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# COMPARISON OF THE METABOLISM OF 3,4-DIMETHOXYPHENYLETHYLAMINE AND MESCALINE IN HUMANS

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**Abstract**—3,4-Dimethoxyphenylethylamine, mescaline, and placebo were administered at weekly intervals to eight subjects. More than 77 percent of the 3, 4-dimethoxyphenylethylamine administered was recovered as 3,4-dimethoxyphenylacetic acid. In contrast, mescaline in considerable amount was not recovered as either unmetabolized compound or acid metabolite. The administered mescaline that was recovered was found in somewhat larger measure as unchanged material. A lesser amount was recovered as 3,4,5-trimethoxyphenylacetic acid.

3,4-DIMETHOXYPHENYLETHYLAMINE (DMPEA) was recently found to be a constituent of urine obtained from schizophrenic patients,[1–4] although there is disagreement whether it is excreted only in this condition.[5, 6] It has been reported that this compound has effects in lower mammals similar to those produced by mescaline, which is trimethoxyphenylethylamine (TMPEA). It was therefore of interest to assess its action in humans and to compare the effects of DMPEA with those of mescaline (TMPEA). In a clinical study carried out at the Veteran's Administration Hospital in Palo Alto, California, DMPEA, TMPEA, or placebo was administered to patient volunteers. Three trials were conducted at weekly intervals.

On the first trial, a 500-mg dose of DMPEA was given to each patient. Either TMPEA or placebo was administered to the same patients on the second trial, the choice for each subject being determined at random. On the third trial, those subjects who received placebo on the second trial were given TMPEA, and those who had received TMPEA were given placebo. The dose of TMPEA in each case was 6 mg/kg, the range being 380 to 536 mg (mean 443 mg). The study had several objectives in addition to the one described here, so that identical doses of DMPEA and TMPEA could not be given. However, the procedure used resulted in generally similar doses of the two compounds, and no differences in results that were related to the small differences in dose were found.

Clinical effects were assessed by observation; self-report of patients on the Clyde mood scale prior to treatment, and at 2, 4, and 6 hr after; and by completion of a symptom–sign check-list after the effects of drugs had worn off. A 24-hr urine sample was collected from each subject after treatment. In all instances in which TMPEA was administered, a typical clinical syndrome ensued, but neither DMPEA nor PBO produced any discernible effects. The details of the clinical aspects of this study will be described in another publication.[7] In the present study, the urine from the first eight

subjects who were evaluated in the clinical study was analyzed in order to compare the metabolism of DMPEA and TMPEA.

In previous investigations numerous metabolites of TMPEA have been determined. An important route for the detoxification of TMPEA appears to be its deamination and oxidation to 3,4,5-trimethoxyphenylacetic acid (TMPAA).[8–10] Charalampous *et al.* found that this derivative does not appear to have significant pharmacological effects on humans.[11] These authors point out that species differences exist in the rate of conversion of TMPEA to TMPAA, but that there is evidence that considerable amounts of TMPEA are excreted unchanged. In humans, they found that only 26·2% of administered mescaline $^{14}C$ was excreted in urine as TMPAA after 12 hr, although 81·9% of administered radioactivity was recovered. In these subjects, therefore, most of the administered mescaline was excreted as unidentified material. Derivatives other than the acid have been described, including 3,4,5-trimethoxyphenylethanol[9] and products resulting from demethylation of one or more of the three methoxy groups,[12] but these compounds are formed in only small amounts.

The metabolism of DMPEA has been little studied in the past, and no reports of its metabolism in humans have been found. It has been demonstrated *in vitro* that this compound is a substrate for monoamine oxidase and it is therefore deaminated to its corresponding acid, 3,4-dimethoxyphenylacetic acid, by this enzyme, although the rate of metabolism of both DMPEA and TMPEA is not rapid when compared with unsubstituted phenylethylamine.[13]

Since differences in the behavioral effects of TMPEA and DMPEA on humans were observed[7] it was of interest to compare the metabolism of these compounds in the same subjects. It was therefore decided to study the excretion of TMPEA and TMPAA after the administration of a dose of TMPEA sufficient to produce behavioral effects and to compare this with the excretion of DMPEA and DMPAA after administration of a dose of DMPEA,

## EXPERIMENTAL

After treatment with one of the agents used in the study—DMPEA, TMPEA, or placebo—urine was collected for the next 24 hr. The specimens were frozen as collected and shipped in the frozen state by air express to New York University School of Medicine where analyses were carried out. Urines were thawed quickly by immersing in warm water. A creatinine determination was made by the Jaffe method, and a volume of urine equivalent to 200 mg of creatinine was taken as the sample. This was acidified to pH 1 and extracted three times with chloroform. The total volume of chloroform used in all three extractions was equal to the volume of the urine sample. The chloroform was dried over anhydrous sodium sulfate, evaporated to dryness, and the residue was suspended in a small volume of ethanol and subjected to gas chromatography. The aqueous phase was adjusted to pH 10 and extracted three times with chloroform in the same proportions as for the acid extract. The chloroform was dried over anhydrous sodium sulfate, evaporated, and the residue suspended in a small volume of ethanol for application to a gas-liquid chromatography column.

Gas chromatography was carried out in an F & M gas chromatograph, biomedical model 400, with a 4ft U-shaped column 4 mm in diameter. The column was packed with 3·8% silicone gum rubber SE 30 on Diatoport S. Column temperature was held at 210° for amines and 230° for the acids. Samples ranged between 2 and 5 $\mu$l.

TABLE 1. COMPOUNDS RECOVERED FROM URINE AFTER TREATMENT OF EIGHT MALE PATIENTS WITH DMPEA AND TMPEA

| | | | After treatment with DMPEA | | | | | | After treatment with TMPEA | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subject | Age | Diagnosis | Dose of DMPEA (mg) | Volume 24 hr (ml) | Creat. 24 hr (mg) | As DMPEA (%) | As DMPAA (%) | As DMPEA & DMPAA (%) | Dose of TMPEA (mg) | Volume 24 hr (ml) | Creat. 24 hr (mg) | As TMPEA (%) | As TMPAA (%) | As TMPEA & TMPAA (%) |
| 1 | 32 | Schizophrenic reaction | 500 | 1,440 | 2,117 | 0·3 | 79·6 | 79·9 | 498 | 1,966 | 1,677 | 9·8 | 17·0 | 26·8 |
| 2 | 36 | Schizophrenic reaction | 500 | 2,180 | 1,707 | 0·3 | 65·0 | 65·3 | 420 | 2,300 | 1,875 | 21·9 | 21·4 | 43·2 |
| 3 | 38 | Depressive reaction | 500 | 2,050 | 1,280 | 0·3 | 68·4 | 68·7 | 408 | 1,405 | 635* | 18·4 | 13·6 | 32·0 |
| 4 | 45 | Schizophrenic reaction | 500 | 1,280 | 1,265 | 0·1 | 42·6 | 42·7 | 437 | 1,947 | 1,860 | 18·3 | 15·0 | 33·3 |
| 5 | 45 | Depressive reaction | 500 | 2,072 | 990 | 0·7 | 95·0 | 95·7 | 408 | 1,670 | 1,534 | 22·3 | 10·9 | 33·2 |
| 6 | 45 | Schizophrenic reaction | 500 | 2,250 | 2,218 | 0·2 | 96·5 | 96·7 | 536 | 2,403 | 2,315 | 37·0 | 28·3 | 65·3 |
| 7 | 30 | Schizophrenic reaction | 500 | 1,900 | 1,989 | 0·5 | 94·0 | 94·5 | 460 | 1,935 | 1,853 | 31·3 | 24·3 | 55·6 |
| 8 | 50 | Depressive reaction | 500 | 2,915 | 1,317 | 0·5 | 75·6 | 76·1 | 380 | 2,005 | 1,477 | 26·1 | 13·3 | 39·4 |
| Mean | | | 500 | 2,010 | 1,610 | 0·4 | 77·1 | 77·5 | 443 | 1,953 | 1,653 | 23·1 | 18·1 | 41·2 |
| Std. Dev. | | | | 504 | 459 | 0·2 | 18·5 | 18·7 | | 317 | 486 | 8·4 | 5·9 | 13·2 |

* From the low creatinine value for this sample, it appears that the total 24-hr sample was not collected. However, this does not affect the overall result. Values are uncorrected for recovery.

in size and were injected directly onto the column. This was equivalent to approximately 10·0 mg of creatinine for DMPEA, 0·2 mg for TMPEA, 0·08 mg for 3,4-dimethoxyphenylacetic acid (DMPAA), and 0·4 mg for (TMPAA). The detector was a hydrogen flame device. With these methods, the recovery of compounds added to urine, in amounts comparable to those actually found in the samples collected from patients, was approximately 75% for the amines and 95% for the acids. Values reported throughout are uncorrected for recovery.

The identity of each compound studied was established by separate means. Both acids and bases were subjected to gas chromatography as free compounds, and their retention times were compared with those of authentic compounds. In addition, the high concentration of compounds excreted after the loading experiment permitted sample concetrations to be sufficiently dilute so that no peaks were found in urine from untreated subjects that corresponded to any of the four compounds that were determined. Each sample was co-chromatographed with an appropriate reference compound. Also, the identity of the acid metabolites DMPAA and TMPAA was further established by first acetylating the urine extract and then preparing methyl esters by the method of Williams and Sweeley.[14] These samples were compared with esters prepared in the same way from reference compounds.

The amount of both acids and amines excreted was determined in the gas chromatograph by introducing into the column amounts of reference material sufficient to match closely the height of each sample peak. That is, varying amounts of reference were injected into the gas chromatograph until a peak was obtained that closely matched each sample peak in height. This procedure was used rather than comparison with a standard curve because it allowed for correction for any changes in chromatograph sensitivity from trial to trial and minimized interpolations. Samples and references were chromatographed five times, and mean peak heights were calculated from these data.

## RESULTS AND DISCUSSION

Table 1 is a summary of the findings from this experiment. From the table it can be seen that after DMPEA treatment, 77·5% of the administered compound can be accounted for in a 24 hr urine sample. Only 0·4% was recovered as unmetabolized amine, and the remaining material was excreted as DMPAA. After TMPEA treatment, however, only 41·2% of administered material was recovered, 23·1% as TMPEA and 18·1% as acid.

Considerably more DMPEA and DMPAA than TMPEA and TMPAA were excreted during the first 24 hr after treatment. Either a considerable amount of TMPEA is not absorbed or else it is stored or is excreted as unidentified and undetected metabolites. The rapid conversion of DMPEA to acid may account for the lack of effect of DMPEA on human subjects after oral administration. This absence of behavioral effects is in contrast to the action of this compound in lower mammals[15, 16] in which it has been found that DMPEA and mescaline have an effect in a comparable dose range. Some differences in the conversion and excretion rate of DMPEA exist among the various patients in the study. However, the patient sample is not sufficiently large to permit intragroup comparison.

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