Human Metabolism of 7-Substituted Theophyllines: N^3-Demethylation and Lack of Oxidation of Proxyphylline

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Abstract □ Proxyphylline metabolism after oral administration to humans was studied. The only metabolic process detected was N^3-demethylation, and 1-methyl-7-(2-hydroxypropyl)xanthine was isolated and identified. Proxyphylline was excreted in urine both as unchanged compound (12.7% of dose) and as its metabolic product (30.2% of dose). The latter substance was not found (detection limit = 1 μg/ml) in the systemic circulation. Thus, it probably does not participate in the pharmacological activity of proxyphylline *in vivo*, although it was as active as the parent drug in relaxing the guinea pig tracheal chain. Lack of metabolism to uric acid derivatives is explained by the low affinity of both substances toward the enzymes that oxidize xanthine (xanthine oxidase) and methylxanthine derivatives. The presence of the metabolite in urine interferes with some analytical methods developed for estimation of unchanged proxyphylline. Published data on the urinary excretion of this drug need reevaluation.

Keyphrases □ Proxyphylline—metabolism after oral administration, N^3-demethylation □ Pharmacokinetics—proxyphylline, diuretics, N^3-demethylation □ Xanthine derivatives—metabolism of proxyphylline in humans □ Diuretics—proxyphylline, metabolism after oral administration, N^3-demethylation

Substitution of the hydrogen atom at position 7 of the theophylline nucleus has received increased attention in the search for better tolerated and pharmacologically more selective theophylline-like compounds (1–9). The biodegradation of 7-substituted theophyllines follows three main metabolic pathways in humans: N-dealkylation of one or two of the alkyl groups at positions 1, 3, and 7; C^8-oxidation of the unchanged drug and/or its N-dealkylated metabolites to uric acid derivatives; and conjugative or oxidative metabolism of the N^7-side chain.

The chemical structure of the N^7-substitution dictates the relative importance of these metabolic pathways for each individual compound. The metabolism of theophyllines with small alkyl side chains such as caffeine (10–13) or with large ones such as pimefylline (14), xanthinol (15), or fenethylline (16) has been described. Little is known, however, about the biodegradation of theophyllines substituted by medium-sized hydroxy alkyl groups (17, 18), although some of them, such as etofylline, dyphylline, and proxyphylline, are widely used in treatment of respiratory tract diseases.

A study of proxyphylline [7-(2-hydroxypropyl)theophylline] metabolism was undertaken because serious discrepancies exist in the literature about the amount of unchanged proxyphylline excreted in the urine of volunteers given the drug orally (19, 20). The variability of the results seems to be unrelated to the specificity of the analytical method used and suggests the existence of metabolic products structurally similar to the parent drug. Other methylxanthines are oxidized to uric acid derivatives either by xanthine oxidase, *i.e.*, 1-methylxanthine (21–23), or by other enzymatic systems (24). In a preliminary step, the possible interaction between proxyphylline and xanthine oxidase was investigated. Nevertheless, relevant information was obtained after oral administration of the drug to volunteers. The results of these studies confirm the existence of a metabolite and indicate that the main, if not the only, metabolic process of the drug in humans is N^3-demethylation.

EXPERIMENTAL

Incubations with Xanthine Oxidase—The determination of enzymatic activity was carried out by the method of Domingo (25), which measures the absorbance at 600 nm of the oxidized form of 2,6-dichloroindophenol. The enzymatic system contained 0.027 mg of xanthine oxidase[1]/ml, 3.5×10^{-5} M 2,6-dichloroindophenol[2], and several concentrations of xanthine[2], proxyphylline[3], and isolated proxyphylline metabolite. The incubation medium and the solutions used were prepared in a 0.05 M phosphate buffer (pH 7.4) (26). Solutions of xanthine, theophylline[3], and metabolite were prepared by dissolving the drugs in a small volume of concentrated sodium hydroxide, followed by addition of the phosphate buffer and final adjustment of the pH to 7.4 with dilute hydrochloric acid. The temperature was maintained at 25 ± 1°, and the absorbance was determined with a spectrophotometer[4].

Drug Administration to Humans—In a preliminary qualitative assay, an oral dose of 300 mg of proxyphylline was administered to two healthy men. Proxyphylline was dissolved in water containing sucrose. No food was allowed from 9 hr before until 2 hr after drug administration. Urine was collected prior to the experiment and for the 0–8 and 8–24-hr periods. Excreted volumes were measured, and 25-ml samples were stored at −20° until analysis by TLC.

In a second quantitative assay, 300 mg of proxyphylline was administered to five healthy men (73–98 kg, mean 81.8 kg; 23–38 years, mean 30.8 years). The administration conditions and urine collection procedures were the same as in the preliminary assay. Blood samples were obtained from the cubital veins of the forearm with heparinized syringes immediately before administration and at 0.5, 1, 2, 4, 6, 8, and 12 hr. The plasma was separated after centrifugation and stored under the same conditions as urine until analysis.

To isolate enough of the proxyphylline metabolite to study its structure and properties, three gelatin capsules, each containing 750 mg of proxyphylline, were administered to six healthy men, one capsule every 12 hr. All urine excreted for 9 hr after the third dose was collected and stored at −20° until analysis.

Isolation and Purification of Proxyphylline Metabolite—Urine excreted by the six volunteers (2.85 liters) was chromatographed through a glass column (30 × 3.5 cm) filled with resin[5]. Excess water in the column then was removed by vacuum applied to the lower end, and the column was eluted with 900 ml of methanol. Air bubbles were removed by gentle agitation of the resin with a glass rod. The methanol eluate was evaporated to dryness *in vacuo*. The residue was washed three times with 50 ml of methanol, once with 35 ml of chloroform, and twice with 14 ml of ethanol and was dried *in vacuo* over phosphoric anhydride for 2 days. A white powder (364 mg) was obtained.

This compound was shown by TLC[6] in Solvent Systems 1 (chloroform–methanol–25% ammonia solution, 10:4:1) and 2 (chloroform–methanol–ethyl acetate–99.5% acetic acid, 78:10:10:2) to be mainly the expected proxyphylline metabolite (R_f 0.42 in Solvent 1 and R_f 0.23 in Solvent 2). Its purity was 84–88% as determined by comparison of its molar absorptivity with that of proxyphylline and xanthine at 270 nm (pH 7.4). The identification of its structure was carried out by spectro-

[1] Extracted from cow milk, Boehringer Mannheim, West Germany.
[2] Merck, Darmstadt, West Germany.
[3] Knoll, Ludwigshafen, West Germany.
[4] Perkin-Elmer model 550.
[5] Amberlite XAD-2, Rohm & Haas, Philadelphia, Pa.
[6] Silica gel 60 F_{254}, Merck, Darmstadt, West Germany.

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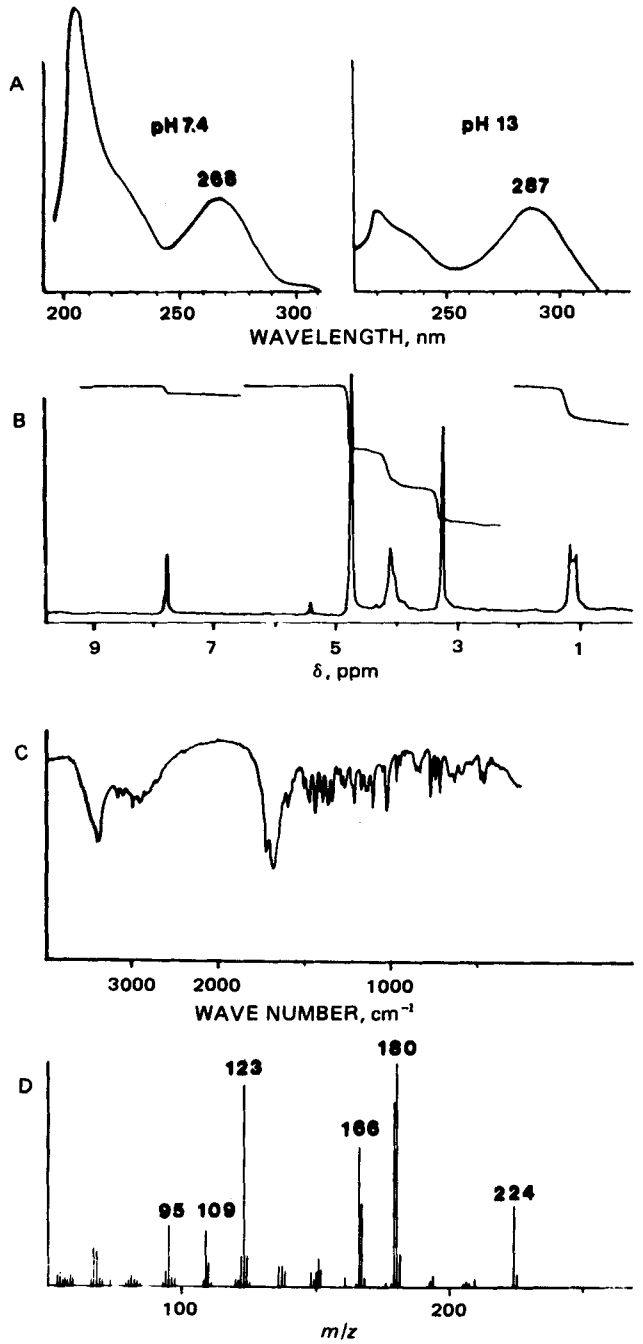

Figure 1—*UV (A), NMR (B), IR (C), and mass (D) spectra of the metabolic product of proxyphylline, 1-methyl-7-(2-hydroxypropyl)-xanthine, isolated from human urine.*

metric methods. Measurements of UV absorption spectra[4] were performed in methanol or aqueous solutions. The spectra in aqueous solutions were obtained at pH 13 (0.5 *N* NaOH) or pH 7.4. [The compounds were dissolved in a minimal amount of concentrated sodium hydroxide, 0.1 *M* phosphate buffer (pH 7.4) was added, and the pH was adjusted to 7.4 with dilute hydrochloric acid]. IR spectra[7] were obtained using potassium bromide pellets. NMR spectra[8] were obtained in a 0.5 *N* NaOD solution in deuterium oxide. Tetramethylsilane was used as the internal standard. Mass spectra[9] were obtained at 70 ev, and samples were introduced by direct-probe insertion.

Pharmacological Activity of Proxyphylline and Its Purified Metabolite on Isolated Guinea Pig Tracheal Chain—A guinea pig tracheal chain was prepared according to the method of Castillo and De Beer (27). It was immersed in a bath containing an oxygenated Kreb's solution and was subjected to an initial tension of 0.5 g. The addition of isoproterenol[10], theophylline, proxyphylline, and the purified proxyphylline metabolite to the bath allowed comparison of their relative myorelaxant effects[11]. Isoproterenol, theophylline, and proxyphylline were dissolved directly in saline (0.9% NaCl). However, to obtain a saline solution of proxyphylline metabolite, it was necessary to boil and reflux the suspension for ~15 min. The metabolite was stable under these conditions. The concentrations studied for each compound are indicated in Fig. 2.

Quantitative Analysis of Proxyphylline and Its Metabolite in Human Plasma and Urine—*Proxyphylline in Plasma*—Plasma samples (1 ml) were made alkaline with 0.5 *N* NaOH (0.2 ml) and were extracted for 1 hr with chloroform (6 ml). The organic phase was separated by centrifugation and evaporated under a nitrogen stream. The residue was dissolved in chloroform, applied to precoated thin-layer plates[6], and developed further with Solvent System 2. Quantification was carried out by photodensitometry[12] by measuring the diminution of background fluorescence at 525 nm (excitation at 254 nm) induced by the proxyphylline spot (R_f 0.36). The calibration curves were obtained after addition of known amounts of proxyphylline to plasma samples subsequently subjected to extraction.

Proxyphylline Metabolite in Plasma—Plasma samples (1 ml) were added to resin[5] (0.3 g) and shaken for 5 min. The aqueous phase was separated, and the resin was eluted three times with 1 ml of methanol with vigorous shaking for 5 min. The extracts were combined and evaporated to dryness under a nitrogen stream, and the residue was dissolved in a small amount of methanol. Quantitation was carried out by TLC and photodensitometry[12] as previously described, using Solvent System 2. The addition of known amounts of purified metabolite to plasma samples showed that the extraction yield was nearly 100%. The detection limit was 1 μg/ml.

Proxyphylline and Its Metabolite in Urine—Samples of urine (40 μl) were applied directly onto precoated thin-layer plates, which were developed with Solvent System 1. Analysis was performed by photodensitometry[12] as previously described. The responses were compared with those obtained from known amounts of proxyphylline and its purified metabolite added to control urines. The R_f value of proxyphylline in this system was 0.79.

RESULTS AND DISCUSSION

The oral administration of caffeine (1,3,7-trimethylxanthine) to rats and humans gives rise to the excretion of the following substances: 1,3,7-trimethylxanthine (10), 1,3,7-trimethyluric acid (11), 1,3-dimethylxanthine (theophylline) (12), 1,3-dimethyluric acid (10), 1,7-dimethylxanthine (paraxanthine) (10), 1,7-dimethyluric acid (13), 1-methylxanthine (10), 1-methyluric acid (10, 13), 7-methylxanthine (10), 7-methyluric acid (13), and 3-methyluric acid (11). Thus, there are two main metabolic pathways for caffeine, *N*-demethylation and C^8-oxidation of the various methylxanthines to uric acid derivatives. The metabolism of theophylline and theobromine, when given orally to humans, is similar (10, 28).

The C^8-oxidative metabolism can be partially studied by following the reaction of each substrate with the enzyme, xanthine oxidase. It is known that caffeine (29) and other methylxanthines are not oxidized by this enzyme, whereas 1-methylxanthine is oxidized to its uric acid derivative by bovine milk (21) or by rat hepatic (22) xanthine oxidases. Recently, it was demonstrated by giving theophylline and allopurinol to humans (23) that 1-methyluric acid seems to be the only metabolite arising from direct oxidation of its substrate (1-methylxanthine) by hepatic xanthine oxidase. Therefore, the oxidative metabolism of proxyphylline and its isolated metabolite by xanthine oxidase was studied.

Bovine milk xanthine oxidase was used since this enzyme and human hepatic xanthine oxidase have a similar specificity for purine derivatives (21). Proxyphylline was incubated at concentrations of 1×10^{-4} and 1×10^{-3} *M*, and its metabolite was incubated at 1×10^{-4} and 5×10^{-4} *M*. These concentrations were equal to and were five and 10 times higher than the concentration of xanthine that saturates the system (21). Under these conditions, no reaction was observed, which may have been due to either a lack of affinity for the enzyme or a lack of intrinsic activity of the enzyme when the substrates are at the active site. The ability of proxyphylline and its metabolite to inhibit competitively the xanthine–xan-

[7] Beckman model Acculab 10.
[8] Perkin-Elmer model R-24.
[9] Hewlett-Packard model 5930A.

[10] Boehringer Ingelheim, West Germany.
[11] Transducer and recorder, Ugo Basile, Milan, Italy.
[12] Vitatron photodensitometer model TLD 100.

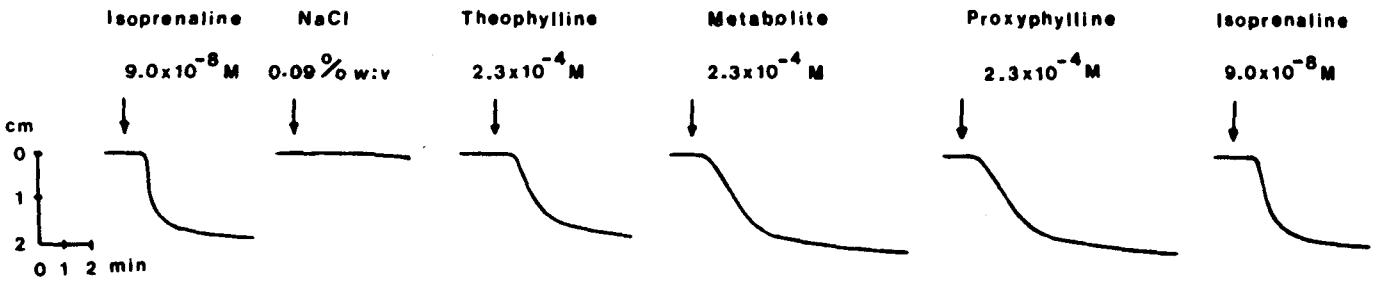

Figure 2—*Effects induced by isoproterenol (isoprenaline), theophylline, proxyphylline, and its metabolite on the myorelaxation of the isolated guinea pig tracheal chain. The substances were dissolved in 0.9% NaCl and were added (4 ml) to the bath (40 ml) to reach the final concentrations indicated in the figure.*

thine oxidase system was studied to distinguish between these possibilities. The xanthine concentrations in the incubation media were 2.5×10^{-6}, 5×10^{-6}, 1×10^{-5}, and 1×10^{-4} *M*. The concentrations of proxyphylline and the metabolite were the same as previously indicated. Neither substance altered the oxidation rate of xanthine, which suggests that they have a low affinity for the enzyme, as is the case for caffeine, theophylline, and theobromine (30). Apparently the di- and trisubstitution of the xanthine nucleus prevents the interaction with xanthine oxidase (21, 30).

When 300 mg of proxyphylline was given orally to two volunteers, visual evaluation (254 nm) of thin-layer plates of urine extracts showed only two new spots compared with control urine. One spot was identified as unchanged proxyphylline. Only 28.4 mg was excreted during the first 8 hr, and 24.8 mg was excreted during the following 16 hr. The second compound had lower R_f values and was excreted in higher concentrations. This metabolite was isolated from the combined urine of six volunteers given high doses of proxyphylline. Its structure was investigated by spectral methods, and it was identified as 1-methyl-7-(2-hydroxypropyl)xanthine based on the following evidence:

1. The UV absorption spectrum of the metabolite in methanol and aqueous neutral solutions (Fig. 1A) was virtually identical to that of proxyphylline and xanthine. Under these conditions, the absorbance maximum of uric acid was at 290 nm. The absorption maximum of the metabolite shifted to 287 nm in alkaline solutions (Fig. 1A), as occurs with xanthine but not with proxyphylline. The tautomerism of N^3-H is involved in the bathochromic shift of the xanthine spectrum (31). No tautomerism exists for N^1-H (31).

2. Apart from the disappearance of the singlet corresponding to a 1-methyl group, the NMR spectrum of the metabolite (Fig. 1B) was similar to that of proxyphylline: δ 1.28 (d, C–CH_3), 3.27 (s, N–CH_3), 3.46 (s, N–CH_3), 4.10 (m, CH_2–CHOH), and 8.08 (s, ≡CH) ppm. It was shown (32, 33) that the N^1-methyl group always appears upfield with respect to the N^3-methyl group. Thus, the methyl group (δ 3.25 ppm) in the spectrum of the metabolite is located at position 1.

3. The IR spectrum of the metabolite (Fig. 1C) confirmed the lack of C^8-oxidation since no variation was observed in the CO stretching bands when compared to proxyphylline (1650 and 1690 cm^{-1}).

4. The mass spectrum (Fig. 1D) confirmed the postulated structure.

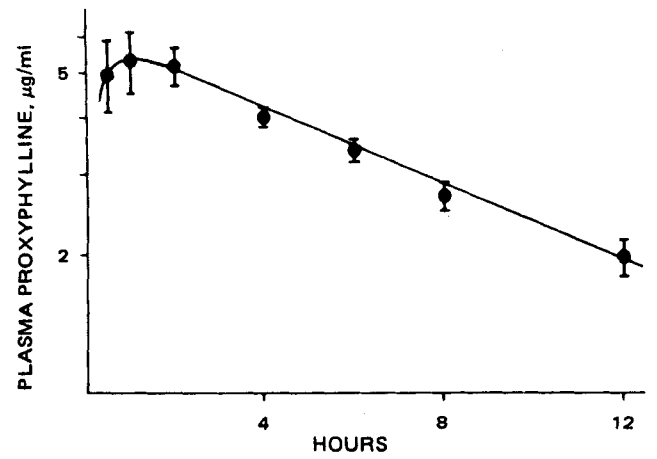

Figure 3—*Mean plasma concentrations of unchanged proxyphylline in five human volunteers given 300 mg of the drug by the oral route. Vertical bars are units of the standard error of the mean.*

The molecular ion (M^+ at *m/z* 224) is in accordance with the formula $C_9H_{12}N_4O_3$. The N^7-side chain is unaltered as indicated by the fragmentation of the α and β bonds (*m/z* 166, 167, 179, and 180) when compared to proxyphylline (34). All ions bearing the purine ring appeared 14 amu lower than the corresponding ions in the proxyphylline spectrum (34), thus confirming the absence of the N^3-methyl group.

5. The solubility of the metabolite in aqueous neutral solutions (pH 7.4) was comparable to that of xanthine but much lower than that of proxyphylline. The solubility of the metabolite increased in strong alkaline media due to the ionization of the tautomeric enolic form involving C^2 and N^3.

N^3-Demethylation of proxyphylline is in accord with the metabolic stability of the caffeine methyl groups (1 > 7 > 3) in humans (10). No N^7- or N^1-metabolic dealkylation of proxyphylline metabolite is subsequently produced, in accordance with the results of Cornish and Christman (10), who found that didealkylation did not occur when theophylline and theobromine were given to humans. They did not observe urinary excretion of xanthine or uric acid above the normal levels. Other N^7-substituted theophyllines with larger side chains are N^7-dealkylated to produce theophylline, *e.g.*, pimefylline {7-[2-[(3-pyridylmethyl)amino]ethyl]theophylline} (14) and fenethylline {7-[2-[(α-methylphenethyl)amino]ethyl]theophylline} (16), whereas xanthinol {7-[2-hydroxy-3-[(2-hydroxyethyl)methylamino]propyl]theophylline} and dyphylline [7-(2,3-dihydroxypropyl)theophylline] behave as proxyphylline and its metabolite since no N^7-dealkylation is observed (15, 17, 18). The latter four compounds carry an hydroxyl group on the β-position of the side chain that may prevent the carbinolamine formation postulated (35, 36) to be the first step of *N*-dealkylation. The complexity of the N^7-side chain also seems to play an important role in the C^8-metabolic oxidation of this class of substances. Proxyphylline and its metabolite, like other theophyllines substituted in position 7 by large groups, are not oxidized, whereas the 7-methylxanthines are excreted partially as uric acid derivatives (10, 11, 13). The enzymatic system involved, however, was not determined. Xanthine oxidase does not seem to be involved (21, 24, 30).

Equimolar amounts of proxyphylline and its metabolite gave an equivalent relaxation of the isolated guinea pig tracheal chain, although these compounds were less active than theophylline and isoproterenol (Fig. 2). The metabolite was not detected (detection limit = 1 μg/ml) in the plasma samples of six volunteers given 300 mg of proxyphylline orally. The levels of the parent drug in the same samples (Fig. 3) were similar to those previously described for an equivalent dose (19, 20, 37–40). These results indicated that in spite of its β-adrenergic activity, 1-methyl-7-(2-hydroxypropyl)xanthine probably does not participate in the clinical actions of proxyphylline. Despite the lack of detection of the metabolite in the systemic circulation, it was verified as the major pathway for the renal excretion of proxyphylline in humans (Table I). The mean values of metabolite excreted in the urine were 16.9% of the dose in the 0–8-hr period and 13.3% of the dose during the following 16 hr. These values were twice those found for proxyphylline (8.5 and 4.1%, respectively).

Table I—Cumulative Urinary Excretion of Proxyphylline and Its Metabolite [a]

Hours	Proxyphylline	Metabolite
8	8.5 ± 3.0[b]	16.9 ± 2.9
24	12.6 ± 2.9	30.2 ± 3.6

[a] Oral administration of 300 mg of proxyphylline to five humans. [b] Percentage of dose (mean ± *SEM*).

The high amounts of 1-methyl-7-(2-hydroxypropyl)xanthine appearing in the urine of humans given proxyphylline and the close similarity between the chemical structure of both compounds indicate the need for specific methods to estimate the unchanged drug concentrations in those samples. Some results obtained by nonspecific spectrophotometric methods (19, 41, 42) will need reevaluation. It has been verified that the method of Driever (43), modified by Ritschel and Banarer (41) to estimate unchanged proxyphylline in urine, does estimate the unchanged drug plus its metabolite, 1-methyl-7-(2-hydroxypropyl)xanthine.

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