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Research Article

Phenotypic Differences in Dextromethorphan Metabolism

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Polymorphic differences in dextromethorphan metabolism were observed in three studies conducted in a total of 44 subjects (of Dutch origin) administered 60 mg dextromethorphan hydrobromide as an OROS tablet. Mean plasma dextromethorphan (DM) concentrations after a single dose and at steady state were 4–75 times higher in the poor metabolizers (PM) relative to the extensive metabolizers (EM). Following a single dose, the mean areas under the plasma concentration–time curve (AUC, 0–24 hr) of DM, total dextrorphan (DR), and total 3-hydroxymorphinan (HM) were 6.9-fold higher, 17.4-fold lower, and 11-fold lower, respectively, for the PM than for the EM. Correspondingly, steady-state AUC values were 52.8 times higher, 6.7 times lower, and 3.3 times lower for DM, total DR, and total HM, respectively, for the PM relative to the EM. Drug/metabolite ratios (DMR) for amounts excreted in the urine of DR and HM indicated polymorphism in *O*-demethylation of DM since DMR for PM was 352 and 338 times higher than that for EM for DR and HM, respectively. However, polymorphism in *N*-demethylation was not observed. Ratios of conjugated/free dextrorphan and 3-hydroxymorphinan excreted in the urine suggest also a lack of conjugative capacity in the PM, relative to the EM. The overall incidence of PM was 9.1% in this population.

KEY WORDS: phenotype; dextromethorphan; polymorphism; *N*-demethylation; *O*-demethylation; conjugation.

INTRODUCTION

Genetic polymorphism associated with the metabolism of drugs has previously been reported for a number of compounds. These drugs include debrisoquin (1–5), sparteine (2,3), isoniazid (6), procainamide (6), hydralazine (6), mephenytoin (7,8), methoxyphenamine (4), and encainide (5). Reported polymorphism in the metabolism of drugs has dealt largely with pharmacogenetics of oxidative drug metabolism, of which debrisoquin and sparteine were the initial probes. However, recent reports have suggested dextromethorphan as a safe probe to investigate the pharmacogenetics of polymorphic drug metabolism (4,9).

Recent studies by Schmid *et al.* (10) demonstrated a significant relationship between dextromethorphan *O*-demethylation and debrisoquin 4-hydroxylation. Their studies also suggested dextromethorphan as a possible safe probe for the investigation of pharmacogenetic differences in debrisoquin metabolism and the classification of subjects into extensive metabolizers (EM) and poor metabolizers (PM).

Recent studies in 268 unrelated Swiss subjects by the same authors (10) confirmed phenotypic differences in dextromethorphan *O*-demethylation. Based on the urinary dextromethorphan/dextrorphan metabolic ratio, a bimodal distribution was reported with the antimode at a metabolic ratio of 0.3 separating the PM (prevalence of 9%) from those of the EM. Further, a strong relationship was demonstrated between the metabolic ratio for dextromethorphan *O*-demethylation and debrisoquin 4-hydroxylation, indicating that the two drug oxidations are possibly under the same genetic control.

The studies reported here further investigate the polymorphism in dextromethorphan metabolism, by quantitating the other major metabolites of dextromethorphan, *viz.*, 3-methoxymorphinan (*N*-desmethyl metabolite), 3-hydroxymorphinan (*N*-*O*-bidesmethyl metabolite), conjugated dextrorphan, and conjugated 3-hydroxymorphinan. Polymorphism in the plasma concentrations of dextromethorphan, total dextrorphan, and total 3-hydroxymorphinan were also investigated. A schematic representation of the dextromethorphan metabolic pathways in humans is represented in Fig. 1.

MATERIALS AND METHODS

Study I

This preliminary study was conducted to determine the bioavailability and pharmacokinetic profile of prototype dex-

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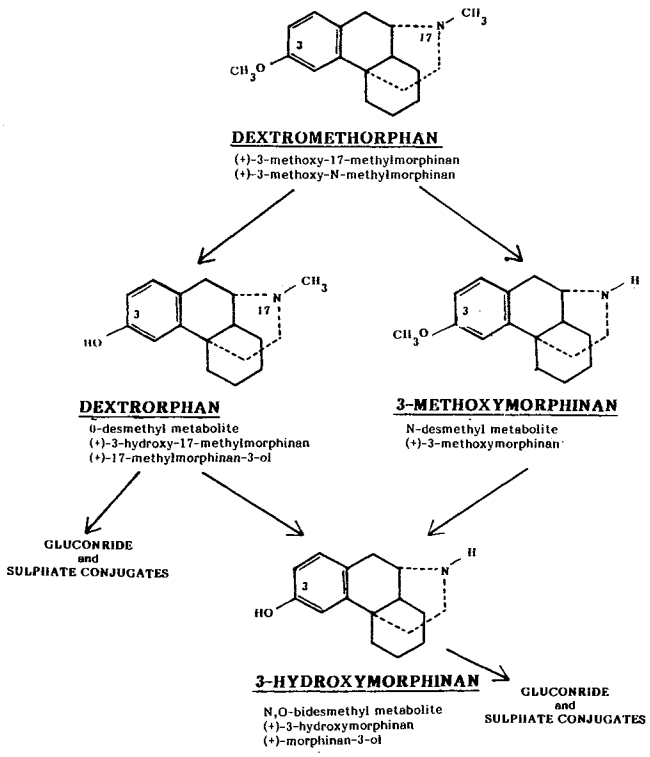

Fig. 1. Major metabolic pathways for dextromethorphan in humans.

tromethorphan OROS 60-mg tablet formulations (CIBA Consumer Pharmaceuticals, Edison, N.J.) after a single-dose administration in comparison to an oral solution of dextromethorphan hydrobromide. The study design consisted of two parallel fully randomized three-way crossover studies each in six normal, male healthy volunteers of Dutch origin, employing a total of 12 subjects. Each subject received three treatments, *viz.*, two of the prototype formulations and the oral solution, each treatment phase being separated by a washout period of 96 hr. The first block of six subjects was randomized to receive prototype formulations (B, C) and the solution (A), whereas, the second block of six subjects was randomized to receive two prototype formulations (D, E) and the solution (A). Blood samples (10 ml) were drawn at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hr postdosing into blood collection tubes (Sarstedt, Nurmbrecht, West Germany) containing Na^+-heparin as the anticoagulant. Blood samples were placed in an ice bath prior to centrifugation and plasma samples were immediately frozen at −20°C until assayed. A 24 hr urine collection was also carried out postdosing. Plasma was assayed for dextromethorphan, total dextrorphan, and total 3-hydroxymorphinan. Urine samples were assayed for dextromethorphan, 3-methoxymorphinan, free (unconjugated) and total (free + conjugated) dextrorphan, and free and total 3-hydroxymorphinan. Dextromethorphan and its metabolites were quantitated using a recently developed high-performance liquid chromatographic (HPLC) procedure (11).

Study II

The study consisted of an open-label, fully randomized two-way crossover study in 16 normal, healthy, male volunteers of Dutch origin, comparing a dextromethorphan hydrobromide OROS 60-mg tablet (CIBA Consumer Pharmaceuticals, Edison, N.J.) given twice daily at 12 hr intervals to a

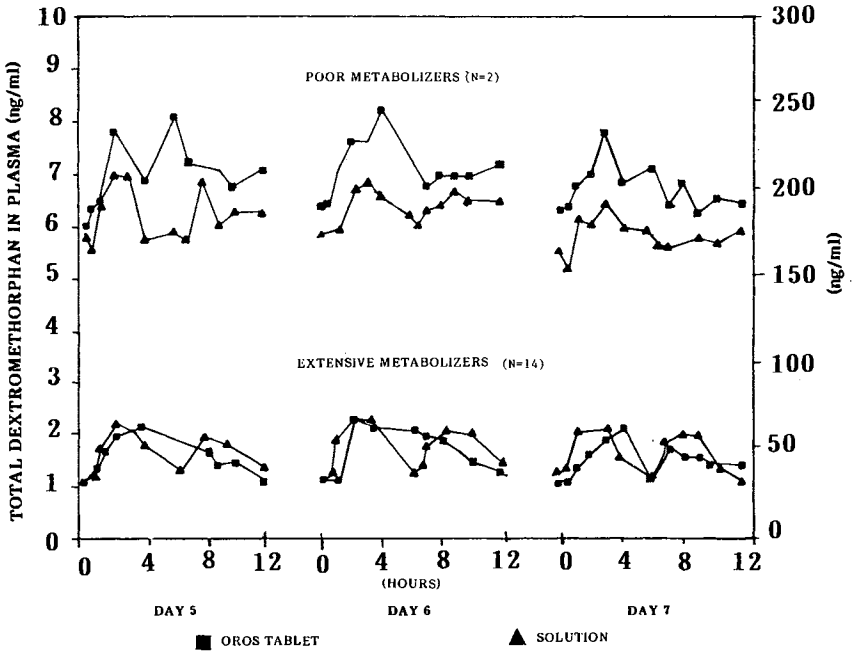

Fig. 2. Mean plasma concentrations of dextromethorphan in normal volunteers (poor metabolizers, axis on the right; extensive metabolizers, axis on the left) following administration of a 60-mg dextromethorphan hydrobromide OROS tablet every 12 hr (squares) and a 30-mg dextromethorphan hydrobromide solution every 6 hr (triangles) over a period of 7 days.

Table I. Derived Pharmacokinetic Parameters for Dextromethorphan and Metabolites Following Administration of a Single Dose of Dextromethorphan Hydrobromide (60 mg) as a Controlled-Release OROS Tablet: Study I[a]

	Extensive metabolizers (EM) (N = 11)	Poor metabolizer (PM) (N = 1)
	Dextromethorphan	
AUC (ng · hr/ml)	109.07 ± 137.10	757.47
C_{MAX} (ng/ml)	12.26 ± 12.47	43.8
T_{MAX} (hr)	2.00 ± 0.60	2.00
	Total dextrorphan	
AUC (ng · hr/ml)	3082.05 ± 911.78	177.35
C_{MAX} (ng/ml)	507.00 ± 153.38	12.00
T_{MAX} (hr)	2.5 ± 0.66	3.00
	Total 3-hydroxymorphinan	
AUC (ng · hr/ml)	1610.2 ± 449.5	146.9
C_{MAX} (ng/ml)	188.9 ± 42.4	7.5
T_{MAX} (hr)	3.6 ± 0.9	8.00

[a] AUC, area under the concentration–time curve 0–24 hr postdosing; C_{MAX}, peak plasma concentration; T_{MAX}, time to peak plasma concentration.

dextromethorphan hydrobromide 30-mg oral solution administered four times daily every 6 hr, over a duration of 7 days. Treatment phases were separated by a 1-week washout period. During the initial 6 days of each treatment, the volunteers were dosed under fed conditions using normal standardized meals throughout. The seventh day of each treatment consisted of an overnight 12 hr fast. Blood samples were withdrawn using procedures similar to those described in study I. Plasma concentrations of dextromethorphan, total dextrorphan, and total 3-hydroxymorphinan were determined. Twenty-four-hour urine recovery was carried out on days 5, 6, and 7. However, analysis of data is limited to the final steady-state recovery on day 7. Dextromethorphan, total dextrorphan, total 3-hydroxymorphinan, and 3-methoxymorphinan were quantitated in the urine. The analytical methods employed for the quantitation of dextromethorphan and its metabolites in the urine were similar to those utilized in Study I. Analysis is limited to data obtained on administration of the 60-mg OROS tablets to permit comparison across studies.

Study III

The study consisted of an open label, two way crossover design in 16 normal, healthy, male volunteers of Dutch origin, comparing the 30-mg dextromethorphan hydrobromide OROS tablet (CIBA Consumer Pharmaceuticals) given as two tablets every 12 hr to the 60-mg dextromethorphan hydrobromide OROS tablet (CIBA Consumer Pharmaceuticals) given as one tablet every 12 hr. Volunteers were dosed for 6 days under fed conditions. A 1-week washout period was employed between treatment phases. Analysis is limited

Table II. Derived Steady-State Pharmacokinetic Parameters for Dextromethorphan and Metabolites Following Multiple Dosing of Dextromethorphan Hydrobromide (60 mg) as a Controlled-Release OROS Tablet: Studies II and III[a]

	Extensive metabolizers (EM) (N = 29)	Poor metabolizers (PM) (N = 3)
	Dextromethorphan	
AUC (ng · hr/ml)	51.17 ± 76.26	2700.67 ± 189.74
C_{MAX} (ng/ml)	5.61 ± 7.87	260.33 ± 21.20
T_{MAX} (hr)	3.76 ± 2.28	8.00 ± 3.27
	Total dextrorphan	
AUC (ng · hr/ml)	2845.10 ± 541.00	427.13 ± 94.17
C_{MAX} (ng/ml)	349.28 ± 68.82	39.27 ± 6.70
T_{MAX} (hr)	3.52 ± 1.52	7.33 ± 1.89
	Total 3-hydroxymorphinan	
AUC (ng · hr/ml)	1762.35 ± 396.71	535.10 ± 106.5
C_{MAX} (ng/ml)	192.47 ± 39.82	49.7 ± 8.91
T_{MAX} (hr)	4.31 ± 1.49	7.00 ± 2.94

[a] AUC, area under concentration–time curve 0–12 hr postdosing; C_{MAX}, peak plasma concentration; T_{MAX}, time to peak plasma concentration.

Table III. Drug/Metabolite Ratios for Cumulative Amounts Excreted in the Urine Following Administration of Dextromethorphan Hydrobromide (60 mg) as a Controlled-Release OROS Tablet: Studies I, II, and III[a]

	Extensive metabolizers (EM)	Poor metabolizers (PM)
M1/M2	0.29 ± 0.40 (N = 26)	24.88 ± 6.25 (N = 2)
M1/M3	0.01 ± 0.02 (N = 40)	3.52 ± 1.70 (N = 4)
M1/M4	0.53 ± 0.85 (N = 26)	38.77 ± 19.3 (N = 2)
M1/M5	0.01 ± 0.03 (N = 40)	3.38 ± 1.57 (N = 4)
M1/M6	7.33 ± 2.74 (N = 40)	3.19 ± 0.61 (N = 4)
M1/M7	0.01 ± 0.02 (N = 26)	2.29 ± 1.12 (N = 2)
M1/M8	0.02 ± 0.04 (N = 26)	2.82 ± 1.65 (N = 2)

[a] M1, dextromethorphan; M2, free dextrorphan; M3, total dextrorphan; M4, free 3-hydroxymorphinan; M5, total 3-hydroxymorphinan; M6, 3-methoxymorphinan; M7, M3–M2—conjugated dextrorphan; M8, M5–M4—conjugated 3-hydroxymorphinan. Since only M1, M3, M5, and M6 were quantitated in study II, rows with N = 28 (EM = 26, PM = 2) represent the total number of subjects for studies I and III, whereas rows with N = 44 (EM = 40, PM = 4) represent subjects of all three studies.

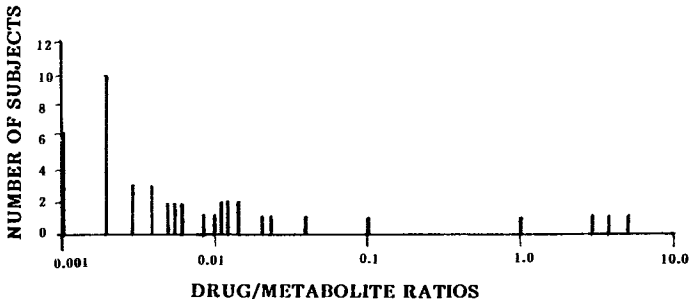

Fig. 3. Frequency distribution of log (drug/metabolite) ratio for cumulative amounts of dextromethorphan (drug) and total dextrorphan (metabolite) excreted in the urine following administration of a 60-mg dextromethorphan hydrobromide OROS tablet.

to data obtained on administration of the 60-mg OROS tablet to permit comparison across studies. Blood samples were drawn at predetermined times. Plasma was assayed for dextromethorphan, total dextrorphan, and total 3-hydroxymorphinan. A 24-hr urine collection was implemented on day 6. Urine samples were quantitated for dextromethorphan, total dextrorphan, free dextrorphan, total 3-hydroxymorphinan, free 3-hydroxymorphinan, and 3-methoxymorphinan.

Volunteers in all three studies were within the ages of 16–35 years and weighed within 10% of the weights described in the 1983 Metropolitan Life Insurance actuary tables. The volunteers were judged to be healthy based upon a complete physical exam, medical history and ECG, hematology, and clinical chemistry of blood and urine. Exclusion criteria included evidence of clinically significant hematologic, hepatic, gastrointestinal, renal, pulmonary, neurologic, or psychiatric disease; a recent (1-year) history of alcoholism or drug addiction; taking prescription or nonprescription medication within 14 days of the start of the study; smoking; and consuming alcoholic or caffeine-containing beverages within 72 hr of the start of the study.

For AUC comparisons, the AUC for a dose of 60-mg dextromethorphan hydrobromide, *viz.*, $AUC_{0-24\ hr}$ (study I) and $AUC_{0-12\ hr}$ (studies II and III), was utilized. For studies II and III $AUC_{0-12\ hr}$ was utilized, since at steady state, $AUC_{0-12\ hr}$ is equivalent to $AUC_{0-infinity}$ following a single dose.

RESULTS

Review of the plasma concentration vs time profiles for dextromethorphan, total dextrorphan, and 3-hydroxymorphinan revealed a bimodal distribution in the circulating levels of these compounds following the oral administration of 60 mg. In the case of one subject (study I), much higher concentrations of dextromethorphan and much lower concentrations of total dextrorphan and total 3-hydroxymorphinan were observed. Based on further analyses (which follow) of the urine data, agreement of the findings from the plasma and urine data of studies II and III, and agreement of the findings from the urine data with those of previous studies (9,10), this subject was labeled as a poor metabolizer (PM) relative to the other subjects, who were labled as extensive metabolizers (EM). Similar results were observed in study II (Fig. 2), where 2 of the 16 subjects were identified as PM, and in study III, where 1 of the 16 subjects was identified as a PM.

Following a single dose of dextromethorphan, 60 mg OROS (study I), peak levels (C_{max}) of dextromethorphan, total dextrorphan, and total 3-hydroxymorphinan were 3.6 times higher, 42.2 times lower, and 25.2 times lower in the case of the PM, relative to the mean for the 11 remaining subjects (Table I). Following multiple doses of dextromethorphan, 60 mg OROS (studies II and III), at steady state, C_{max} values for dextromethorphan, total dextrorphan, and total 3-hydroxymorphinan were 46.4 times higher, 8.9 times

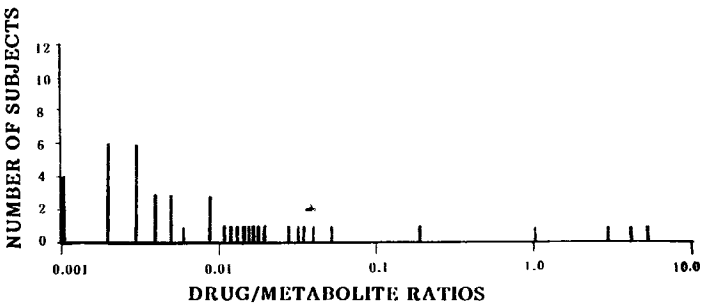

Fig. 4. Frequency distribution of log (drug/metabolite) ratio for cumulative amounts of dextromethorphan (drug) and total 3-hydroxymorphinan (metabolite) excreted in the urine following administration of a 60-mg dextromethorphan hydrobromide OROS tablet.

Table IV. Cumulative Amounts of Dextromethorphan and Metabolites Excreted in the Urine (mg) Following Administration of Dextromethorphan Hydrobromide (60 mg) as a Controlled-Release OROS Tablet[a]

	Study I (single dose)	
	Extensive metabolizers (EM) (N = 11)	Poor metabolizers (PM) (N = 1)
Dextromethorphan	0.24 ± 0.33	3.92 ± 0.0
Total dextrorphan	15.30 ± 4.26	1.27 ± 0.0
Total 3-hydroxy morphinan	8.54 ± 2.10	0.94 ± 0.0
3-Methoxy morphinan	0.03 ± 0.04	1.26 ± 0.0
	Studies II and III (multiple dose at steady state; doses administered at 12-hr intervals)	
	Extensive metabolizers (EM) (N = 29)	Poor metabolizers (PM) (N = 3)
Dextromethorphan	0.25 ± 0.41	20.30 ± 4.40
Total dextrorphan	48.48 ± 17.41	7.81 ± 4.30
Total 3-Hydroxy morphinan	33.38 ± 11.45	8.46 ± 3.80
3-Methoxy morphinan	0.04 ± 0.06	6.44 ± 1.31

[a] Urine collection intervals were 0–24 hr postdosing for study I and 0–24 hr postdosing at steady state for studies II and III.

lower, and 3.9 times lower in the case of the PM relative to the EM (Table II).

A bimodal distribution in the metabolic disposition of dextromethorphan is also suggested by the 6.9-fold higher AUC for dextromethorphan, the 17.4-fold lower AUC for total dextrorphan, and the 11-fold lower total 3-hydroxymorphinan, in the case of the PM (study I), relative to the mean for the other 11 subjects. For the PM in studies II and III, a 52.8-fold higher AUC for dextromethorphan, a 6.7-fold lower AUC for total dextrorphan, and a 3.3-fold lower AUC for total 3-hydroxymorphinan were observed.

Phenotyping of oxidative drug metabolism generally takes into consideration the metabolic ratio of unchanged drug and metabolite excreted in the urine over a fixed time period (4,10,12,14). The underlying reason for the above is that the parent drug/metabolite excretion ratio (DMR) takes into consideration possibilities of incomplete urine collection and/or impaired absorption. Further, using the DMR comparison across studies (I–III) was now possible. The DMR for the free and conjugated metabolites of dextromethorphan are given in Table III.

Table V. Parent Drug/Metabolite Excretion Ratio for Dextromethorphan/Total Dextrorphan Following Administration of Dextromethorphan Hydrobromide (60 mg) as a Controlled-Release OROS Tablet

	Poor metabolizers (PM)	Extensive metabolizers (EM)
Present study (studies I–III)	3.52 (N = 4)	0.01 (N = 40)
Schmid *et al.* (Ref. 10)	3.58 (N = 23)	0.01 (N = 245)

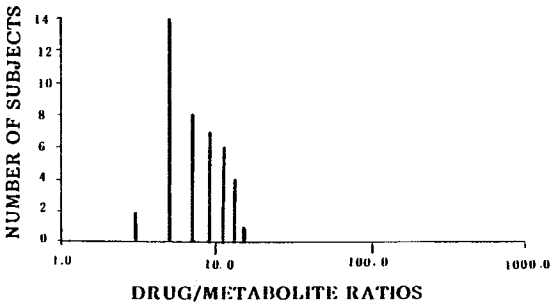

Fig. 5. Frequency distribution of log (drug/metabolite) ratio for cumulative amounts of dextromethorphan (drug) and total 3-methoxymorphinan (metabolite) excreted in the urine following administration of a 60-mg dextromethorphan hydrobromide OROS tablet.

Much higher DMR are observed for free and total dextrorphan and 3-hydroxymorphinan for PM. For PM, the DMR for total dextrorphan and total 3-hydroxymorphinan were 352 and 338 times the mean DMR for the EM. The log-normal distribution plots of DMR for total dextrorphan and total 3-hydroxymorphinan also indicate a bimodal distribution, with an antimode between 0.1 and 1.0 (Figs. 3 and 4). Although the total number of poor metabolizers studied is small (N = 4), the DMR for total dextrorphan are in excellent agreement with those reported by Schmid *et al.* (10) (Table V). Thus these results support the polymorphic *O*-demethylation of dextromethorphan reported by Schmid *et al.*

In contrast to dextrorphan and 3-hydroxymorphinan, the DMR for 3-methoxymorphinan for the PM was only 0.46 times the mean DMR for the EM. Since, dextrorphan and 3-hydroxymorphinan are the *O*-demethylated products of dextromethorphan, and 3-methoxymorphinan is the *N*-demethylated product of dextromethorphan, the results indicate that the *O*-demethylation of dextromethorphan is subject to polymorphic metabolism, while *N*-demethylation is not. The absence of polymorphism in the *N*-demethylation of dextromethorphan has not been previously reported. Analysis of the cumulative amounts excreted in the urine (Table IV) indicated that, in study I, the PM excreted 42 times and 16.3 times the mean amounts of 3-methoxymorphinan and dextromethorphan excreted by the EM, respectively. Similarly, in studies II and III, the PM excreted 161 times and 81.2 times the mean amounts of 3-methoxymorphinan and dextromethorphan excreted in the urine by the EM, respectively.

Analysis of cumulative amounts excreted in the urine (Table IV) would lead the naive reader to believe that the formation of 3-methoxymorphinan (*N*-demethylation) may also be subject to polymorphic metabolism. However, the DMR for 3-methoxymorphinan for the PM is 3.19 ± 0.61 and is similar to the corresponding DMR for the EM, *viz.*, 7.33 ± 2.74 (Table III). These results indicate that the formation of 3-methoxymorphinan is not subject to polymorphic metabolism. Further, as mentioned before, the DMR for dextrorphan and 3-hydroxymorphinan for the PM was 352 and 338

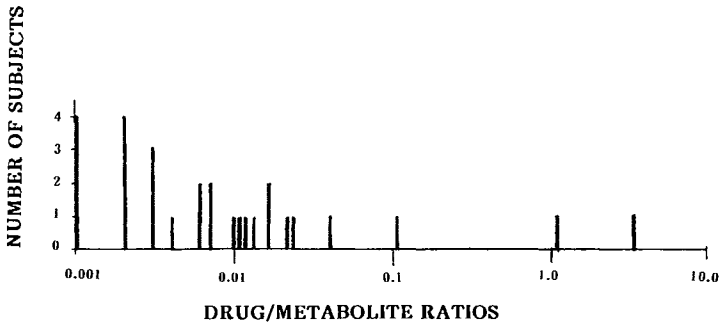

Fig. 6. Frequency distribution of log (drug/metabolite) ratio for cumulative amounts of dextromethorphan (drug) and conjugated dextrorphan (metabolite) excreted in the urine following administration of a 60-mg dextromethorphan hydrobromide OROS tablet.

times the mean DMR for the EM. These similar values lead additional support to the results that the *N*-demethylation process is not subject to polymorphism, since 3-hydroxymorphinan is produced primarily by the *N*-demethylation of dextrorphan. Further, similar ratios of total dextrorphan/total 3-hydroxymorphinan are observed for both the PM and the EM. In study I the ratio was 1.4 and 1.8 for the PM and EM, respectively. In studies II and III the corresponding ratios were 1.4 and 0.92 for the PM and EM, respectively. Since the 3-hydroxymorphinan is produced primarily by the *N*-demethylation of dextrorphan, the similar ratios obtained indicate that *O*-demethylation is the rate-limiting step in the metabolic process.

Therefore, the increased amounts of dextromethorphan and 3-methoxymorphinan excreted by the PM are only a consequence of the increased amount of parent drug being eliminated by these two pathways (since the oxidative pathway is lacking), and are not indicative of an increase in the rate or capacity of these elimination processes in the case of the PM. Lack of polymorphism in *N*-demethylation is also borne out by the unimodality of the log-normal distribution plot for DMR for 3-methoxymorphinan (Fig. 5).

The DMR in the case of the PM was much higher relative to that for the EM for conjugated dextrorphan (229 times) and conjugated 3-hydroxymorphinan (141 times). Ratios of conjugate/free drug for both dextrorphan and 3-hydroxymorphinan in the EM were similar and were 29 and 26.5, respectively. The corresponding ratios in the PM were 10.9 and 13.7, respectively. These results indicate that in the case of both the EM and the PM, dextrorphan and 3-hydroxymorphinan are excreted largely as conjugates. The similar ratios for both metabolites in the EM indicate that the conjugation step may not be a rate-limiting step in the overall formation and elimination process of these two metabolites. However, the much lower ratios for the PM relative to the EM indicate that a much larger fraction of both dextrorphan and 3-hydroxymorphinan is excreted as the free (unconjugated) drug by the PM. Further, a bimodal distribution is evident from the log-normal distribution plots of the DMR for conjugated dextrorphan and conjugated 3-hydroxymorphinan (Figs. 6 and 7).

The bimodality suggests a polymorphism in the conjugative capacity for the metabolites of dextromethorphan and that the PM may also be lacking in conjugative capacity (presumably from a lack of conjugating enzymes) relative to the EM. However, no conclusions may be drawn from these limited data and additional studies possibly involving the administration of dextrorphan and 3-hydroxymorphinan to both the PM and the EM are needed to explore this possibility.

DISCUSSION

For the first time, polymorphism in dextromethorphan metabolism has been demonstrated in a Dutch population. An incidence of 9.1% is observed and is in agreement with an incidence of 9% reported earlier in a Swiss population (10). For the first time polymorphic differences in the steady-state

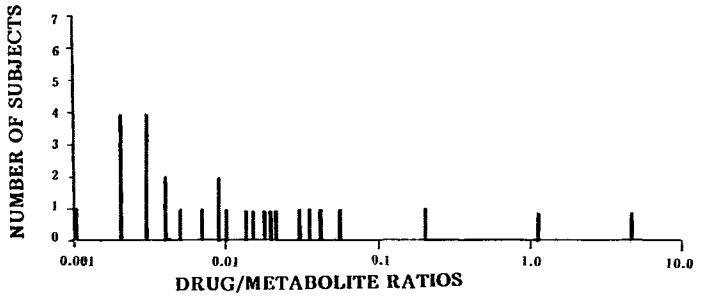

Fig. 7. Frequency distribution of log (drug/metabolite) ratio for cumulative amounts of dextromethorphan (drug) and conjugated 3- hydroxymorphinan (metabolite) excreted in the urine following administration of a 60-mg dextromethorphan hydrobromide OROS tablet.

plasma concentrations of dextromethorphan and its major metabolites dextrorphan and 3-hydroxymorphinan have been reported. Concentrations of dextromethorphan were about 4, 75, and 30 times higher in the case of the PM relative to the EM in studies I, II, and III, respectively. The consequence of these metabolic differences in the clincial effects of dextromethorphan and its metabolites needs further investigation. It has also been demonstrated that *O*-demethylation of dextromethorphan exhibits polymorphism, whereas *N*-demethylation does not. Additional studies involving administration of the metabolites also need to be conducted to elucidate completely the disposition of dextromethorphan and its metabolites. Further studies are also needed to establish the incidence of PM in other demographic populations.

REFERENCES

1. A. Mahgoub, J. R. Idle, L. G. Dring, R. Lancaster, and R. L. Smith. *Lancet* 2:584–586 (1977).
2. M. Eichelbaum, L. Bertilsson, J. Sawe, and C. Zekorn. *Clin. Pharmacol. Ther.* 31(2):184–186 (1982).
3. D. A. P. Evans, D. Harmer, D. Y. Downham, E. J. Whibley, J. R. Idle, J. Ritchie, and R. L. Smith. *J. Med. Gen.* 20:321–329 (1983).
4. S. D. Roy, E. M. Hawes, J. W. Hubbard, G. McKay, and K. K. Midha. *Lancet* 2:1393 (1984).
5. R. L. Woosley, D. M. Roden, G. Dai, T. Wang, D. Atenbern, J. Oates, and G. R. Wilkinson. *Clin. Pharmacol. Ther.* 39(3):282–287 (1986).
6. D. E. Drayer and M. M. Reidenberg. *Clin. Pharmacol. Ther.* 22(3):251–258 (1977).
7. P. J. Wedlund, W. S. Aslanian, C. B. McAllister, G. R. Wilkinson, and R. A. Branch. *Clin. Pharmacol. Ther.* 36(6):773–780 (1984).
8. A. Kupfer and R. Preisig. *Eur. J. Clin. Pharmacol.* 26:753–759 (1984).
9. A. Kupfer, B. Schmid, and G. Pfaff. *Xenobiotica* 16(5):421–433 (1986).
10. B. Schmid, J. Bircher, R. Preisig, and A. Kupfer. *Clin. Pharmacol. Ther.* 38(6):618–624 (1985).
11. J. H. G. Jonkman (in press).
12. E. Jacqz, S. D. Hall, R. A. Branch, and G. R. Wilkinson. *Clin. Pharmacol. Ther.* 39(6):646–653 (1986).
13. W. M. Benson, P. L. Stefko, and L. O. Randall. *J. Pharmacol. Ther.* 109:189–200 (1953).
14. A. Kupfer, B. Schmid, R. Preisig, and G. Pfaff. *Lancet* 2:517–518 (1984).