2D6 phenotypic difference between healthy volunteers and patients with Gilbert's syndrome, a common hereditary disorder associated with decreased hepatic UDP-glucuronyltransferase activity. Similarly, Duche and coworkers[35] reported that they found no phenotypic difference in the capacity of dextrorphan glucuronidation in a French population. Therefore, the urinary recoveries of the free metabolites may reflect the capacity to excrete these compounds, which is independent from CYP2D6 phenotypes.

In conclusion, the data presented here demonstrate that the polymorphic CYP2D6 activity significantly af-

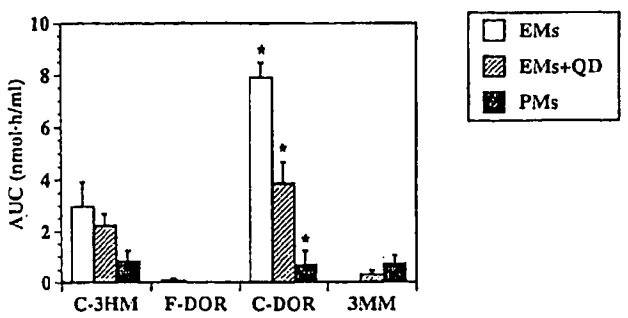

FIG. 3. Comparison of AUC values for dextromethorphan metabolites in EMs, EMs pretreated with quinidine (QD), and PMs. * $p < 0.05$. C-3HM, conjugated 3-hydroxymorphinan; F-DOR, free dextrorphan; C-DOR, conjugated dextrorphan; 3MM, 3-methoxymorphinan.

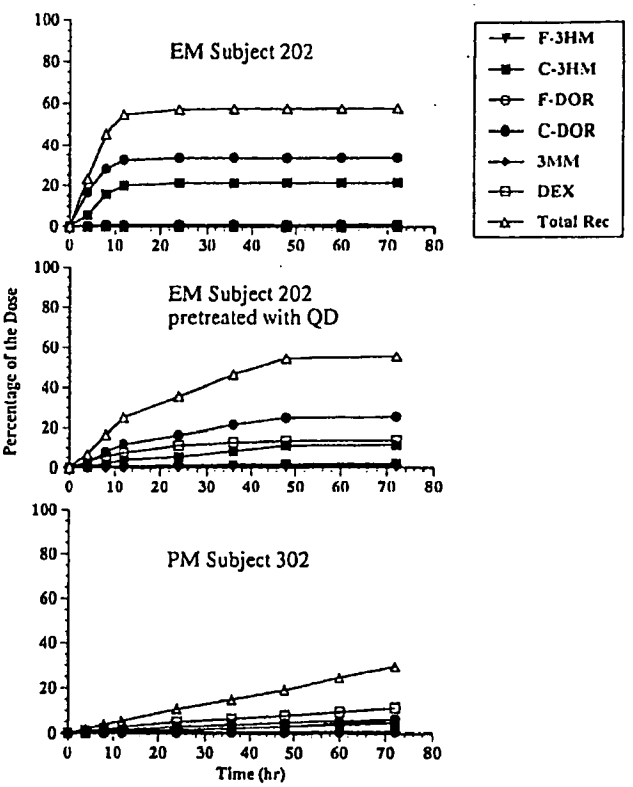

FIG. 4. Cumulative urinary recoveries of dextromethorphan and its metabolites in a representative EM subject (top panel), the EM subject pretreated with quinidine (QD) (middle panel), and a PM subject (bottom panel). F-3HM, free 3-hydroxymorphinan; C-3HM, conjugated 3-hydroxymorphinan; F-DOR, free dextrorphan; C-DOR, conjugated dextrorphan; 3MM, 3-methoxymorphinan; DEX, dextromethorphan; Rec, recovery.

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fects not only the peak levels of dextromethorphan and its metabolites in plasma, but also the duration of these compounds in human subjects. Whether the genetic polymorphism of CYP2D6 affects the pharmacologic and behavioral responses of dextromethorphan remains to be determined. A double-blind, placebo-controlled study of dextromethorphan's abuse liability in EMs and PMs is in progress in our laboratory.

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