

Urinary Concentrations of Morphine and Codeine After Consumption of Poppy Seeds

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Abstract

A quantitative analysis of morphine and codeine in human urine was performed after oral intake of cakes containing commercially available poppy seeds in order to estimate the possibility of positive doping results. Therefore, eight products from different manufacturers (poppy seeds or baking mixtures) and origin were obtained and analyzed by gas chromatography–mass spectrometry for the presence of the alkaloids. One selected batch of poppy seeds was used as an ingredient in a typical cake and was the object of an excretion study with nine volunteers. After application, several urine specimens contained morphine with concentrations higher than 1 µg/mL, and peak values of approximately 10.0 µg/mL were detected. Because the International Olympic Committee set a cutoff limit for morphine at 1 µg/mL, high-performance athletes could possibly test positive in doping control after consumption of products containing poppy seeds.

Introduction

Since 1968, the International Olympic Committee (IOC) has prohibited doping substances and methods; this change was initiated by the sudden death of cyclist Tom Simpson in 1967 during his participation in the Tour de France. The first list of banned substances contained the classes of amphetamines and narcotics such as morphine, which were already tested for in 1968 in Mexico City (Olympic summer games) and Grenoble (Olympic winter games) (1). In 1996, the International Amateur Athletic Federation (IAAF) first officially mentioned a cutoff limit for morphine concentrations in human urine of 1 µg/mL (2), and the IOC added this limit to its medical code in 1998 (3). This was based on studies showing a possible occurrence of morphine caused by the metabolism of allowed medicines containing codeine (4) and other investigations proving the presence of alkaloids in commercially available poppy seeds with alkaloids including morphine and codeine (5–10).

The aim of this study was to determine the possibility of positive morphine test results caused by the intake of common poppy seed products available in Germany. Therefore, poppy seeds from different shops and of different origins were tested for alkaloid residues, and urine samples collected after the oral intake of cakes prepared with these products were analyzed quantitatively for morphine and codeine.

Experimental

Chemicals

Codeine hydrochloride, ethylmorphine hydrochloride, and imidazole were purchased from Sigma (Deisendorf, Germany); β-glucuronidase/arylsulfatase (from *Helix pomatia*) was from Boehringer (Mannheim, Germany); ethylacetate was from Kraemer & Martin (St. Augustin, Germany); and *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (MSTFA) was from Chem. Fabrik Karl Bucher (Waldstetten, Germany). Morphine hydrochloride was a gift from the Institute of Forensic Medicine of the University of Cologne.

Materials and methods

The analyses were performed on an HP5890 gas chromatograph interfaced to an HP5971 mass selective detector after enzymatic hydrolysis of the urine or poppy seed specimens, liquid–liquid extraction, and subsequent trimethylsilylation of the analytes. Sample preparation comparable to methods reported in the literature (11–13) was performed using ethylmorphine as internal standard. The ions selected for quantitation were *m/z* 429 and *m/z* 371 for morphine-bis-TMS and codeine-TMS, respectively.

Results and Discussion

Morphine content of poppy seeds

Eight poppy seed specimens from different suppliers or ori-

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gins were obtained commercially in supermarkets, health food shops, or bakeries and tested for traces of a possible content of morphine and codeine. In Table I, the individual data concerning origin, country, and morphine concentration are summarized. Every charge contained morphine and codeine and especially one (number 3) showed high amounts of morphine with 151.6 $\mu\text{g/g}$ of poppy seeds. The analysis of a second package of the same batch number lead to comparable results while other batches of the same manufacturer contained only low amounts of 1.1 $\mu\text{g/g}$. The codeine values of all products were negligible.

Excretion study with poppy seed cake

The batch containing high concentrations of morphine (number 3, Table I) was used as ingredient for a typical poppy seed cake, and 9 healthy volunteers aged 25–48 (2 females and 7 males, Table II) consumed different numbers of pieces. Because of precise preparation of single cake pieces the amount of applicated poppy seeds was known, and thus the amount of orally administered morphine was also known. In Table II, the consumption of poppy seeds and morphine by the different volunteers is listed.

The qualitative evidence for the presence of morphine or codeine in urine or poppy seed samples was performed by means of three diagnostic ions. The bis-TMS-derivative of mor-

phine generates the fragments m/z 429, m/z 414, and m/z 236 (Figure 1) and codeine m/z 371, m/z 343, and m/z 178 (Figure 2). The quantitation of morphine and codeine was done by peak-area ratios of the ions m/z 429 or m/z 371 (codeine) and m/z 385 (ISTD), respectively.

The complete urine of all volunteers was collected in aliquots for 24 h after consumption and a final sample was taken after 46–48 h. In Table III, the concentrations of morphine in micrograms per milliliter are presented for every urine sample collected from each volunteer. Those values above 1 $\mu\text{g/mL}$ are bolded. Because concentrations of morphine higher than 4 $\mu\text{g/mL}$ of urine were not expected prior to this study, the values above 4 $\mu\text{g/mL}$ are estimated, based on the prepared calibration curve.

It is obvious that every volunteer showed a positive doping result at least at two sample collections according to the IOC rules. Most participants had urinary morphine concentrations higher than 1 $\mu\text{g/mL}$ for several hours, and one volunteer (V8) showed a maximum concentration of approximately 10.0 $\mu\text{g/mL}$ of urine. The 48-h urine sample from this subject still contained morphine at a concentration of more than 1 $\mu\text{g/mL}$. The determination of codeine in the collected urine samples showed concentrations of 0.06–0.82 $\mu\text{g/mL}$.

Several other articles published on this topic describe comparable results and findings concerning the content of morphine and codeine in commercially available poppy seeds. The reported concentrations vary from 17 to 294 $\mu\text{g/g}$ (10) and are responsible for urinary morphine concentrations reaching peak values of 18 $\mu\text{g/mL}$ of urine (14). Obviously, the problem of positive morphine drug tests after the consumption of poppy seeds is present in different countries and should also be taken into consideration in doping control analyses. A possible support for

Table I. Products Investigated for Possible Morphine Contamination, Place of Acquisition, and Analyzed Morphine Content

No.	Trade name/ composition	Store	Origin	Morphine content ($\mu\text{g/g}$)
1	Neuform®	health food shop	Denmark	8.4
2	Neuform®	health food shop	Hungary	6.9
3	Müller's Mühle®	supermarket	unknown	151.6
4	Insula®	supermarket	unknown	2.1
5	FJD®	supermarket	unknown	4.1
6	Rapunzel®	health food shop	Turkey	0.8
7	Davert®	health food shop	Turkey	0.9
8	baking mixture	bakery	unknown	0.6

Table II. List of Volunteers with Details of Oral Intake of Poppy Seeds

Volunteer	Gender	Body weight (kg)	Poppy seed intake (g)	Morphine intake (mg)	Duration of application (min)
V1	female	62	12.5	1.6	20
V2	male	79	16.8	2.2	10
V3	female	68	16.3	2.1	20
V4	male	81	29.9	3.9	40
V5	male	77	31.9	4.2	60
V6	male	88	30.5	4.0	45
V7	male	83	36.4	4.8	30
V8	male	70	38.1	5.0	60
V9	male	67	52.3	6.8	120

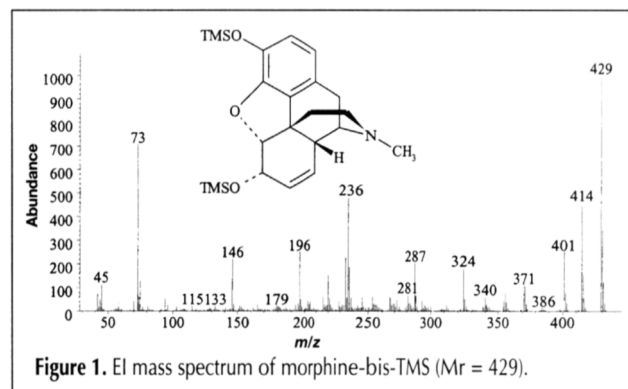


Figure 1. EI mass spectrum of morphine-bis-TMS ($M_r = 429$).

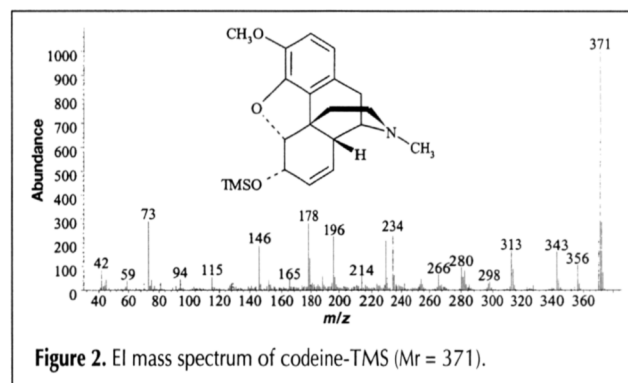


Figure 2. EI mass spectrum of codeine-TMS ($M_r = 371$).

the so-called "poppy seed defense" of athletes is demonstrated by Cassella et al. (15), who investigated the presence of thebaine in urine specimens of poppy seed eaters and true drug abusers.

The particular alkaloid was detected only in the case of poppy seed consumption and not after administration of morphine, codeine, or street heroin.

Table III. Concentrations of Morphine in Urine Samples of Volunteers after Oral Intake of Poppy Seeds*

V1		V2		V3	
Morphine application: 1.8 mg		Morphine application: 2.4 mg		Morphine application: 2.5 mg	
Time after application (h)	Conc. ($\mu\text{g/mL}$)	Time after application (h)	Conc. ($\mu\text{g/mL}$)	Time after application (h)	Conc. ($\mu\text{g/mL}$)
2.00	0.06	2.00	1.50	2.50	1.76
4.00	0.79	4.25	5.88	4.50	2.75
6.00	0.93	6.25	3.55	6.25	2.61
8.25	1.12	8.00	1.03	9.50	0.78
11.00	1.93	9.50	0.37	10.25	1.04
12.75	0.83	12.00	1.53	13.50	0.19
21.25	0.50	21.00	0.74	21.50	0.34
24.00	0.40	24.00	0.31	24.50	0.70
46.00	0.23	46.00	0.23	46.00	0.34
V4		V5		V6	
Morphine application: 4.7 mg		Morphine application: 4.5 mg		Morphine application: 4.4 mg	
Time after application (h)	Conc. ($\mu\text{g/mL}$)	Time after application (h)	Conc. ($\mu\text{g/mL}$)	Time after application (h)	Conc. ($\mu\text{g/mL}$)
2.00	1.40	2.00	2.96	2.00	0.55
4.00	3.23	4.00	5.76	4.00	3.46
6.00	3.91	6.00	1.98	6.00	3.53
8.00	3.08	8.00	0.71	8.00	2.44
10.00	2.49	10.00	1.72	10.00	1.73
14.25	1.95	12.00	1.60	14.50	1.14
21.75	1.50	21.75	1.46	19.75	0.84
24.50	0.99	24.00	0.84	24.00	0.83
48.00	0.28	46.25	0.20	43.75	0.24
V7		V8		V9	
Morphine application: 5.3 mg		Morphine application: 5.6 mg		Morphine application: 7.7 mg	
Time after application (h)	Conc. ($\mu\text{g/mL}$)	Time after application (h)	Conc. ($\mu\text{g/mL}$)	Time after application (h)	Conc. ($\mu\text{g/mL}$)
2.00	1.39	2.25	2.57	2.00	2.14
4.00	4.50	4.00	8.36	4.00	5.25
6.00	5.90	6.00	10.04	6.00	5.88
8.00	5.16	8.25	9.54	8.00	5.09
10.00	3.50	12.00	6.92	10.00	4.55
12.00	2.97	21.00	3.63	20.00	2.22
14.75	1.65	24.00	1.25	24.00	1.17
21.00	0.79	47.50	1.21	44.00	0.25
24.00	0.43				
45.00	0.36				

* All values higher than 1 $\mu\text{g/mL}$ are bolded and would represent positive test results according to the IOC rules.

Conclusions

The results of this study point out the possibility of a positive doping test according to the rules of the IOC. Athletes being selected for doping controls may be sanctioned because of urinary morphine concentrations higher than the established cutoff limit of 1 $\mu\text{g/mL}$ that are caused by the intake of food containing poppy seeds. Contamination of poppy seeds is obviously present in various amounts in many products commercially available in Germany and may be reason for the presence of morphine in urine specimens of athletes in a high concentration. The present data show that, even 48 h after the oral intake of cake containing poppy seeds, the urinary level of morphine can exceed the allowed threshold. Morphine is not one of those compounds that are administered in training periods, and thus it is not analyzed in out-of-competition tests. The consumption of poppy seed products in those out-of-competition time spaces might be considered as non problematic, but the long length of stay of morphine in urine samples can lead to positive doping results in competition tests up to two days after oral intake of poppy seeds, although this phenomenon was only proven in one volunteer after consumption of high amounts of poppy seeds. The presented data may be used for education of athletes concerning the possible problems arising with products containing poppy seeds. Thus, athletes should avoid such foods before and during participation at competitions.

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