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Inter-individual variation in the metabolism of dextromethorphan

G. Pfaff, P. Briegel and I. Lamprecht

Abteilung für Pharmazie des Bereiches Forschung und Entwicklung, Heinrich Mack Nachf., 7918 Illertissen (F.R.G.)

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Summary

After ingestion of 25 mg of dextromethorphan-HBr in 12 healthy volunteers, the plasma concentrations of dextromethorphan and conjugated dextrorphan as well as the cumulative excretion of dextromethorphan and the conjugated metabolites dextrorphan, 3-hydroxymorphinan and 3-methoxymorphinan in the urine within 48 h were determined.

Based on the results, the volunteers were divided into 3 groups. Conjugated dextrorphan was prevailing in the plasma and urine of the 6 volunteers of Group 1, whereas no unmetabolized dextromethorphan was detectable in the plasma and only slight traces of it in the urine. The plasma elimination of dextrorphan has a half-life of 1.2–2.2 h. After 48 h an average amount of 86% of the dosage was excreted.

The second group comprised those volunteers whose plasma contained clearly determinable concentrations of unmetabolized dextromethorphan (maxima: 11.7–14.4 ng/ml) besides dextrorphan, and whose dextrorphan plasma level curves showed an additional β-phase with half-lives of about 6 h. The urine of these volunteers contained an average of 2.6% of the dosage, i.e. approximately 20 times as much dextromethorphan as the volunteers of Group 1. The cumulative excretion in the urine of 74% was lower than that of the first group. An individual case that is already reported in the literature was also classified into this second group (Barnhart, 1980).

Compared with other volunteers the remaining 3 volunteers showed the most obvious deviations: only unchanged dextromethorphan and no dextrorphan could be detected in the plasma, whereby an increased plasma elimination half-life of approximately 45 h was found. Moreover, the excretion in the urine was slower (approximately 20% of dose in 48 h) and unmetabolized dextromethorphan was, with more than 50% of the excreted amount, the main excretion product.

The 12 volunteers investigated had been selected after a preliminary trial from a population of 46 persons. Based on the results presented, the frequency of the different metabolization occurring in this population could be subsequently determined as approximately 6% and 13% for Groups 2 and 3, respectively.

Introduction

Dextromethorphan, being classified as a safe and effective antitussive (Federal Register, 1976), is used on a broad scale in pharmaceuticals for cough and cold. Due to the very quick and extensive metabolism, sensitive analytical methods like gas chromatography by means of an electron capture detector (Barnhart and Massad, 1979) or a radioimmunoassay (Dixon et al., 1978) with a detection limit of approximately 1 ng/ml of plasma, have so far proved to be insufficient in carrying out pharmacokinetic plasma level examinations with unchanged dextromethorphan in humans after oral application of therapeutic dosages. For this reason the main metabolite, i.e. conjugated dextrorphan, (+)-3-hydroxy-N-methylmorphinan, contained in plasma and urine at considerably higher concentrations, was so far analytically determined within bioavailability tests (Ramachander et al., 1977). The other metabolites are (+)-3-hydroxymorphinan and (+)-3-methoxymorphinan (Willner, 1963; Hoffmann-La Roche, 1979).

In the following we report about pharmacokinetic investigations of dextromethorphan and different metabolites in the plasma and urine of 12 healthy volunteers. These results were evaluated within a biopharmaceutical trial for the characterization of different dosage forms.

Materials and methods

Volunteers and blood sampling

For this study 12 healthy volunteers were chosen out of a population of 22 healthy women and 24 healthy men after a preliminary trial in which plasma was sampled after 2 h and urine collected during 24 h after an oral dosage of 25 mg dextromethorphan-HBr in a hard gelatine capsule. The preliminary study has been carried out because during the first steps of analytical development we could clearly determine dextromethorphan in plasma and urine in some volunteers whereas in other volunteers the drug concentrations were in the range of or below the detection limits. We selected 6 volunteers (3 male, 3 female) with only slight traces of dextromethorphan in plasma and urine and 6 volunteers (3 male, 3 female) with dextromethorphan plasma concentrations between 6 and 14 ng/ml and a urinary excretion of approximately 1 mg dextromethorphan/24 h.

The 6 male participants were between 27 and 38 years old and weighed between 64 and 85 kg. The female participants were between 21 and 46 years and weighed between 46 and 70 kg. Their appearance, blood screen and urinalysis showed each to be in good health.

The volunteers, who gave their written consent after having been informed, took a freshly prepared solution of 25 mg of dextromethorphan-HBr in 15 ml of water and then drank 100 ml of water of approximately 20°C. They fasted for 10 h prior to the intake of the drug (taken at about 07.00 h) and for 2.5 h afterwards until they received a standard breakfast (2 rolls, 40 g butter, 50 g jam and 200 ml fruit juice). They were then permitted to resume their usual diet. Smoking and the ingestion of caffeine were not permitted during the course of the study. The volunteers were ambulatory but did not engage in strenuous exercise during the first 12 h.

Blood samples were collected from an arm vein immediately before start of the trial and at the following times afterwards: 20 min, 40 min, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 33 h and 48 h. Urine samples were collected 1 h prior to the administration and at the following intervals afterwards: 0–2 h, 2–4 h, 4–8 h, 8–14 h, 14–24 h and 24–48 h. Plasma was separated by centrifugation within 30 min of blood collection and both plasma and urine were stored at −20°C until analysis.

Determination of dextromethorphan and metabolites in plasma and urine

Materials

Dextromethorphan hydrobromide [1], dextrorphan [1], (+)-3-methoxymorphinan hydrochloride [2], (+)-3-hydroxymorphinan [2], β-glucuronidase [3], arylsulfatase [4], ethylmorphine hydrochloride [5], diethyl ether [5] freshly distilled, 0.1 N hydrochloric acid [5], absolute ethanol [5]. Stock solutions of internal standard and determined compounds were used: ethylmorphine (internal standard) 10 μg and 1 mg/ml water; dextromethorphan 1 μg, 10 μg and 100 μg/ml water; dextrorphan 10 μg, 100 μg and 1 mg/ml water; 3-methoxymorphinan 10 μg and 100 μg/ml water; 3-hydroxymorphinan 100 μg and 1 mg/ml ethanol. Further stock solutions were prepared using glass-distilled water and analytical-grade materials [5]: 3 N acetic acid, 0.1 N acetate buffer pH 5.1, carbonate solution pH 11.6 (700 g $Na_2CO_3 \times 10\ H_2O$/l), 0.1 M carbonate buffer pH 10.5, alkaline mixture pH 11.8 (50 ml 1 N sodium hydroxide solution + 150 ml 0.5 M dipotassium hydrogen phosphate solution).

I. Determination of dextromethorphan in plasma

100 ng ethylmorphine (as internal standard) and 2 ml 0.1 M carbonate buffer pH 10.5, were added to 2 ml plasma. The mixture was vortexed for 10 s, extracted with 4 ml freshly distilled ether by mechanical shaking for 30 min and centrifuged at 1500 *g* for 10 min. The ether layer was transferred to another centrifuge tube and evaporated to dryness under a nitrogen stream in a water bath (37°C). The residue was dissolved in 1 ml freshly distilled ether, the ether phase was extracted with 2 ml

[1] Hoffmann-La Roche AG.
[2] Synthesized by MACK Research Dept.
[3] No. 127680, Boehringer Mannheim, F.R.G.
[4] No. 102890, Boehringer Mannheim, F.R.G.
[5] Merck, Darmstadt, F.R.G.

of 0.1 N hydrochloric acid (1 min on a Vortex mixer) and centrifuged at 1500 *g* for 5 min. The aqueous solution was alkalized with 1 ml alkaline mixture pH 11.8, and shaken mechanically with 4 ml ether for 30 min. After centrifugation (1500 *g*), the ether layer was transferred to another centrifuge tube and evaporated to dryness at 37°C in a water bath using a nitrogen stream. The residue was reconstituted in 30 µl absolute ethanol and 3–5 µl were injected into the gas chromatograph [6] equipped with a nitrogen-phosphorus detector. The 1 m × 2.4 mm i.d. on-column glass column was packed with 3% OV 61 on Gas Chrom Q 100–120 mesh [7]. The column temperature was maintained at 235°C; injector and detector temperatures were both 270°C. The flow rate of the carrier gas (nitrogen) was 30 ml/min. The detector was supplied with 2 ml/min hydrogen and 80 ml/min synthetic air. Retention times: dextromethorphan 144 s, ethylmorphine 384 s.

II. Determination of total dextrorphan in plasma

17 µl 3 N acetic acid, 20 µl β-glucuronidase, and 20 µl arylsulfatase were added to 1 ml plasma and the plasma was hydrolyzed during the night (14 h) while shaking in a water bath at 37°C. From this point, the same procedure was followed as in method I, but 300 ng ethylmorphine was added as internal standard and the plasma was alkalized with 1 ml carbonate solution pH 11.6, instead of carbonate buffer pH 10.5. Finally the residue was dissolved in 50 µl absolute ethanol and transferred to a 100 µl sample vial for automatic injection of 3 µl into the gas chromatograph [8]. A nitrogen-phosphorus detector and a 1 m × 2.4 mm i.d. on-column glass column packed with 3% OV 61 on Gas Chrom Q 100–120 mesh [7] were used. The column temperature was maintained at 250°C, the injector at 270°C and the detector at 320°C. The flow rate of the carrier gas (nitrogen) amounted 30 ml/min; the detector was supplied with 3.5 ml/min hydrogen and 100 ml/min synthetic air. Retention times: dextrorphan 198 s, ethylmorphine 378 s.

III. Determination of dextromethorphan in urine

With dextromethorphan concentrations less than 50 ng/ml the procedure was followed as in method I, but 50 ng ethylmorphine, 1 ml carbonate solution pH 11.6, and 1 ml urine were used. Except for the oven temperature of 220°C, all gas chromatographic conditions were the same as in method I. Retention times: dextromethorphan 264 s, ethylmorphine 690 s.

IV. Determination of dextromethorphan, 3-methoxymorphinan, total dextrorphan and total 3-hydroxymorphinan in urine

After adding 1 ml 0.1 N acetate buffer pH 5.1, 20 µl β-glucuronidase and 20 µl arylsulfatase to 1 ml urine, the urine was hydrolyzed at 37°C while shaking in a water bath overnight (14 h). In the morning 10 µg ethylmorphine, 1 ml carbonate

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[6] Model F 22, Bodenseewerk Perkin Elmer, Uberlingen, F.R.G.
[7] Chrompack Deutschland, Berlin, F.R.G.
[8] Model 6800 equipped with sampler ALS, Dani, Mainz-Kastel, F.R.G.

solution pH 11.6, and 4 ml freshly distilled ether were added and the mixture was shaken gently for 30 min and centrifuged at 1500 *g* for 5 min. The upper ether layer was transferred to another centrifuge tube and evaporated to dryness in a water bath (37°C) under a nitrogen stream. The residue was dissolved in 50 µl absolute ethanol and transferred to a 100 µl sample vial for automatic injection of 3 µl into the gas chromatograph [8]. The gas chromatographic conditions were the same as in method II except for the oven temperature of 200°C. Retention times: dextromethorphan 564 s, 3-methoxymorphinan 636 s, dextrorphan 840 s, 3-hydroxymorphinan 948 s, ethylmorphine 1956 s.

For every compound separate calibration curves were prepared daily under the same conditions described above.The peak height ratio method was employed and linear relationships were found between the height ratio and the amount in the examined ranges:

Method I	1	—	30 ng/ml	dextromethorphan in plasma
II	20	—	700 ng/ml	dextrorphan in plasma
III	3	—	50 ng/ml	dextromethorphan in urine
IV	50	—1	400 ng/ml	dextromethorphan in urine
	0.2	—	25 µg/ml	dextrorphan in urine
	50	—1	400 ng/ml	3-methoxymorphinan in urine
	0.2	—	10 µg/ml	3-hydroxymorphinan in urine

No interfering peaks resulted from the blank plasma and blank urine (Fig. 1).

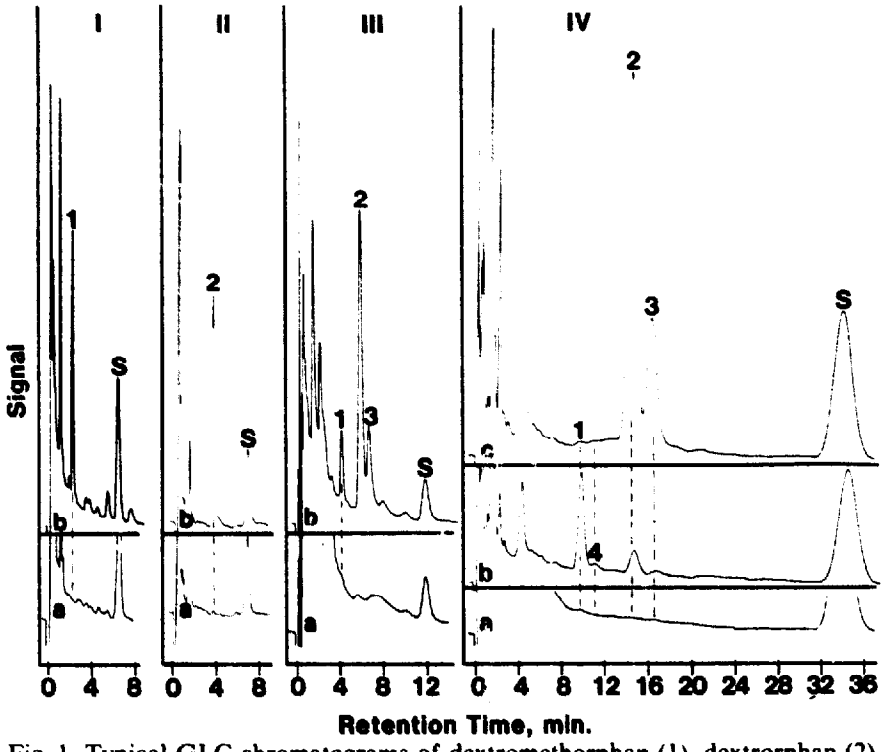

Fig. 1. Typical GLC chromatograms of dextromethorphan (1), dextrorphan (2), total hydroxymorphinan (3), 3-methoxymorphinan (4) and internal standard (S) in plasma (I, II) and urine (III, IV). Key: blank samples (a), dextromethorphan plasma sample 6 h of vol. 11, Group 3 (Ib); dextrorphan plasma sample 1 h of vol. 6, Group 1 (IIb); dextromethorphan urine sample 4–8 h vol. 6, Group 1 (IIIb); metabolites (2, 3, 4) in urine sample 4–8 h of vol. 11, Group 3 (IVb) and urine sample 4–8 h of vol. 6, Group 1 (IVc).

Results and discussion

Plasma levels

After ingestion of 25 mg of dextromethorphan-HBr, the plasma of 6 volunteers (Nos. 1, 2, 6, 7, 8, 12 = Group 1) contained only traces of unmetabolized dextromethorphan within the range of the detection limit of the analytical procedure, i.e. about 1 ng/ml. After a short time, however, metabolized dextromethorphan occurred in the plasma in the form of conjugated dextrorphan (Table 1). The plasma concentrations were rather high with maxima of 381–690 ng/ml after 1–2 h. All individual dextrorphan plasma level curves can be described excellently by means of an open 1-compartment model with elimination half-lives of 1.2–2.2 h (Table 2).

Contrary to this, the plasma of volunteers No. 5 (♀), 9 (♂) and 10 (♂) (Group 2) contained easily measurable concentrations of non-metabolized dextromethorphan with maxima of 11.7–14.4 ng/ml after 2–4 h. That means that the dextromethorphan plasma level maxima of these volunteers are 10–20 times as high as those of the volunteers of Group 1. Besides dextromethorphan there is also conjugated dextrorphan as main metabolite in the plasma of Group 2. The plasma concentrations of this metabolite are approximately 10–20 times as high as those of the simultaneously measured dextromethorphan (Fig. 2). Compared with the plasma levels of the first group the dextrorphan concentrations of the second group are considerably lower, which is also obvious when comparing the average maxima height of 539.8 (Group 1, Table 1) with 163.6 ng/ml (Group 2).

Moreover, there are differences in the apparent pharmacokinetics of dextrorphan compared with the first group. The individual plasma level curves of the second group indicate that, instead of a 1-compartment model, they can be better fitted to a pharmacokinetic 2-compartment model with half-lives of the β-phase of 6.2 h on average (Table 2).

TABLE 1

STANDARDIZED (70 kg) PLASMA CONCENTRATIONS OF TOTAL DEXTRORPHAN (ng/ml) IN THE VOLUNTEERS OF GROUP 1 AFTER INGESTION OF 25 mg DEXTROMETHORPHAN-HBr

Time (h)	Volunteer no.							
	1	2	6	7	8	12	Mean	S.E.M.
0.33	37.6	–	39.4	34.1	62.5	48.5	44.4	5.1
0.66	300.7	139.2	279.2	408.2	551.0	371.4	341.6	56.5
1.00	405.4	689.1	381.5	553.3	593.4	555.5	529.7	47.6
2.00	384.9	529.0	377.9	580.2	574.6	589.1	505.9	40.3
3.00	238.5	413.1	250.3	373.2	379.1	452.1	351.0	35.7
4.00	137.9	318.1	175.0	265.7	283.8	335.1	252.6	32.4
6.00	43.5	141.9	85.4	130.8	106.2	188.1	116.0	20.3
8.00	27.5	78.0	43.1	50.5	60.7	104.0	60.6	11.1
12.00	23.8	73.5	18.5	15.0	44.3	36.2	35.2	8.9

TABLE 2

INDIVIDUAL PLASMA ELIMINATION HALF-LIVES OF DEXTROMETHORPHAN AND DEXTRORPHAN IN GROUPS 1–3

Volunteer	Dextrorphan	Dextromethorphan
Group 1 [a]		
1	1.2	-
2	2.4	-
6	1.7	-
7	1.7	-
8	1.9	-
12	2.2	-
Mean ± S.D.	1.85 ± 0.4	
Group 2 [b,c]		
5	7.1	11.6
9	5.6	16.2
10	5.8	8.5
Mean ± S.D.	6.2 ± 0.8	12.1 ± 3.9
Group 3 [b]		
3	-	42.6
4	-	50.3
11	-	41.6
Mean ± S.D.		44.8 ± 4.8

[a] One-compartment model. No β-phase could be detected.
[b] β-Phase of a 2-compartment model.
[c] Theoretically the half-lives of both substances should be identical. For analytical reasons the longer half-life of dextromethorphan seems to be more probable.

In the third group (volunteers No. 3 (♂), 4 (♀), 11 (♀)) dextrorphan, generally considered to be the main metabolite, could not be detected with the analytical method available; i.e. the peak concentrations of this metabolite were less than 20 ng/ml of plasma. Thus the dextrorphan plasma maxima of Group 3 were 20–35 times lower than those of Group 1 (Table 1) and 5–10 times lower than those of Group 2 (Fig. 2). As in the second group, the plasma of the third group also contained distinctly detectable dextromethorphan concentrations with maximum values of 12.8–24 ng/ml after 3–4 h and values of 5.6–9.1 ng/ml after 33 h (Figs. 1 and 3). These curves could also be sufficiently described with a pharmacokinetic 2-compartment model whereby half-lives of the β-phase of 45 h on average were received, i.e. an elimination which is 4 times as slow as that of group 2 (Table 2).

Urinary excretion

The volunteers of Group 1 mainly excreted conjugated dextrorphan. Besides this there was a slight amount of 3-hydroxymorphinan developed from dextrorphan in an additional metabolization reaction (N-demethylation) and a very small amount of non-metabolized dextromethorphan (Table 3). Contrary to this, 3-methoxy-

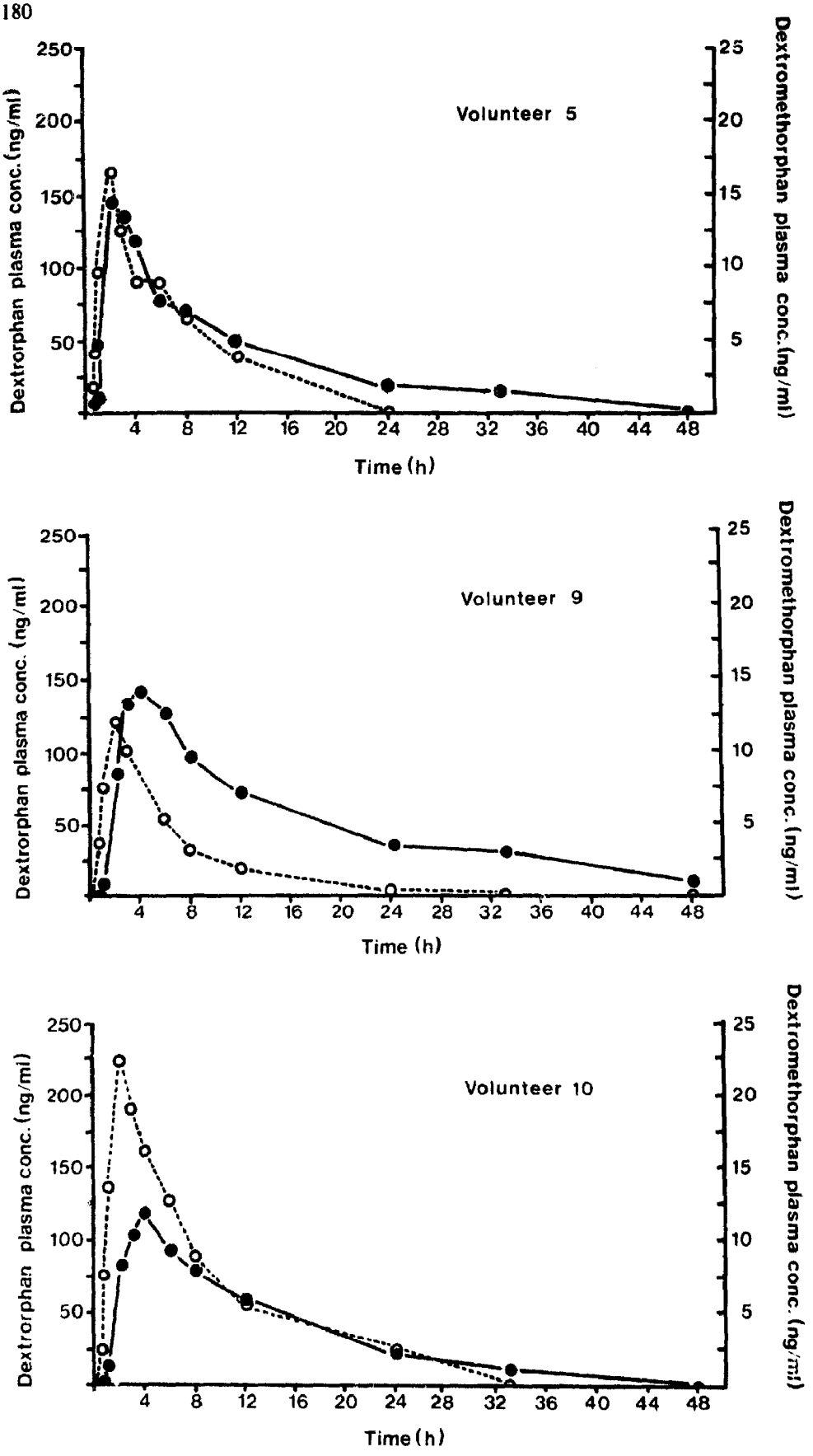

Fig. 2. Dextrorphan (○, left scale) and dextromethorphan (●, right scale) plasma concentrations in the 3 volunteers of Group 2.

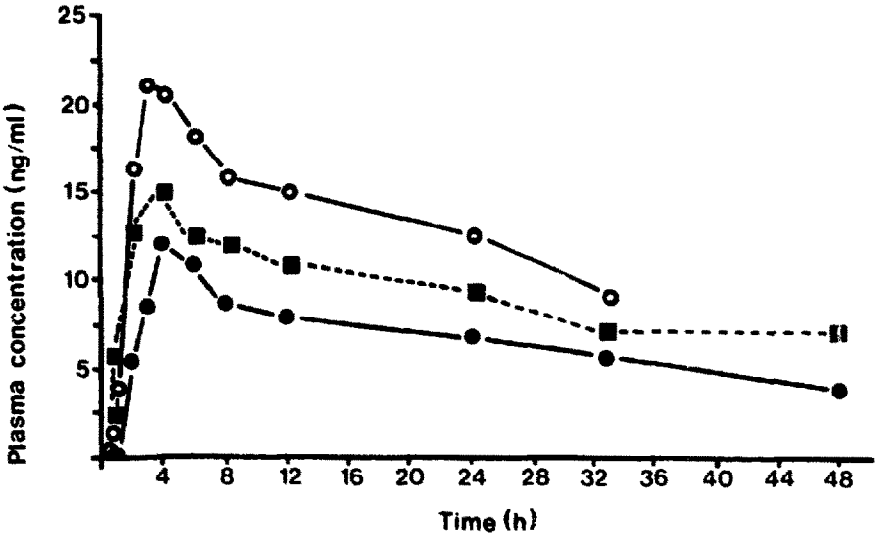

Fig. 3. Dextromethorphan plasma concentrations in volunteers Nos. 3 (●), 4 (■) and 11 (○) of Group 3.

morphinan that may be developed parallel to dextrorphan by N-demethylation of dextromethorphan, could not be detected in the urine of these volunteers.

The excretion of the metabolites in the urine was completed after 14–24 h (Fig. 4). After 48 h an average amount of 62.5% of the dosage was detected in the urine as dextrorphan, 23.5% as 3-hydroxymorphinan and 0.125% as dextromethorphan, giving a total of 86.1% (Table 3). This value is in good agreement with the total recovery of 79.4% already reported in the literature (Barnhart, 1980).

Thus for Group 1 the values found in the urine verified the results of the blood level determinations, especially the rapid and extensive metabolization of dextromethorphan to dextrorphan.

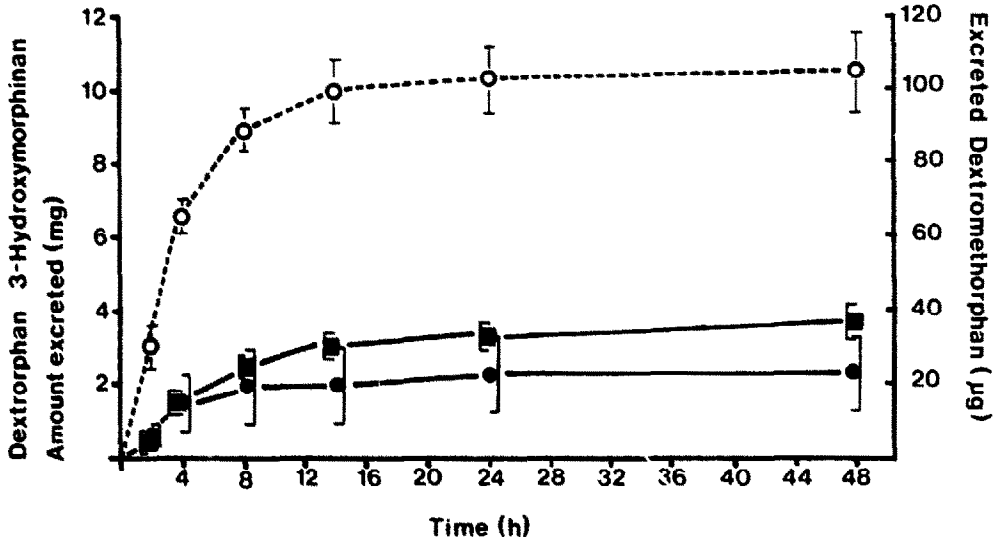

Fig. 4. Cumulative mean (n = 6) urinary excretion of dextrorphan (○), 3-hydroxymorphinan (■) (left scale) and dextromethorphan (●) (right scale) ±S.E.M. in the volunteers of Group 1.

TABLE 3

URINARY EXCRETION OF DEXTROMETHORPHAN AND ITS METABOLITES DURING 48 h IN GROUP 1 AS PERCENTAGE OF DOSE

Volunteer	Dextromethorphan		Dextrorphan		3-Hydroxy-morphinan		Total %	Ratio	
	mg	%	mg	%	mg	%		Dextrorphan/ Dextromethorphan	Dextrorphan/ 3-Hydroxymorphinan
1	0.0287	0.149	13.7	75.1	4.0	23.4	98.6	504	3.21
2	0.0047	0.024	9.3	51.1	3.1	18.2	69.3	2 129	2.81
6	0.0720	0.373	11.4	62.4	5.2	29.9	92.7	167	2.09
7	0.0135	0.070	11.7	63.8	4.8	27.9	91.8	911	2.29
8	0.0158	0.082	8.7	47.4	3.1	18.1	65.6	578	2.62
12	0.0103	0.054	13.7	75.1	4.0	23.4	98.6	1 391	3.21
Mean	0.0242	0.125	11.4	62.5	4.0	23.5	86.1	947	2.71
S.D.	0.0248	0.128	2.1	11.6	0.9	4.8	14.8	712	0.46

TABLE 4

URINARY EXCRETION OF DEXTROMETHORPHAN AND ITS METABOLITES DURING 48 h IN GROUPS 2 AND 3 AS PERCENTAGE OF DOSE

Volunteer	Dextro-methorphan		Dextrorphan		3-Hydroxy-morphinan		3-Methoxy-morphinan		Total %	Ratio	
	mg	%	mg	%	mg	%	mg	%		Dextrorphan/ Dextromethorphan	Dextrorphan/ 3-Hydroxymorphinan
Group 2											
5	0.81	4.2	8.8	47.9	2.7	15.6	-	-	67.7	11.4	3.08
9	0.48	2.5	7.1	38.8	6.1	35.3	0.17	0.90	77.5	15.5	1.10
10	0.22	1.2	8.2	45.0	5.0	28.7	0.10	0.56	75.5	37.5	1.57
Mean	0.50	2.6	8.0	43.9	4.6	26.5	0.14	0.73	73.6	21.5	1.92
Group 3											
3	2.10	10.9	0.6	3.3	0.9	5.3	0.38	2.08	21.6	0.3	0.63
4	2.34	12.1	1.0	5.5	0.5	2.7	0.27	1.48	21.8	0.5	2.05
11	1.42	7.4	0.5	3.0	0.4	2.6	0.26	1.42	14.4	0.4	1.15
Mean	1.95	10.1	0.7	3.9	0.6	3.5	0.30	1.66	19.3	0.4	1.28

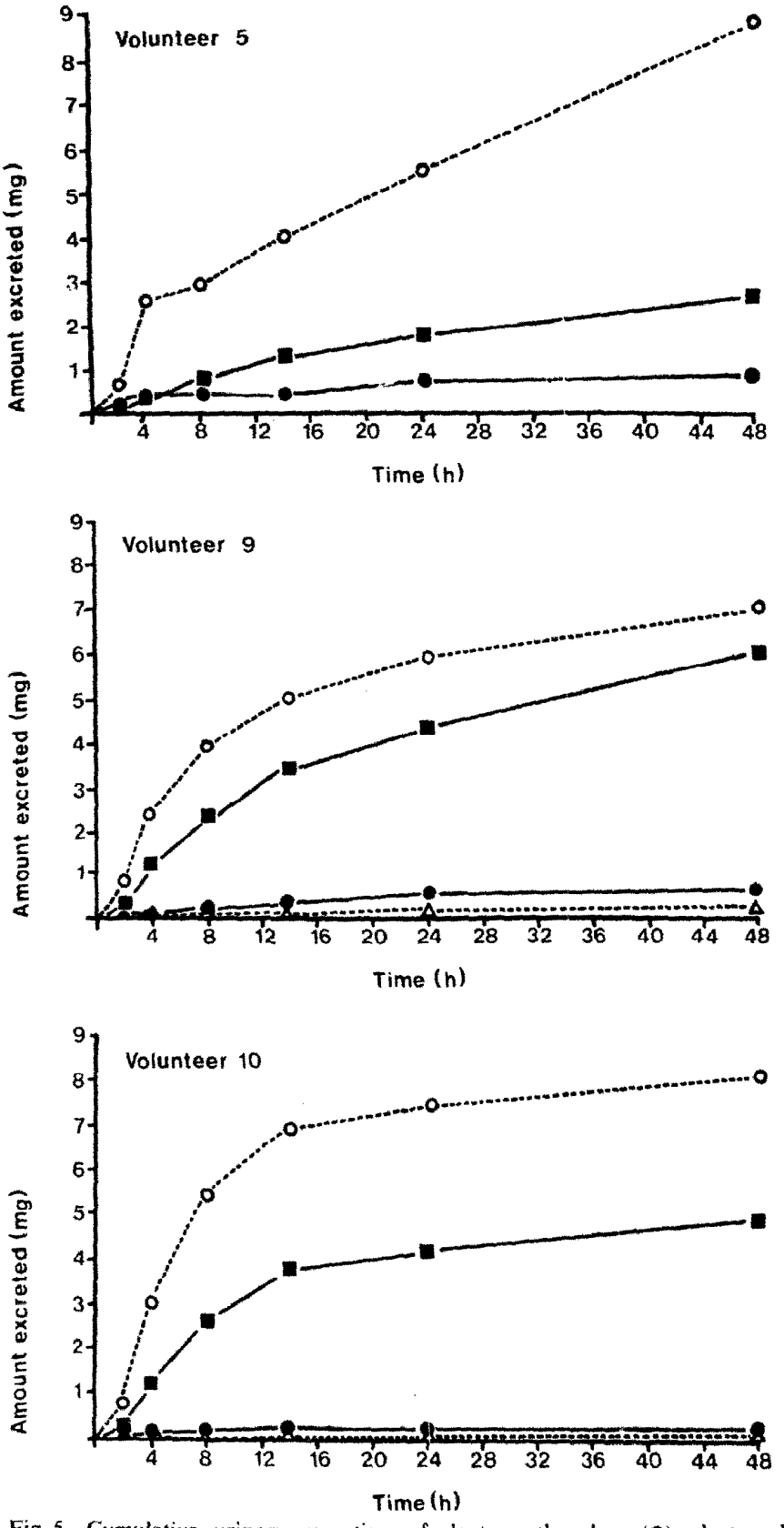

Fig. 5. Cumulative urinary excretion of dextromethorphan (●), dextrorphan (○) and 3-hydroxymorphinan (■) in the 3 volunteers of Group 2.

With the volunteers of Group 2, the 43.9% of the dose excreted as dextrorphan was clearly lower than the reference value of Group 1 of 62.5%. The amount of non-metabolized dextromethorphan in the urine of Group 2 was found to be 2.6%, which is 20 times that found in Group 1. Slight amounts of 3-methoxymorphinan were also detected (Table 4). In this volunteer group also, the results determined from the urine correlated well with the results of the plasma level determinations. The higher dextromethorphan plasma concentrations corresponded to an increased amount of dextromethorphan in the urine and the slower elimination of dextrorphan from the plasma is represented by a prolongation of the total excretion. Thus between 24 and 48 h there were still some amounts of the substances in the urine (Fig. 5) and the total excretion in 48 h was reduced to 73.6% compared to 86.1% in Group 1.

In Group 3 the amount excreted as dextrorphan in the urine during 48 h was even more reduced and the average value was only 3.9% of the dose compared to 62.5 and 43.9% in Group 1 and Group 2, wheras the portion of non-metabolized dextromethorphan in Group 3 was again considerably higher (Tables 3 and 4; Figs. 1 and 6). Thus the content of dextromethorphan of 10.1% of the dosage in the urine of the volunteers of Group 3 was approximately 80 times (resp. 3.9 times) as high as that of the volunteers of Group 1 (resp. Group 2). The pharmacokinetics determined from the renal excretion clearly confirmed the results obtained from the plasma concentrations. The very poor total excretion of only 19% within 48 h corresponded with the extended plasma half-life of dextromethorphan and the circumstance that dextrorphan could not be detected in the plasma of these volunteers corresponds to the fact that the portion of dextrorphan in the amount totally excreted was only 20%. Because of this low cumulative excretion in 48 h, the amounts of substances in the urine of the volunteers of Group 3 can only be compared to the other groups on the basis of the relative amounts of the excretion in 48 h (Table 5). This procedure is only valid on the assumption that the portions of metabolites measured at 48 h do not change until the excretion is completed.

Thus the most pronounced variations between the groups were observed with dextromethorphan, increasing the relative percentage from 0.145% to 3.5% and 52.3% in Groups 1, 2 and 3, respectively. That means that the percentages excreted in Groups 2 and 3 were 24 and 360 times higher than in Group 1. In Group 3 non-metabolized dextromethorphan was the main excretion product whereas in the other groups the metabolization into dextrorphan was prevailing. The relative excretion of dextrorphan decreased from Group 1 through Group 3, respectively, from 72.6% to 59.6% and 20.2% at least. Major changes were also detected with 3-methoxymorphinan increasing the portion from undetectable to 1% and 8.6% in Groups 1, 2 and 3, respectively. The excretion of 3-hydroxymorphinan seems to be reduced in Group 3 compared to the other groups.

Since the ratio of excreted dextrorphan: 3-hydroxymorphinan changed only slightly, the N-demethylation of dextrorphan into 3-hydroxymorphinan seemed to occur to almost the same extent in all volunteers (Tables 3 and 4), whereas the O-demethylation of dextromethorphan into dextrorphan was obviously very different in the 3 groups (ratio dextrorphan : dextromethorphan, Tables 3 and 4). At a

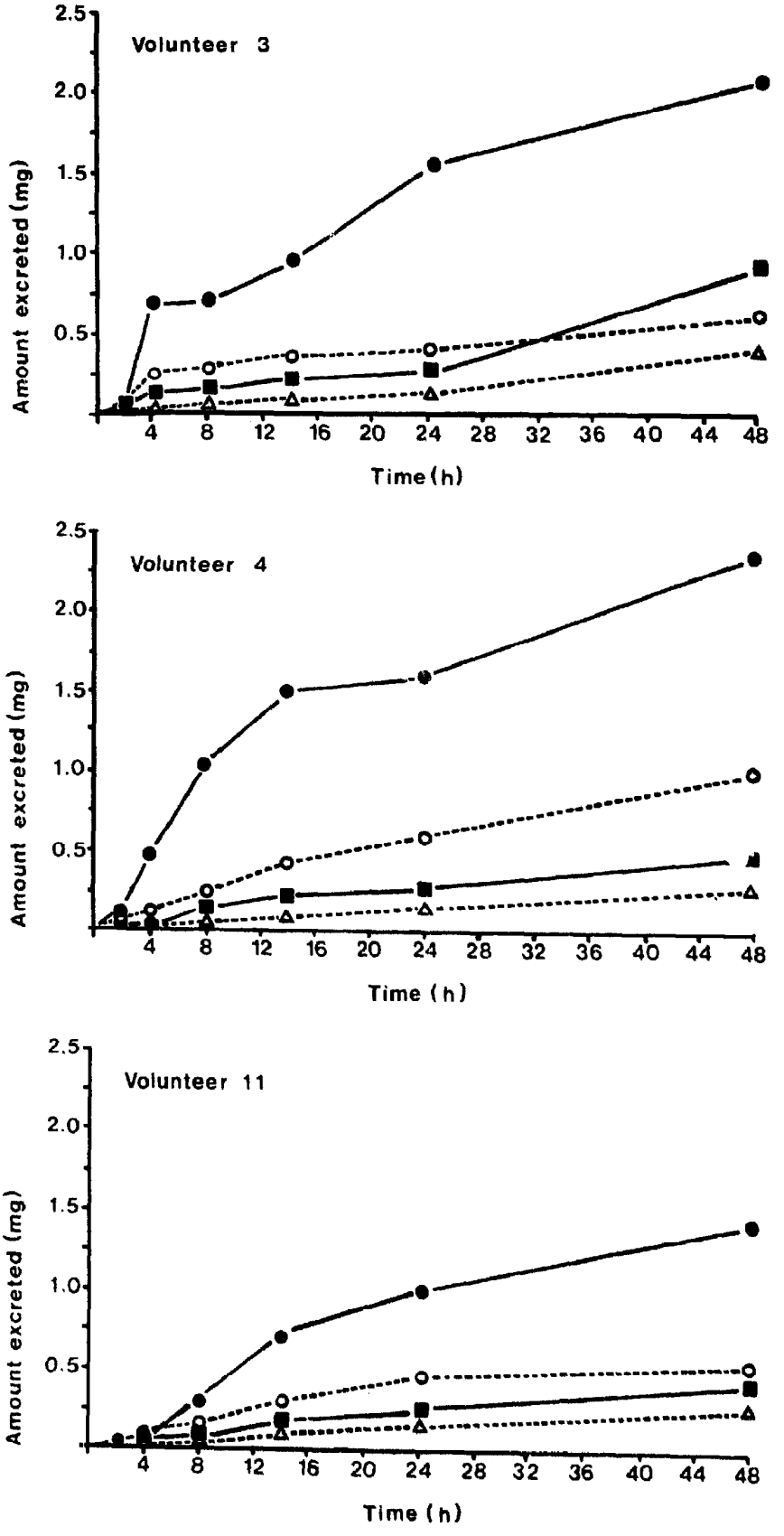

Fig. 6. Cumulative urinary excretion of dextromethorphan (●), dextrorphan (○), 3-hydroxymorphinan (■) and 3-methoxymorphinan (△) in the three volunteers of Group 3.

TABLE 5

MEAN URINARY EXCRETION OF DEXTROMETHORPHAN AND ITS METABOLITES AS PERCENTAGE OF TOTAL AMOUNT EXCRETED WITHIN 48 h

Volunteer group	Dextro-methorphan	Dextrorphan	3-Hydroxy-morphinan	3-Methoxy-morphinan
1	0.145	72.6	27.3	–
2	3.5	59.6	36.0	1.0
3	52.3	20.2	18.1	8.6

portion of 8.6% of the excreted amount, the alternative metabolism of dextromethorphan into 3-methoxymorphinan was clearly increased in Group 3 compared to Group 2. The capacity of this reaction, however, was insufficient to completely replace the reduced O-demethylation.

The division of the volunteers into 3 groups may to a certain extent be dependent on the sensitivity of the analytical procedures used. The following findings, however, justify this division.

(1) In Group 1 no dextromethorphan was found in the plasma and only traces of the substance were found in the urine. The plasma level curves of dextrorphan can be described excellently with a 1-compartment model; the elimination half-lives are 1.2–2 h.

(2) Besides the simultaneous occurrence of dextromethorphan and dextrorphan in the plasma, it was noticed in Group 2 that the apparent pharmacokinetics of dextrorphan have changed compared to Group 1. Therefore a 2-compartment model was used in this group to sufficiently characterize the dextrorphan plasma levels with an elimination half-life of 6.2 h (β-phase). The urine data show that the dextromethorphan excretion was about 20 times as high as that of Group 1. A volunteer described in the literature (Barnhart, 1980) whose urine contained 3.9% of dextromethorphan, 38.8% of dextrorphan and 27.9% of 3-hydroxymorphinan can be classified into this group (see Table 4) too.

(3) Compared to the other volunteers, the volunteers of Group 3 were marked by the fact that no dextrorphan could be detected in the plasma and that dextromethorphan became the main excretion product at a portion of more than 50% (Table 5). Moreover, in Group 3 the half-life of the elimination phase of dextromethorphan was on average approximately 7 times as long as that of Group 2 (Table 2) and the percentage of dose excreted in 48 h of 19.3% is significantly reduced compared to Groups 1 and 2 (Tables 3 and 4). In addition, the relative excretion of 8.6% of 3-methoxymorphinan clearly exceeds the excretion in the other 2 groups with values of 1% and less.

(4) Within repetitive trials with all volunteers an intra-individual reproducibility of dextrorphan and dextromethorphan plasma levels of approximately 10% and better could be found. Thus the differences between the different volunteer groups exceeded by far any intra-individual variation as well as the inter-individual variations within a group (Tables 1–5).

(5) Significant differences between the groups also arose when the quotient of the amounts of dextrorphan and dextromethorphan excreted in the urine was evaluated. Thus on average the amount of dextrorphan excreted was 950 times greater in Group 1 and 20 times greater in Group 2 compared to dextromethorphan. The quotient of 0.4 of Group 3 showed again that these volunteers excreted mainly unmetabolized dextromethorphan (Tables 3 and 4).

Based on the last-mentioned criterion from the results of the preliminary trial (see Experimental), 3 additional persons (2 ♀, 1 ♂) out of the remaining 34 volunteers could be assigned subsequently to Group 3 according to their urinary dextrorphan : dextromethorphan ratios of 0.31, 0.75 and 0.25 (Tables 3 and 4). Thus, out of the population of 46 persons investigated in the preliminary trial, a total of 3 volunteers (1 ♀,2 ♂) were assigned to Group 2, and 6 volunteers (4 ♀, 2 ♂) to Group 3; that is roughly a frequency of 6 and 13% for Groups 2 and 3, respectively.

Lately the genetically determined limitation of the oxidative metabolism for various medical substances such as debrisoquine (Mahgoub et al., 1977), sparteine (Eichelbaum et al., 1979), carbocisteine (Waring et al, 1981) and nortryptiline (Bertilsson et al., 1980) has been reported. Analogous to this, it may be presumed that in humans the ability to change dextromethorphan into dextrorphan by oxidative O-demethylation is perhaps genetically also differently determined. This is indicated by the size of the differences between the groups, but proof of this hypothesis is yet to be established.

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Federal Register, Vol. 41, No. 176, Sept. 9, 1976

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