THEBAINE METABOLITES IN THE URINE OF RHESUS MONKEYS

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Abstract—The metabolic fate of thebaine in rhesus monkeys was investigated. Using thin layer chromatography, more than four metabolites were detected in the urine of monkeys given thebaine (8 mg/kg, s.c.). Two of the metabolites isolated by high performance liquid chromatography were not consistent with those reported previously. With the use of gas chromatography-mass spectrometry, the structures were identified as oripavine (3-O-demethylthebaine) and nororipavine (3-O,N-di-demethylthebaine) from the mass spectra of their trimethylsilyl and propionyl derivatives. Further experiments with liver microsomes from rhesus monkeys showed that, in addition to these metabolites, northebaine was also formed from thebaine in the presence of NADPH.

Like morphine and codeine, thebaine is a compound contained in the capsules and roots of some *Papaver* species plants. This compound is now used as raw material in the manufacture of opioid agonists including codeine and etorphine. Concerning the pharmacological properties of thebaine, it is well known that its predominant effects are central nervous system stimulation (1), and strychnine-like convulsions have been observed at the higher doses in experimental animals (1–3). Naloxone, a morphine antagonist, antagonizes thebaine-induced convulsions in mice (4). Until recently, thebaine was considered to be devoid of meaningful analgesic activity and physical dependence potential, irrespective of its structural similarities with morphine. There is apparently no report on the dependence potential in rats.

Yanagita et al. reported that intravenous self-administration of thebaine produced definite and significant withdrawal signs in rhesus monkeys (5). The results of this and more recent studies from our laboratory regarding the potent reinforcing effect of thebaine (6) suggested that the metabolite(s) might be responsible for the dependence potential of the thebaine.

Regarding the metabolism and disposition of thebaine, Misra et al. demonstrated with thin layer chromatography that codeinone, codeine, morphine, and 14-hydroxycodeinone are excreted in residual amounts in the urine of rats treated with *3H*-thebaine (7, 8), however the details of the metabolic fate of thebaine remain to be elucidated.

In the present study, the metabolism of thebaine was investigated in rhesus monkeys in an attempt to determine whether the findings in rats and rhesus monkeys, regarding the dependence potential of thebaine, could be attributed to species differences in the metabolic fate of the compound.
MATERIALS AND METHODS

Chemicals: Thebaine, codeine phosphate, and morphine hydrochloride were obtained from Sankyo Co., Ltd. (Tokyo, Japan). Codeinone was prepared by oxidation of codeine phosphate after the method of Bowers et al. (9). Normorphine, oripavine, and dihydrothebaine were synthesized by the methods of Von Braun (10), Rapoport et al. (11), and Homeyer (12), respectively. Authentic compounds of codeinone, normorphine, and norcodeine were kindly donated by Dr. S.J. Mule of the New York State Addiction Research Institute, while Dr. K. C. Reid of MacFarlan Smith Limited, U.K., graciously donated the authentic oripavine.

Thebaine N-oxide was synthesized as follows: thebaine (200 mg) was added to 4 ml of a mixture of 30% aqueous hydrogen peroxide and methanol (1:1), and the mixture was left to stand for 1 week at room temperature. After the methanol was distilled off, the solution was adjusted to pH 5 by adding sodium, potassium-phosphate, and then the mixture was extracted with chloroform-isopropanol (3:1). The residue of the organic extract was recrystallized from a benzene-acetone mixture. The yellowish crystal obtained gave a single spot in thin layer chromatography and was reduced back to thebaine by treatment with TiCl₃, a reagent used in the reduction of N-oxides to tertiary amines (13).

N,O-Bis-trimethylsilyl acetamide (TMS-BSA) and propionic anhydride were produced by Pierce (Rockford, Illinois, U.S.A.), and Wako Pure Chemical Industries (Osaka, Japan), respectively. NADP, glucose 6-phosphate, and glucose 6-phosphate dehydrogenase were purchased from Oriental Yeast Co., Ltd. (Tokyo, Japan), and β-glucuronidase was purchased from Sigma (St. Louis, Mo., U.S.A.).

Treatment of animals: Rhesus monkeys of both sexes (n=6) weighing about 6.9 kg were treated with single doses of thebaine at 8 mg/kg s.c. Urine specimens were collected for 24 hr prior to and 24 and 48 hr after administration and frozen for storage.

Enzymatic hydrolysis of the urine: β-Glucuronidase (Sigma type I, bacterial origin, 2000 units) was added to a 1 ml mixture containing 200 μl of urine and 200 μmoles of sodium, potassium-phosphate (pH 6.8). The mixture was incubated for 3 hr at 37°C.

Thin layer chromatography: A ten ml portion of urine (3–5% of the total urine from each monkey) was adjusted to pH 9 with 5% Na₂CO₃ or 2N NaOH, and then extracted with 10 ml of ethylacetate-isopropanol (10:1). After centrifugation at 2,500 rpm for 10 min, the upper layer (8.5 ml) was transferred to another tube and about 1 g of dibasic sodium phosphate (powder) was added to the aqueous layer, which was then re-extracted with the solvent described above. Combined organic extracts were evaporated to dryness under a current of nitrogen. The residue was dissolved with small amounts of methanol and applied to a silica gel plate (Merck Art 5567). After development with the solvent systems described in the Results section, compounds were located with ultra violet (UV) quenching (254 nm) and with various reactive reagents. To isolate the metabolites by thin layer chromatography, the areas corresponding to the thebaine metabolites on the silica gel plates were scraped off and the metabolites were extracted with methanol.

Gas chromatography: Gas chromatography was performed with a Shimadzu Model GC-6A gas chromatograph equipped with a flame ionization detector and a glass column (3 mm I.D. x 1 m) packed with 3% OV-1 coated on Chromosorb W HP (80–100 mesh), with a column temperature range of 235–280°C. An aliquot of the extracts was derivatized to propionyl derivatives using
propionic anhydride-pyridine (1:1) after Yeh et al. (14). After the excess reagents were evaporated off under a current of nitrogen at 40°C, 1–2 μl of the reconstituted solution (ethylene dichloride, 50 μl) was injected into the gas chromatograph. In order to convert metabolites to trimethylsilyl (TMS) derivatives, 5% (V/V) TMS-BSA in dry ethylacetate was added to the extracts and allowed to react for 30 min at 50°C.

Gas chromatography-mass spectrometry: The mass spectral data were obtained using a JEOL D-300 mass spectrometer equipped with a JMA 2000 computer system and a 20K gas chromatograph containing a glass column packed with 3% OV-1 coated on Chromosorb W HP (80–100 mesh). The temperatures of the injector, column, and ion source were 280, 235–280, and 260°C, respectively. The electron impact ionization mode was used for the analysis.

High performance liquid chromatography: High performance liquid chromatography (HPLC) was performed on a component system consisting of a 6000A solvent delivery pump, U6K injector,μBondapak C18 column (3.9 mm × 30 cm, Waters Assoc.), and a UV/DEc-100 II spectrophotometer (Japan Spectroscopic Co., Ltd.) monitored the absorbance at 280 nm. Unless otherwise stated, a mobile phase of acetonitrile-0.02M monobasic potassium phosphate (25:75) was used at a flow rate of 1.2 ml/min. A precolumn (3.9 mm × 2.5 cm) containingμBondapak C18 or Bondapak C18/carasil was utilized to prevent deterioration of the main column. In analyzing the urine metabolites, an aliquot of the urine was treated with an equal volume of acetonitrile and centrifuged at 2,500 rpm for 10 min after standing for 5 min. The resultant supernatant obtained was subjected to the analysis.

Microsomal incubation system: Microsomal fractions were prepared from a liver excised from a male, adult rhesus monkey by the method of Imai et al. (15). Protein concentration was determined by the method of Lowry et al. (16). The incubation mixture consisted of 0.8 mM NADP, 6 mM glucose 6-phosphate, 1 unit glucose 6-phosphate dehydrogenase, 6 mM MgCl2, 50 mM sodium, potassium-phosphate (pH 7.4), 1 mg protein of microsomes, and 0.5 μmole of thebaine or oripavine in a final volume of 1 ml. After 1.5 hr incubation at 37°C, the mixture was adjusted to pH 9 with 0.5 M dibasic sodium phosphate and 1 N sodium hydroxide solution, and then extracted with chloroform-isopropanol (3:1).

RESULTS
Thin layer chromatography of the extracts: To obtain preliminary information on the metabolic pathway of thebaine in rhesus monkeys, chloroform-isopropanol extracts of urine samples obtained from the monkey before and after treatment with thebaine were applied to a thin layer plate. As shown
in Fig. 1, thebaine was excreted unchanged in the urine and was identified by comparison of the RF values with the standard using the solvent system of ethylacetate-methanol-30% ammonium hydroxide (86:10:4). Excretion of thebaine in the urine was also detected with systems of chloroform-methanol-ethanol (8:1:1) and benzene-ethylacetate-methanol-30% ammonium hydroxide (800:100:100:0.5), (data not shown).

Moreover, by spraying iodoplatinate, a compound used to detect morphine-like compounds, four or more spots were observed in the chromatogram of the urinary extract of thebaine-treated monkeys, while no positive spot was detected in the extract of the control urine (Fig. 1). However, RF values of spots of the possible metabolites, M-1 (RF 0.39), M-2 (RF 0.23), M-3 (RF 0.15), and M-4 (RF 0.10) were in agreement with those of codeinone (RF 0.34), codeine (RF 0.31), morphine (RF 0.17), norcodeine (RF 0.12), or normorphine (RF 0.06). The spot tests of these metabolites with various reagents that react with phenolic or amino groups of organic compounds were examined (Table 1). M-1 and M-2 reacted with the reagents of ferric chloride-pyridine (dark brown) and phosphomolybdic acid-ammonium hydroxide (blue), both used in the detection of phenols. In addition, M-2 was also detected by sprays of the reagents, ninhydrin and nitroprusside.

Most narcotics are excreted in the urine in their conjugated forms (17, 18). To determine whether thebaine metabolites were also so excreted, enzymatic hydrolysis of the urine from thebaine-treated monkeys was attempted using β-glucuronidase. However, this treatment did not increase the amounts of M-1 and M-2 recovered from the urine, while acid hydrolysis of the same urine sample with 2N HCl at 100°C rather diminished the amounts of metabolites.

Gas chromatography of the extracts: In the gas chromatogram of the underivatized extracts of urine, no metabolite peak other than that of thebaine was observed (data not shown). After derivatization with propionic anhydride, a peak having a retention time of 5.7 min was detected (Fig. 2B), while no corresponding peak was demonstrated at this retention time in the control urine (Fig. 2A). The retention time of this peak was not identical with the peak of codeinone or the peaks of propionyl derivatives of codeine, morphine, norcodeine, and normorphine. The

| COMPOUND      | Iodoplatinate | Ammonium-phosphomolybdate | Ferric chloride-pyridine | Ninhydrin | Nitroprusside |
|---------------|---------------|----------------------------|--------------------------|-----------|--------------|
| M-1           | + (brown)     | + (blue)                   | + (dark brown)           | -         | -            |
| M-2           | + (brown)     | + (blue)                   | + (dark brown)           | + (red)   | + (purple)   |
| Thebaine      | + (brown)     | -                          | -                        | -         | -            |
| Codeinone     | + (brown)     | -                          | -                        | + (orange)| -            |
| Codeine       | + (brown)     | -                          | -                        | -         | -            |
| Morphine      | + (brown)     | + (blue)                   | + (dark brown)           | -         | -            |
| Norcodeine    | + (brown)     | -                          | + (red)                  | + (purple)| -            |
| Normorphine   | + (brown)     | + (blue)                   | + (red)                  | + (purple)| -            |

+, positive, -, negative. After thin layer chromatography with the same system as described in Fig. 1, reagents were sprayed on the plates, and the colors developed are shown in parentheses.
relationship between this metabolite and M-1 or M-2 was next investigated. After preparative thin layer chromatography of extracts of the monkey urine, the fractions containing M-1 or M-2 were derivatized to their corresponding propionates. The unknown metabolite peak found in the gas chromatogram had the same retention time as the peak obtained from the derivatized fraction of M-1. M-2 was also converted to a propionyl derivative which had a peak with a retention time of 6.0 min at 280°C.

**Mass spectral analysis of the metabolites:**
To obtain structural evidence for M-1 and M-2, their mass spectra were compared to those of compounds suspected of having related structures. As shown in Table 2, the propionyl derivatives of M-1 and M-2 had molecular ion peaks at m/e 353 and at m/e 395, respectively. Fragment ions probably formed by the loss of the propionyl group were also detected in these mass spectra as intense peaks at m/e 297 (M-1) and at m/e 339 (M-2). These mass spectra were not compatible with those of the propionyl derivatives of codeine, morphine, dihydrothebaine, 6-O-methylmorphine, norcodeine, or normorphine. M-1 and M-2 were also converted to their corresponding TMS

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**Table 2. Typical fragment ions of thebaine metabolites and the related compounds**

| Compound       | Free                  | Propionyl-derivative | Trimethylsilyl-derivative |
|----------------|-----------------------|-----------------------|---------------------------|
| M-1            | N.D.*                 | 353 (M⁺ 76)***        | 369 (M⁺ 100)              |
|                |                       | 287 (100)             | 364 (9), 286 (18)         |
| M-2            | N.D.                  | 395 (M⁺ 61)           | 427 (M⁺ 100)              |
|                |                       | 339 (95), 311 (100)   | 412 (15), 383 (29)        |
| Thebaine       | 311 (M⁺ 100)          |                       |                           |
|                | 296 (61)              |                       |                           |
| Codeinone      | 297 (M⁺ 100)          |                       |                           |
|                | 269 (11)              |                       |                           |
| Codeine        | 299 (M⁺ 100)          | 355 (M⁺ 100)          | 371 (M⁺ 100)              |
|                | 282 (8), 242 (10)     | 298 (18), 282 (58)    | 366 (10)                  |
| Morphine       | 285 (M⁺ 100)          | 397 (M⁺ 36)           | 429 (M⁺ 100)              |
|                | 268 (11), 267 (10)    | 341 (100), 324 (28)   | 414 (3)                   |
| Normorphine    | N.D.                  | 439 (M⁺ 3)            | 487 (M⁺ 100)              |
|                | 383 (16), 327 (5)     | 472 (24), 308 (37)    |                           |

*N.D. not detected, **M⁺ molecular ion, ***Numbers in parenthesis are relative intensities (%) of the ion compared to that of the respective base ion. Mass spectra were obtained by e.i. mode of GC-MS.
derivatives using TMS-BSA. In the mass spectra of TMS derivatives of M-1 and M-2, molecular ion peaks were detected at m/e 369 and at m/e 427, respectively. Typical fragment ion of trimethylsilylated compounds, M-15, were also detectable as prominent peaks in these mass spectra (Table 2).

Alkaline hydrolysis of the propionyl derivatives of M-1 and M-2: To examine the properties of the functional groups of M-1 and M-2, their propionyl derivatives were treated with 5% aq. potassium hydroxide-methanol (1:1) solution. As shown in Fig. 3, the propionyl derivative of M-1 was hydrolyzed to the parent compound, M-1, by exposure to alkaline solution. However, the same treatment converted the propionyl derivative of M-2 to a compound other than either M-2 or M-2-propionate, as shown by thin layer chromatography. After derivatization with TMS-BSA, this compound showed a molecular ion peak and a base peak at m/e 411 and at m/e 338, respectively.

High performance liquid chromatography of the extracts: The metabolites excreted in the urine were detected by the method of reverse-phase column chromatography. The supernatant of acetonitrile-treated urine was injected onto the column. As shown in Fig. 4, two peaks which were not observed in extracts of the control urine were eluted with retention times of 4.7 min and 3.8 min, respectively. The retention times of these peaks were identical with those of M-1 and M-2 obtained from preparative thin layer chromatography. Normorphine, morphine, codeine, codeinone, and thebaine were eluted in this condition with retention times of 2.1 min, 2.3 min, 3.6 min, 6.0 min, and 12.7 min, respectively.

Recently, N-oxide formation was reported to be a minor metabolic pathway of narcotics (19, 20). Further, the reduction of the 7,8-double bond of morphine is also known to occur in the monkey (14, 19). Therefore, thebaine N-oxide and dihydrothebaine were
examined as possible metabolites, but peaks with the retention times of these compounds (8.3 and 9.0 min) were not apparent in the monkey urine.

**UV spectra of the metabolites:** The absorption spectra of M-1 and M-2 which had been isolated by preparative TLC and HPLC were measured to obtain structural information on the metabolites. As shown in Fig. 5, the absorption maximum of M-1 was observed at about 286 nm, while in the spectrum of M-2, the absorption maximum was at about 283 nm.

**Identification of M-1:** As previously described, the mass spectra of M-1 suggested that this compound was a dealkylated product of thebaine. The existence of a phenolic hydroxyl group in M-1 was further demonstrated by the results of the spot test and alkaline hydrolysis experiments. These results are highly indicative that M-1 is 3-O-demethylated thebaine, oripavine. This conclusion was clearly evidenced by the comparison of M-1 with authentic oripavine using TLC, HPLC, GC-MS, and UV spectral
Analysis of metabolites formed in microsomal systems: Postulating the formation of M-1 (oripavine) and M-2 from thebaine via dealkylation by enzymes in the liver, the metabolism of thebaine in vitro was studied with hepatic microsomes from rhesus monkeys.

In agreement with results of the previously described in vivo experiments, the peaks of M-1 (oripavine) and M-2 were detected with HPLC in the extract of the incubation mixture containing liver microsomes, NADPH, and thebaine (Fig. 6-A). In addition, a peak was eluted from the column with a retention time of 10.2 min, which was not identical with those of the compounds described above. Mass spectra of TMS or propionyl derivatives of this metabolite indicated that this compound also was a dealkylated product of thebaine. The experiments with the nitroprusside and ninhydrin reagents strongly suggest that this metabolite was N-demethylated theaine, northebaine. Further, the absorption maximum of this compound (286 nm in 95% ethanol) was consistent with the value reported previously (21). In the chromatogram of the extract of the incubation mixture using M-1 (oripavine) as the substrate, M-2 was detected as a metabolite of oripavine (Fig. 6-B), and the formation of M-2 was also confirmed by thin layer chromatography (data not shown).

DISCUSSION

It has been established that morphine (14) and related compounds including codeine (22), ethylmorphine (23), hydrocodone (24), and oxycodone (20) are dealkylated at their 3,6-O- or N-alkyl positions prior to excretion from the body. Misra et al. reported that thebaine was converted to codeinone, codeine, morphine, and 14-hydroxycodeinone via 3- or 6-O-dealkylations in the rat following a 5 mg/kg, subcutaneous dose of 3H-thebaine (7).

In the present study, we isolated two new metabolites from the urine of monkeys treated with thebaine. The major metabolite, M-1, accounting for about 10% of the administered drug, was identified as oripavine in comparison with the synthetic standard using TLC, GC-MS and HPLC. Although Misra et al. had already suggested that oripavine was excreted in the urine of rats (7), isolation and unequivocal identification of this metabolite has apparently not been reported.

In the thin layer chromatogram of the urine extract (Fig. 1), another metabolite showing a lower Rf value than that of oripavine was detected. This compound reacted with reagents to detect phenols and amines (Table 1) and was converted to di-TMS or di-propionyl derivatives (Table 2). Molecular ions of both derivatives were in close agreement with predicted values for di-dealkylated thebaine. Moreover, one of the reactive functional groups of the propionyl derivative was readily hydrolyzed by alkaline solution but the other resisted this treatment (Fig. 3). These results indicated that M-2 is N,O-di-demethylated thebaine, nororipavine. This was further confirmed by the in vitro experimental results that M-2 (nororipavine) was formed during the incubation with NADPH, hepatic microsomes from rhesus monkeys, and oripavine. Nororipavine (M-2) was also formed in the incubation mixture containing thebaine as the substrate, but the amount formed was less, as compared to the experiment using oripavine.

In the incubation mixture containing hepatic microsomes from rhesus monkeys and thebaine, northebaine was identified as the metabolite using gas chromatography-mass spectrometry. The absorption maximum of this metabolite was in good agreement with the data reported previously (21). However, northebaine was not detected in the urine of
monkeys treated with thebaine in the present experiment. This result may indicate that northebaine formed by the dealkylation of thebaine is further metabolized to other compounds including nororipavine prior to excretion. It is also possible that nororipavine was formed from oripavine in rhesus monkeys as suggested by the in vitro experiments. Therefore, to clarify the metabolic pathway of thebaine to nororipavine, more detailed studies on the metabolism of thebaine are required.

In rats, the metabolites of thebaine excreted in the urine were reported to be formed by 6-O-dealkylation (7, 8). In this study, all compounds identified as the metabolites of thebaine in monkeys were formed both in vivo and in vitro through dealkylation of either or both the 3-O- and N-methyl groups. This difference in the metabolic pathway of thebaine is of special interest in relation to differences in the pharmacological effects of thebaine. Detailed studies of the metabolism of thebaine in rats and the pharmacological properties of oripavine in rats and monkeys are under way in our laboratory.

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