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The Synthetic Drug 3-Methylfentanyl: Identification and Quantitation of Powdered Samples

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ABSTRACT: Paraphernalia, residue in plastic bag corners, and powdered street samples analyzed by gas chromatography/mass spectrometry (GC/MS) revealed the presence of cis and trans isomers of 3-methylfentanyl (3-MF). The isomers were differentiated by their retention times and by the smaller abundance ratios of ions at *m/z* 160 and 203 to the base ion of 259 for the more stable trans isomer.

Quantitation of powdered samples was accomplished using a gas chromatograph/mass spectrometer with a HP5 column (25 m by 0.20 mm) and ketamine as an internal standard. Two cut street samples revealed higher percentages of the more potent cis isomer (0.26 and 0.37%) than the trans isomer (0.15 and 0.16%). With an average purity of 0.47% (4.7 μg/mg), about 100 μg of 3-MF would be present in a typical 20-mg packet, in comparison with 2000 μg of heroin with an average street composition of 10%. Since the potency of 3-MF is about 1000 times that of heroin, the 3-MF samples should have been diluted another 50-fold to contain about 0.1 μg/mg. The difficulty of cutting and inexperience with 3-MF contributed to the rash of overdoses in our area.

KEYWORDS: toxicology, 3-methylfentanyl, fentanyl, heroin, synthetic drugs

In 1984, an analog of fentanyl identified as 3-methylfentanyl (3-MF) and sold on the street as "China White" appeared as a street drug for the first time in California [*1*]. It was given the term "designer drug," in that it was synthesized to produce the desired effects in the drug user and avoid being on the list of controlled substances [*1*]. At present, it and many other fentanyl analogs are controlled by the U.S. Drug Enforcement Administration.

In October and November of 1988, a rash of overdoses occurred in the Pittsburgh, Pennsylvania, area, some of which were fatal. With several of these initial overdoses, miscellaneous items such as plastic bag corners or spoons with residues were found on the person or at the scene. These items, along with the normal postmortem biological specimens, were submitted to the Allegheny County Department of Laboratories for toxicological testing. Most of the overdoses occurred in a certain section of the city, so street samples of what was being called "super-heroin" were purchased by undercover narcotic agents and submitted to the drug chemistry section for analysis. Through analysis of the powder residues found with the overdose victims and the initial purchased street samples, the authors were able to identify the drug as 3-MF. We are reporting on several

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of the techniques used to identify the drug in powder specimens and on the purity of the drug as found in several street samples.

Methods

Thin-Layer Chromatography

Four different solvent systems were employed to separate 3-MF from other components. In all of the systems, the drug ran near the solvent front. The compounds were visualized with acidified iodoplatinate. The thin-layer chromatography (TLC) systems were the following:

(*a*) ethyl acetate/chloroform/methanol/ammonium hydroxide (50:30:12:15),
(*b*) isopropyl ether/methanol-saturated sodium bromide (60:40),
(*c*) chloroform-saturated ammonia/methanol (18:1), and
(*d*) chloroform/methanol (9:1).

Gas-Liquid Chromatography

Using a gas chromatograph (GC) equipped with a nitrogen/phosphorus detector, *trans*-3-MF emerged at 12.52 min, and *cis*-3-MF at 12.7 min on a 15-m by 0.53-mm DB-17 column, with retention times relative to lidocaine of 2.43 and 2.47, respectively.

The following parameters were employed: Initial temperature = 140°C; initial time = 0 min; program rate = 10°C/min; final temperature = 270°C; final time = 2 min; injector and detector temperature = 290°C; helium flow = 20 mL/min.

Gas Chromatography/Mass Spectrometry

Electron impact mass spectra were acquired from a Hewlett-Packard Model 5970 mass selective detector. The retention times for *trans*-3-MF and *cis*-3-MF were 18.3 and 19.2 min, respectively, produced on a 25-m by 0.2-mm HP-5 column with these parameters: splitless; purge-off time = 0.75 min; initial temperature = 60°C; initial time = 2 min; program rate 1 = 70°C/min; final temperature 1 = 200°C; final time 1 = 1 min; program rate 2 = 10°C/min; final temperature 2 = 270°C; final time 2 = 20 min; injector = 250°C; transfer line = 280°C.

Quantitation of Powdered Samples

The purity of 3-MF in street samples was determined using the above gas chromatography/mass spectrometry (GC/MS) configuration. Selected ion monitoring was employed with a monitoring of *m/z* 259 for 3-MF and *m/z* 180 for the internal standard ketamine.

Samples were prepared by dissolving 10 mg of powder in 1 mL of a ketamine methanolic solution (20 mg/L). The calibration standards for *cis*-3-MF ranged from 25 to 300 mg/L and for *trans*-3-MF from 8 to 200 mg/L. The cis and trans powders used for standards were obtained from Janssen Research Foundation, Beerse, Belgium. The standard curves were linear for both compounds ($Y = 14.96X - 0.061$, $r^2 = 0.9837$ for *cis*-3-MF; $Y = 26.26X - 0.2859$, $r^2 = 0.9712$ for *trans*-3-MF). The coefficient of variation was less than 2% for both isomers at a level of 50 mg/L ($n = 3$). The detection limit was about 0.5 mg/L. Accuracy was demonstrated by the analysis of an ampule containing 10 mg/L *trans*-3-MF (Janssen Life Sciences Products, Piscataway, New Jersey). The relative error was less than 11%.

Results and Discussion

Identification of 3-Methylfentanyl

A total ion chromatogram (TIC) of a typical street sample containing 3-MF is shown in Fig. 1. All the samples tested contained the two diastereoisomers *trans*- and *cis*-3-MF. Figure 2 displays the structures and mass spectra of *cis*- and *trans*-3-MF.

The structure of 3-MF is exactly the same as that of the pharmaceutical compound fentanyl, except that a methyl group is present at the 3 position of the piperidine ring. In the chair conformation, the cis isomer has the methyl group in the axial position and the trans isomer in the equatorial position. The ions formed by fragmentation of the isomers are nearly identical. There is no ion at its molecular weight of 350. The base ion 259 is formed by the cleavage of a benzyl radical [*2*]. The extent of further fragmentation of the base 259 ion will depend upon the stability of the ion [*2*]. Of the two isomers, the trans isomer is more stable, so there is less fragmentation of its base ion in comparison with the cis isomer. Thus, the principal feature that distinguishes the two spectra is the larger abundance of *m/z* 160 and 203 ions relative to the base ion 259 for the cis isomer (Fig. 2). In all samples analyzed, the relative abundance of the 160 ion in comparison with the 259 ion ranged from 35 to 57% for the cis isomer and from 19 to 32% for the trans isomer; thus, the cis isomer showed a 1.5 to 2.0 times greater abundance of the 160 ion. The relative abundance of the 203 ion in comparison with the 259 ion ranged from 32 to 46% for the cis isomer and from 10 to 14% for the trans isomer, and here the 203 ion of the cis isomer was 2.8 to 3.8 times more abundant. The 203 ion is formed after the removal of a propionyl group and the 160 ion is from further fragmentation of the piperidine ring [*2*].

Two other compounds frequently appeared in street samples varying in amounts relative to the isomers of 3-MF. These compounds eluted at 14.17 and 14.31 min (Fig. 1). Based on their mass spectra (Fig. 3) and the pathway of synthesis [*3*], these compounds are probably isomeric precursors of the final compound before the addition of a propionyl group (despropionyl-3-methylfentanyl or *N*-[1-(2-phenylethyl)-3-methyl-4-piperidi-

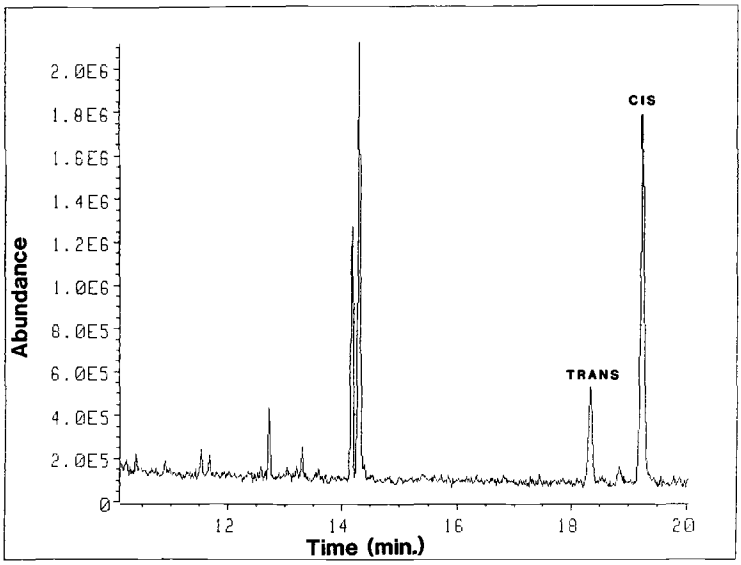

FIG. 1—*A total ion chromatogram of a street sample of 3-methylfentanyl.*

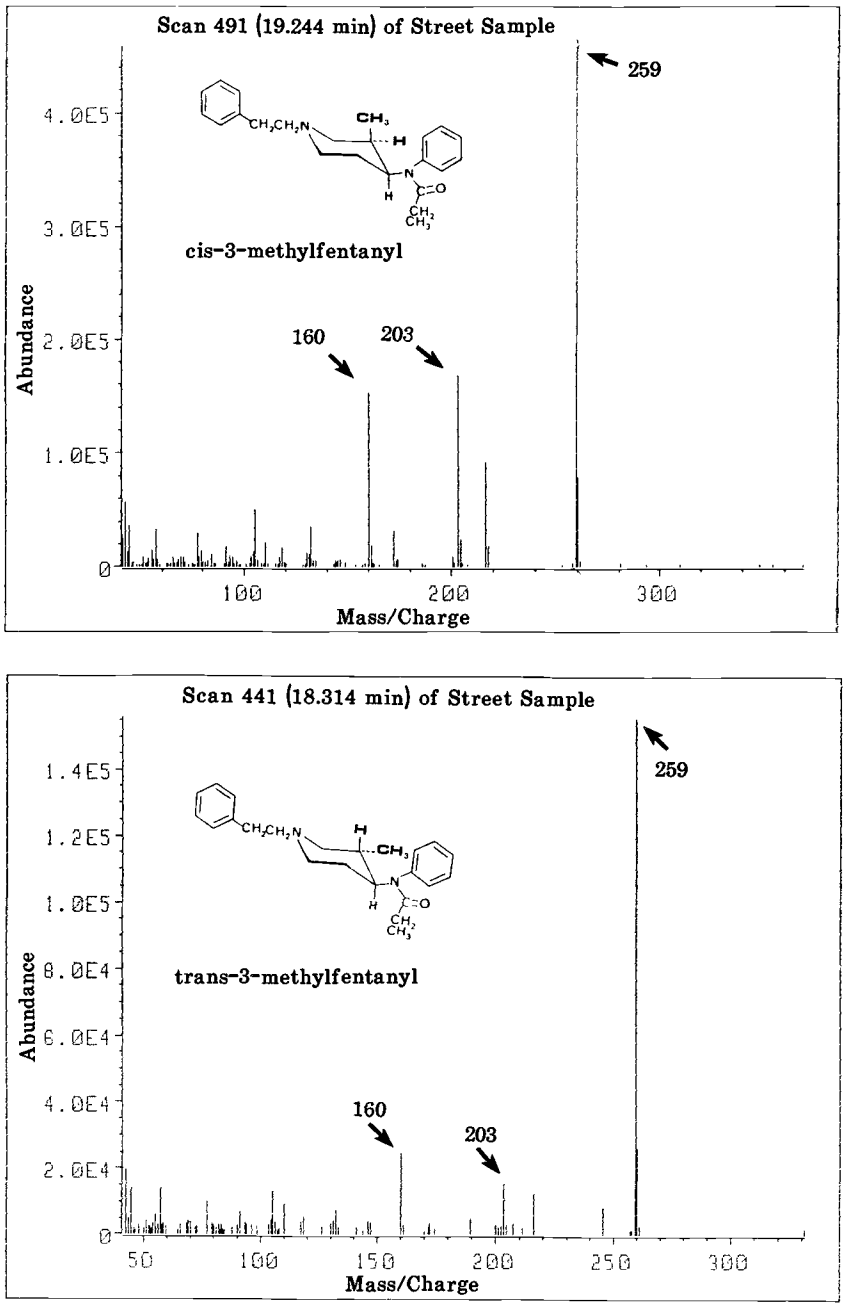

FIG. 2—*Electron mass spectra of the isomers of a 3-methylfentanyl street sample.*

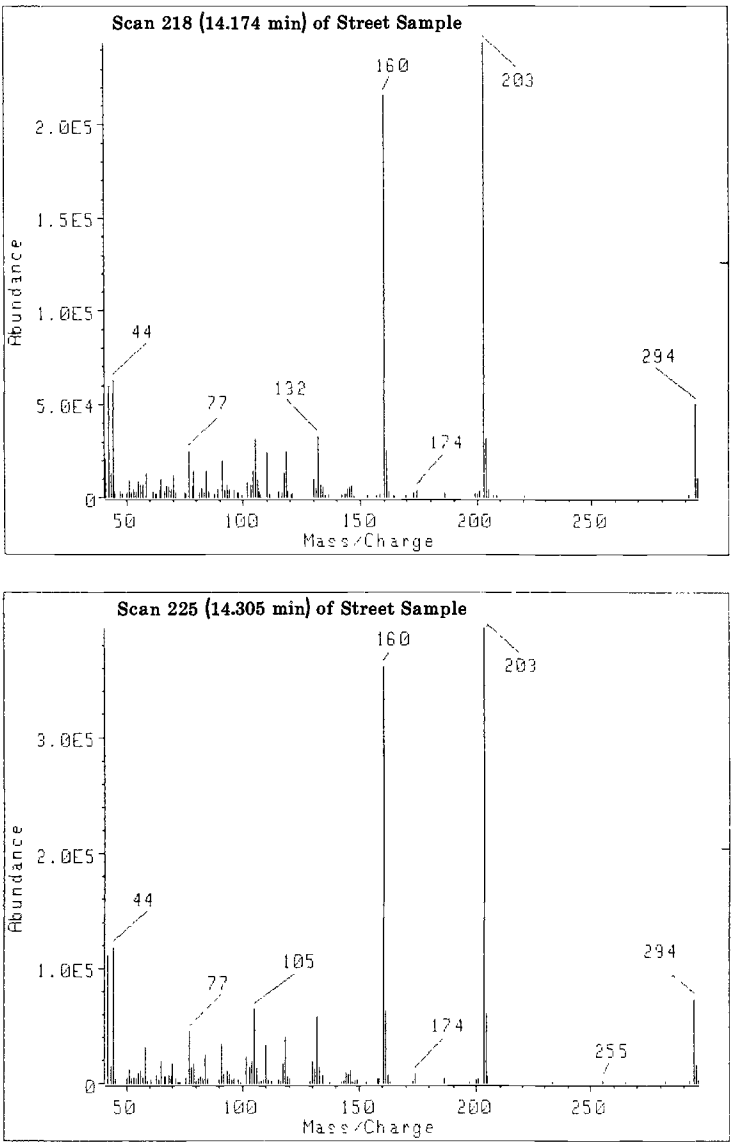

FIG. 3—*Electron impact mass spectra of two precursors appearing in Fig. 1.*

nyl]aniline). As with 3-MF, removal of a benzyl radical from the molecular ion 294 and further cleavage of the piperidine ring produces *m/z* ions of 203 and 160.

Thin-layer and gas-liquid chromatography were used in addition to GC/MS for identifying adulterants. Of the 14 cases submitted for analysis (many with multiple items), 4 cases had other drugs present besides 3-MF. In 2 cases cocaine was present; 1 case had heroin and quinine present and 1 had quinine. Dextrose was identified as being present in several cases and was probably the major adulterant, although its presence was not confirmed in most cases because of the small sample size.

Quantitation of 3-Methylfentanyl

Table 1 summarizes the quantitative results for 3-MF from three street samples. In all three cases, the cis isomer, which is more potent pharmacologically [*4*], was present in a greater percentage than the trans isomer.

Specimens from Cases No. 4011 and 4485/A were probably prepared for street distribution in that they were packaged in knotted plastic bag corners. Their appearance was that of an off-white powder with a slightly coarse texture. Their average content of 4.7 μg/mg was higher than that of street samples of a similar synthetic street drug, alpha-methylfentanyl, which were reported to contain 0.4 to 0.9 μg/mg [*5*]. The third specimen (Case No. 4485/B) had a purity and appearance different from those of the other samples. Its purity was about five times greater and its appearance was that of a yellowish powder with a coarse texture. Because of the course of events and other items confiscated from the individual's residence, this specimen may have represented the purity of the manufactured sample as it was prepared by the clandestine chemist, before it was distributed to drug dealers for further dilution and preparation for sale.

The drug 3-MF is a synthetic narcotic analgesic with all the properties of an opiate, including a strong euphoric effect and the acute toxic effect of respiratory depression [*6*]. Since the pharmacological actions of 3-MF are similar to those of heroin, the drug is usually taken by heroin addicts.

Table 2 compares doses of 3-MF with typical heroin doses. The average purity of the two cut street samples of 3-MF was 0.47% (4.7 μg/mg). We have found that the average purity of street heroin samples in the Pittsburgh area is about 10% (100 μg/mg). At a

TABLE 1—*The purity of 3-methylfentanyl in three street samples, in percentages.*

Case No.	Cis	Trans	Total
4011	0.37	0.16	0.53
4485/A	0.26	0.15	0.41
4485/B	1.81	0.61	2.42

TABLE 2—*Comparative doses of 3-methylfentanyl and heroin.*

	3-MF	Heroin
Average purity		
%	0.47	10
μg/mg	4.7	100
Package size, mg	20	20
Amount per package, μg	100	2000
Potency	1000	1
Equivalent doses, μg	2	2000
Doses per 1 g	500 000	500

package size of 20 mg for both drugs, the amount of drug per package would be about 100 μg for 3-MF and 2000 μg for heroin. The potency of 3-MF, based on the tail withdrawal reflex of laboratory rats, is about 1000 times that of heroin [*4*]. If 2000 μg of heroin is found in a typical package dose, then 2 μg should be present in a 3-MF sample. But the 3-MF street samples we analyzed revealed about 100 μg/package unit; thus, the street samples should have been diluted another 50-fold to contain about 0.1 μg/mg or 2 μg in a 20-mg package unit. It has been estimated that a fatal dose of *cis*-3-methylfentanyl is about 300 μg for a 70-kg man with positive ventilation and less than 300 μg without ventilation [*2*]. Hence, a possible explanation for many of the 3-MF overdoses could be the improper dilution and preparation of street samples.

If we conclude that 2 μg of drug should be present in a 20-mg package unit, then 1 g of pure 3-MF could be diluted to 500 000 package doses for street consumption, in comparison with 500 for heroin. This, plus high profitability, elimination of drug smuggling, easy concealment of small quantities of 3-MF, the difficulty in detecting the drug in biological and powder samples, similarities in its effects to those of heroin, and illegal production in legitimate laboratories [*1*], makes the manufacturing and distribution of this drug an attractive enterprise to the drug community.

This drug also provides an illustration of the importance of analyzing paraphernalia and residues in plastic bag corners and spoons and other items found on the deceased or at the scene. Prior analysis of the solid dose form will alert the toxicologist to analyze for this drug, since most routine screens for drugs of abuse in biological specimens do not include this synthetic drug.

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