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Renal excretion profiles of psilocin following oral administration of psilocybin: a controlled study in man

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Abstract

In a clinical study eight volunteers received psilocybin (PY) in psychoactive oral doses of 212 ± 25 μg/kg body weight. To investigate the elimination kinetics of psilocin (PI), the first metabolite of PY, urine was collected for 24 h and PI concentrations were determined by high-performance liquid chromatography with column switching and electrochemical detection (HPLC-ECD). Sample workup included protection of the unstable PI with ascorbic acid, freeze-drying, and extraction with methanol. Peak PI concentrations up to 870 μg/l were measured in urine samples from the 2–4 h collection interval. The PI excretion rate in this period was 55.5 ± 33.8 μg/h. The limit of quantitation (10 μg/L) was usually reached 24 h after drug administration. Within 24 h, 3.4 ± 0.9% of the applied dose of PY was excreted as free PI. Addition of β-glucuronidase to urine samples and incubation for 5 h at 40 °C led to twofold higher PI concentrations, although 18 ± 7% of the amount of unconjugated PI was decomposed during incubation. We conclude that in humans PI is partially excreted as PI-*O*-glucuronide and that enzymatic hydrolysis extends the time of detectability for PI in urine samples.

Keywords: Psilocybin; Psilocin; Pharmacokinetics; Excretion; HPLC-ECD; Human study

1. Introduction

Psilocybin (PY, Fig. 1) is a psychoactive indolealkylamine with a unique hallucinogenic profile. The widespread use of PY-containing mushrooms (e.g. *Psilocybe cubensis*, *Psilocybe semilanceata*) as a recreational drug is well documented [1–5]. The increasing popularity of 'magic mushrooms' is also due to the relatively easy access to psychoactive fungi and cultivation kits via the Internet [6] and 'smart shops' in Europe. In recent years, PY also has become an important experimental tool to study the neurobiological basis of altered states of consciousness. An increasing number of scientific publications reveal a renaissance of research with PY [7–15]. In contrast to these projects, mostly dealing with the

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"model-psychosis" paradigm, only a few studies have investigated the pharmacokinetic properties of PY in man [16–19]. In vivo, PY is rapidly dephosphorylated to the pharmacologically active hydroxy metabolite psilocin (PI, Fig. 1) [17–19]. Investigations in rats [20] and humans [16–18] revealed the metabolic formation of 4-hydroxyindol-3-yl-acetic acid (4-HIAA) and 4-hydroxytryptophol (4-HTP) by deamination and oxidation of PI.

Eivindvik and Rasmussen [21] postulated the formation of psilocin-*O*-glucuronide (PI-G, Fig. 1) in a manner analogous to the formation of 5-hydroxytryptamine-*O*-glucuronide in serotonin metabolism. Recently, Sticht and Käferstein [22] analyzed PI in urine and serum from a recreational mushroom user. Their analysis of the untreated urine found 0.23 mg PI/l. When the urine was first treated with glucuronidase, however, they measured 1.76 mg PI/l, clearly implicating the formation of the glucuronide. The corresponding concentrations for PI in serum were 0.052 mg/l (total) and 0.018 mg/l (unconjugated), respectively. The isolation of PI-G from biological samples and confirmation of the chemical structure by spectroscopic methods has not yet been performed, thus direct evidence for the existence of this metabolite is still lacking. Nevertheless, the manifold higher concentrations of PI measured after sample hydrolysis and the selectivity of the β-glucuronidase used for conjugate cleavage in the experiments of Sticht and Käferstein [22] strongly support the hypothesis of metabolic formation of PI-G in humans.

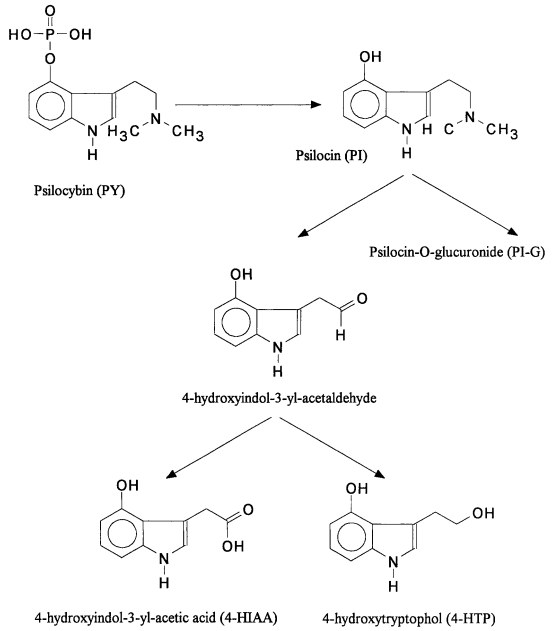

Fig. 1. Metabolism of PY.

Up to the present, only a very limited number of analytical methods for the determination of PI in biological samples have been published. Paper chromatography [20,23] and later high-performance liquid chromatography with electrochemical detection (HPLC-ECD) [24] were used to investigate the metabolism of PY in rats. For metabolism studies in humans, HPLC-ECD methods with different sample workup strategies (liquid–liquid extraction and automated on-line solid-phase extraction) were established [16,19]. For use in the field of forensic toxicology, a method involving gas chromatography–mass spectrometry (GC–MS) after derivatization of PI with *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (MSTFA) was recently published [22]. For reliable determination of PI and 4-HIAA in plasma samples obtained from two clinical trials investigating the pharmacokinetic properties of oral and intravenous PY in man, we established a novel HPLC–ECD method with column-switching [17,18]. In contrast to other methods, sample workup includes protection of the highly oxidation-labile phenolic analytes [17–19] with ascorbic acid, freeze-drying, and in-vitro microdialysis. In order to achieve a more complete characterization of the PY pharmacokinetics derived from PI-plasma concentration data investigated in two earlier clinical studies [17,18], the analytical method was also adapted for determination of PI in urine samples. Validation of the modified analytical method, renal excretion profiles of free and conjugated PI, as well as pharmacokinetic estimates derived from eight volunteers receiving active oral doses of PY are presented in this paper.

Table 1
Subjects and dosage of PY

Subject	Sex	Age (years)	Weight (kg)	Dosage of PY (μg/kg b.wt.)	Dosage of PY (mg)
A	m	30	59	272	16
B	f	29	54	203	11
C	f	27	60	200	12
D	f	28	56	196	11
E	m	34	62	210	13
F	m	46	87	207	18
G	f	32	52	192	10
H	m	39	85	212	18
Mean	–	33	64	212	14
SD	–	6	14	25	3

2. Experimental section

2.1. Study design

The clinical study in humans investigating the urinary excretion profiles of PI was approved by the Ethics Committee of the University Hospital of Psychiatry, Zürich (PUK-ZH). The administration of PY to healthy volunteers under controlled conditions was authorized by the Swiss Federal Office for Public Health, Department of Pharmaceutics and Narcotics, Bern. Volunteers were recruited by word-of-mouth within the University of Bern and the PUK-ZH. The subjects were four female and four male volunteers who agreed to participate in the study with informed consent. The subjects were screened by psychiatric interview to assure that the subjects had neither personal nor family histories of major psychiatric disorders in first-degree relatives. Subjects with a history of illicit drug abuse were excluded from the study. Additional exclusion criteria were scores exceeding two SD from the mean values of normative data in the 'openness' and 'neuroticism' subscales of the Freiburger Personality Inventory (FPI) [25]. Subjects were healthy according to physical examination, electrocardiogram, blood and urine analysis. Detailed data for the eight subjects are listed in Table 1. At least one experienced psychiatrist supervised each of the experiments. After an overnight fast, the participants received psychoactive oral doses of 212 ± 25 μg PY per kg body weight as capsules containing 1% PY and 99% lactose. In addition to the collection of total urine for 24 h after drug administration, the Adjective Mood (AM) rating scale [26] was completed at the beginning of the session and every hour, and the Altered State of Consciousness (ASC) rating scale [27] was answered at the end of the experiments. In order to assess possible delayed effects, follow-up Lists of Complaints (LC) [28] were handed out to the subjects with the instruction to fill them out and send them back to our institution 1 week after the PY session.

2.2. Urine collection and sample preparation

Two 6 ml aliquots of urine collected at time intervals 0–2, 2–4, 4–6, 6–8, 8–12, 12–16, and 16–24 h after PY administration were transferred into centrifuge tubes. All samples were stabilized by adding 350 μl of a concentrated, freshly prepared solution of ascorbic acid (94 mg/ml), stored at -78 °C over dry-ice and freeze-dried overnight. The control urine samples collected from each subject 15–30 min before PY ingestion were treated in the same manner. The residues of the samples used for determination of unconjugated PI were extracted with 1 ml of methanol and 10 μl of the membrane-filtered solutions used for HPLC-ECD analysis.

2.3. Glucuronide cleavage

The urine samples of subjects E, F and G were also submitted to an enzymatic glucuronide cleavage procedure prior to HPLC-ECD analysis in order to estimate the amount of PI excreted in glucuronidated form. The sample residues resulting from the freeze-drying procedure were therefore reconstituted with 6 ml of water. By addition of ammonia solution 10% (v/v), aliquots of 3 ml were adjusted to pH 5.0 (optimum pH condition for highest β-glucuronidase activity according to supplier). Glucuronide hydrolysis was achieved by adding 60 mg of lyophilized β-glucuronidase (11 200 units/ml urine) and incubation in a water bath at 40 °C for 5 h. Optimum concentrations of β-glucuronidase, incubation time, and incubation temperature were determined by preliminary experiments with aliquots of the actual urine samples. For determination of the amount of PI lost due to thermal degradation, the remaining 3 ml of reconstituted urine was also incubated, but without adding β-glucuronidase. All samples were again freeze-dried, extracted with 0.5 ml of methanol and membrane-filtered prior to analysis.

2.4. Analytical procedure for PI quantification

Concentrations of PI were measured using the HPLC-ECD method established earlier for quantitation of PI in plasma samples [18]. This analytical procedure involves a column-switching step and achieves separation on a Spherisorb RP-8 column with 46% (v/v) water, containing 0.3 M ammonium acetate buffered to pH 8.3 with ammonia 25% (v/v), and 54% (v/v) methanol as mobile phase. The EC detector is operated at a detection voltage of + 150 mV. In order to enable the determination of the higher PI concentrations present in urine samples, the 100% EC-detector response range was set at 5 μA.

2.5. Calibration

Blank urine was spiked with four different amounts of PI from a freshly prepared standard solution (10, 100, 500, 1000 μg/l urine). The calibration graph was obtained by analysis of these samples and linear regression using the corresponding detector signal AUC. Control samples with known amounts of PI were determined at the beginning and at the end of a sample series and were also interspersed throughout all the HPLC-ECD quantifications, to ensure accuracy of the results. Deviations of less than ± 10% from nominal values were found to be acceptable [29]. Inter-day precision of the HPLC-ECD assay was estimated by measuring spiked blank urine (10, 100, 500, 1000 μg PI/L) in triplicate within 2 weeks and determination of the corresponding coefficients of variation (CV). The difficulty in finding a structurally related compound suitable for use as an internal standard in this analysis has been previously discussed [18].

2.6. Pharmacokinetic analysis

Knowing the total volume of urine excreted during each time interval (due to complete sampling), the absolute amount of PI eliminated could readily be calculated from the PI concentrations determined in the analyzed samples. From the individual PI excretion profiles of each subject, the following parameters characterizing the elimination kinetics of unconjugated PI were either determined directly by visual inspection of the raw data or calculated by use of the TOPFIT® Vers. 2.0 PC software [30]. Ae_{max} (μg/h) determines the maximum urinary excretion rates of PI during the corresponding collection intervals t_{max} (h). F_e (%) is the fraction of administered PY dose excreted in urine as PI within 24 h. Molecular weight differences between PY and PI were considered in the calculations. The terminal (plasma) elimination half-life $t_{1/2\beta}$ (h) of a drug can also be estimated using its excretion rates in urine [30]. From cumulative excretion data, elimination rates are calculated by division of the excreted amounts of a drug (A_e) by the length of the corresponding collection intervals. Thus, the elimination rate is $A_e\ (t_{n+1}) - A_e(t_n)/t_{n-1} - t_n$ [30]. Logarithmic regression analysis of excretion rates against time intervals leads to the terminal elimination rate constant λ_z. Finally, division of ln(2) by λ_z gives $t_{1/2\beta}$.

2.7. Chemicals and materials

4-Phosphoryloxy-*N*,*N*-dimethyltryptamine (PY) and 4-hydroxy-*N*,*N*-dimethyltryptamine (PI) were obtained through the Swiss Federal Office for Public Health, Department of Pharmaceutics and Narcotics, Bern, and checked for identity and purity by IR, NMR, MS, and HPLC-UV analysis. PY capsules (1 and 5 mg) were prepared at the Pharmaceutical Institute of the University of Bern, Switzerland. Ascorbic acid (Microselect, $>99.5\%$ pure), and ammonia solution 25% in water (Microselect, puriss. p.a.) were purchased from Fluka BioChemika (Buchs, Switzerland). Ammonia solution 10% for pH adjustment in glucuronide cleavage experiments was prepared by dilution of 25% ammonia. Lyophilized β-glucuronidase (type B-1 from bovine liver; 560 000 units/g) was purchased from Sigma (Buchs, Switzerland) and stored at -25 °C. HPLC grade methanol and ammonium acetate (puriss. p.a.) were obtained from Merck (Zürich, Switzerland). Twice distilled water was used for all purposes. Standard solutions of PI were prepared in water containing 25 mM of ascorbic acid and stored in light-protected vials at -25 °C. Under these conditions, the solutions were found to be stable for at least 3 weeks. HPLC separation of PI was performed on Spherisorb RP-8 cartridges (particle size 3 μm, 50×4.6 mm I.D. and 150×4.6 mm I.D., respectively) supplied by Chemie Brunschwig (Basel, Switzerland).

2.8. Instrumentation

Freeze-drying was achieved on a Lyo-System GT 2 supplied by Leybold Heraeus (Köln, Germany). For incubation of urine samples with β-glucuronidase, a Haake Model R 20 Type NBE thermostated waterbath (Karlsruhe, Germany) was used. The HPLC-ECD system consisted of an Altex LC pump Mod. 100 from Beckman (Zürich, Switzerland) with additional external pulsation damper, two Rheodyne injection valves Mod. 7125 from Kontron (Zürich, Switzerland), an ESA Coulochem II EC detector from Stagroma (Wallisellen, Switzerland) and a Kontron CT-10 integrator coupled with a Model 800 plotter from Kontron (Zürich, Switzerland).

3. Results and discussion

3.1. Psychotropic effects of PY

Oral doses of 10–18 mg PY induced markedly altered states of consciousness (ASC) in all volunteers. During the peak effect of the drug 60–90 min after intake (lasting 1–2 h), the subjects experienced pronounced changes in sensory perception, affect and mood, thought processes, and ego functioning. Alterations in perception of time and space as well as visual illusions, complex hallucinations and synaesthesias were frequently observed. The PY dose employed in our study was well tolerated, with all subjects unequivocally reporting a positive experience. Only slight and short-term physical adverse reactions such as nausea and dizziness were observed during onset of PY effects in some subjects. None of our volunteers reported negative delayed effects in the follow-up Lists of Complaints. In accordance with previous reports, when applied under controlled clinical conditions, PY was found to be safe for experimental use in healthy subjects.

3.2. Analytical method

At the low (10 μg PI/l urine) and high (1000 μg PI/l urine) end of the standard curve, the CV were 7.9 and 5.1%, respectively. Recovery, precision, and limits of quantitation (signal-to-noise ratio 1:5) of the assay are summarized in Table 2. The detector response to analyte concentration was linear within the concentration range tested. The correlation coefficient (r) of the least-squares linear regression was 0.999. Representative chromatograms of blank, spiked, and post-dose urine samples are shown in Fig. 2. The analytical procedure originally established for PI measurement in plasma samples [17,18] was successfully adapted for PI quantification in urine. For several reasons, the determination of PI in urine samples is more easily accomplished compared to the challenging task of PI quantitation from a plasma matrix. First, the PI concentrations found in urine specimens are 10–1000 times higher than the corresponding PI concentration levels in plasma. This allows the sensitivity of the EC detector to be

Table 2
Recovery, precision and limit of quantitation of the HPLC-ECD method

PI concentration examined (μg/l urine)	Recovery (%)	Precision (CV (%); $n = 3$)	Limit of quantitation (abs., (ng); rel. (μg/l urine))
10	88.3	7.9	0.4; 10
100	112.7	3.2	
500	103.6	1.8	
1000	106.2	5.1	
Mean ± CV (%)	102.7 ± 10.1	4.5 ± 58.7	–

decreased to a 100% response range of 5 μA, resulting in an improved signal-to-noise ratio. Furthermore, sample volumes are not limited to 2 or 3 ml, and the time-consuming sample work-up technique for in vitro microdialysis with low analyte recoveries (typically $< 25\%$) can be replaced by simple methanol extraction of the freeze-dried urine residues, because no chromatographically interfering compounds from urine are co-extracted. Since PI is an easily oxidizable compound, the immediate stabilization of urine samples with ascorbic acid is the crucial step to prevent degradation and achieve accurate quantitation results.

3.3. Renal excretion profiles and pharmacokinetic parameters of unconjugated PI

PI concentrations found in urine samples ranged from 17 μg/l (subject B, 0–2 h post-dose) to 871 μg/l (subject E, 2–4 h post-dose). The limit of quantitation of the analytical method (10 μg

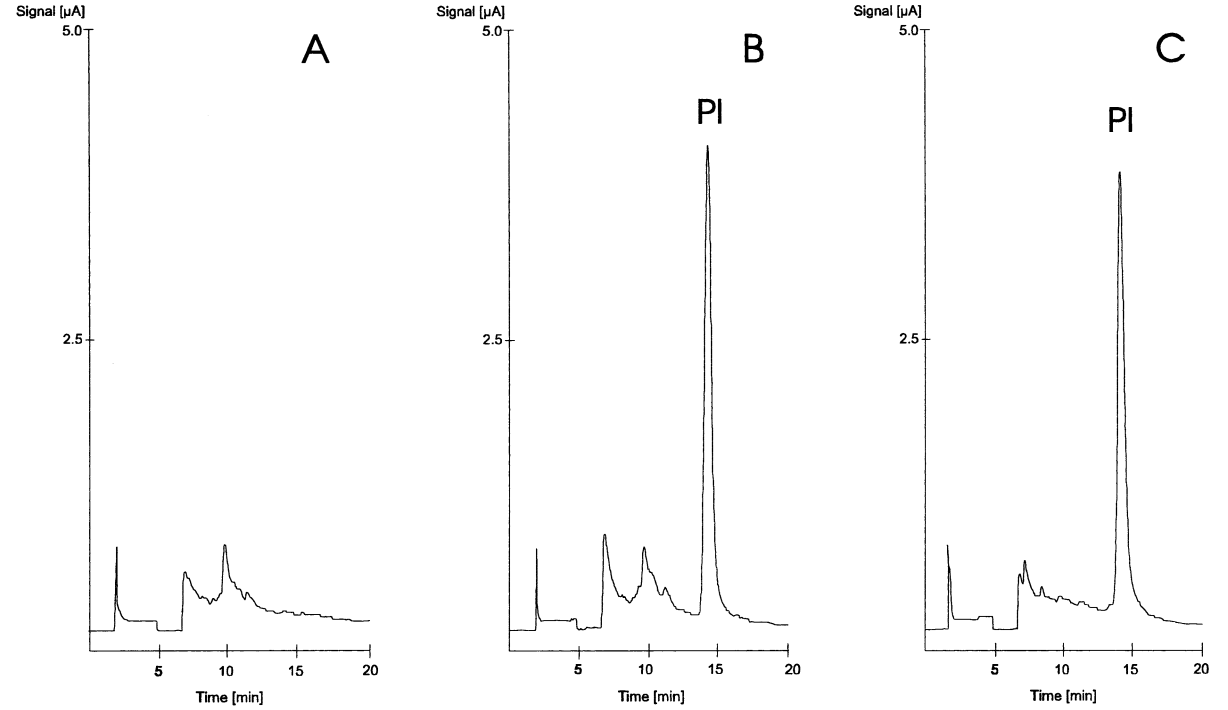

Fig. 2. HPLC-ECD determination of PI. Representative chromatograms obtained from blank (A), spiked (B, 500 μg PI/l) and post-dose urine samples (C, subject A, 4–6 h after oral administration of 11 mg PY).

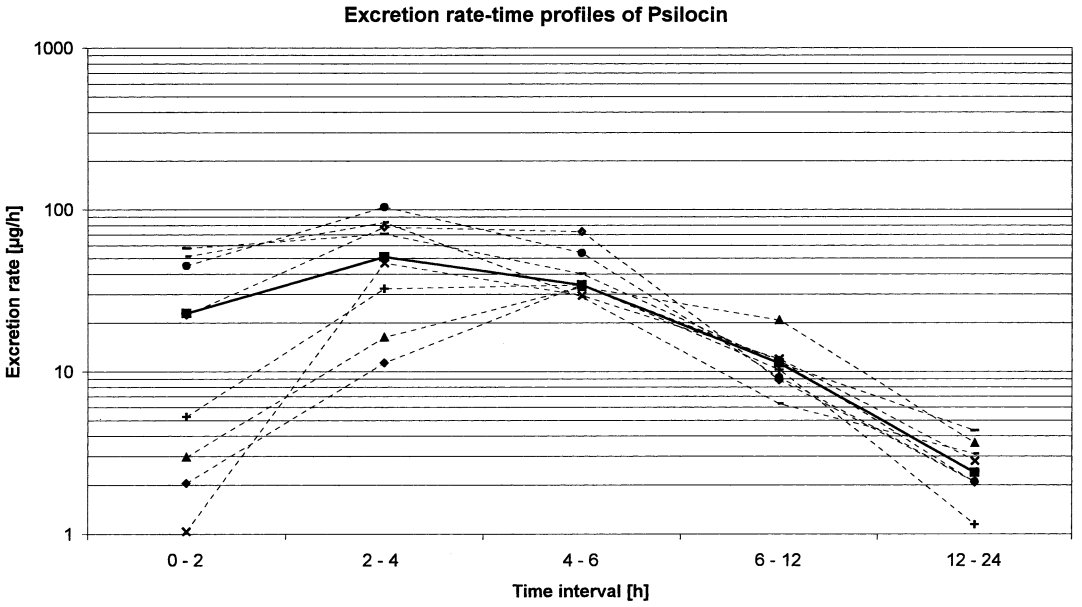

Fig. 3. Individual excretion rates of PI following oral administration of 212 ± 25 µg PY/kg body weight ($n = 8$; dashed lines) and median excretion values (solid line).

PI/l urine) was usually reached 24 h after drug administration. Minimum and maximum total amounts of PI excreted within a defined time interval were 1.9 µg (subject G, 12–24 h post-dose) and 207.8 µg (subject F, 2–4 h post-dose), respectively. In urine samples collected within the interval 2–4 h after drug administration, maximum PI excretion rates were determined of 55.5 ± 33.8 µg/h (mean $\pm$ SD; $n = 8$). Corresponding excretion rates of free PI found in the last sampling interval (12–24 h post-dose) declined to 3.6 ± 3.8 µg/h (mean $\pm$ SD; $n = 8$). Describing metabolite elimination by calculation of excretion rates (in µg/h) enables the comparison of data resulting from different urine volumes and different collection intervals. Little inter-subject variability is seen with respect to t_{max} (h). All maximum urinary excretion rates for PI were found in the intervals 2–4 h (rel. frequency 0.63) and 4–6 h (rel. frequency 0.27), respectively. Fig. 3 depicts the individual urinary excretion rates of PI following oral doses of 212 ± 25 µg PY/kg body weight and median excretion values. 3.4 ± 0.9% (mean $\pm$ SD; $n = 8$) of the administered dose of PY was excreted as unconjugated PI within 24 h. Terminal elimination half-lives ($t_{1/2\beta}$) of PI calculated earlier from plasma concentration-time data (2.72 ± 1.06 h; $n = 6$) [17,18] are now confirmed with the values estimated from cumulative urinary excretion rates (3.29 ± 0.57 h; $n = 8$). Pharmacokinetic parameters of free PI from renal excretion data are summarized in Table 3.

3.4. Influence of glucuronide hydrolysis on PI concentration

HPLC-ECD quantification of PI in our control samples revealed a loss of analyte of 18 ± 7% (mean $\pm$ SD; $n = 20$) due to partial thermal degradation during the incubation process for glucuronide cleavage in spite of stabilization with ascorbic acid. The experimental conditions required for efficient glucuronide hydrolysis (40 °C for 5 h) resulted in PI recovery rates in control samples ranging from 71 to 95%, thus enabling only semi-quantitative assessment of urinary PI concentrations excreted in the form of glucuronides. Nevertheless, glucuronide cleavage experiments performed with 20 post-dose urine samples from three subjects (E, F, and G) re-

Table 3
Pharmacokinetic parameters of unconjugated PI

Subject	Ae_{max}[a] (μg/h)	t_{max} (h)	Ae_{tot}[b] (μg)	F_e[c] (%)	$t_{1/2}$[d] (h)
A	34.5	4–6	190.7	2.4	2.59
B	83.6	2–4	403.3	4.7	3.83
C	47.0	2–4	260.1	3.4	2.88
D	70.5	2–4	457.3	4.0	2.77
E	78.4	2–4	381.5	4.1	3.06
F	103.9	2–4	396.3	3.1	4.25
G	34.2	4–6	216.5	3.0	3.59
H	33.3	4–6	267.4	2.1	3.33
Mean	60.6	2–4 (0.63)[e]	321.6	3.4	3.29
SD	27.1	—	99.4	0.9	0.57

[a] Maximum excretion rates of PI.
[b] Total amount of PI excreted in urine within 24 h.
[c] Fraction of administered PY dose excreted as PI in urine within 24 h; molecular weight differences considered in calculation.
[d] Terminal elimination half-life, calculated with excretion rates.
[e] Highest relative frequency.

vealed higher PI concentrations in every single sample ($209 \pm 81\%$ compared to PI concentrations determined in untreated samples; mean $\pm$ SD; $n = 20$). Thus, enzymatic hydrolysis of urine samples extends the period of analytical detectability of PI. This fact might be of considerable interest in the field of forensic science. Taking into account the substrate selectivity of the β-glucuronidase used for PI-G hydrolysis, the detection of higher PI concentrations following enzymatic hydrolysis can be considered as an indirect proof for the metabolic formation of PI-G in humans. We suggest that further research should aim to examine directly PI-G from PY post-dose urine samples by means of liquid chromatography–tandem mass spectrometry (LC–MS/MS). Fig. 4 shows the PI 24 h-urine excretion profile of subject G following an oral dose of 10 mg PY. Concentrations of PI excreted in the unconjugated form and after enzymatic glucuronide cleavage are compared.

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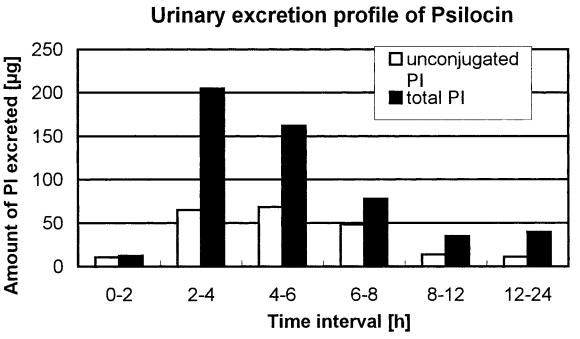

Fig. 4. Influence of glucuronide cleavage on PI levels. Urinary excretion profiles of subject G following oral administration of 10 mg PY. Comparison of amounts of unconjugated PI (□) and semi-quantitative estimated amounts of PI after enzymatic glucuronide hydrolysis (■).

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