Pharmacokinetic Properties of Δ^9-Tetrahydrocannabinol in Serum and Oral Fluid

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Abstract

In a study on the effects of smoked cannabis (18.2 ± 2.8 mg as low and 36.5 ± 5.6 mg as high dose) paired blood and oral fluid samples were collected from 10 study participants up to 6 h after smoking and analyzed for the cannabinoids Δ^9-tetrahydrocannabinol (THC), 11-hydroxy-THC (THC-OH) and 11-nor-9-carboxy-THC (THCA) using gas chromatography–mass spectrometry. Highest concentrations in serum were 47.8 ± 35.0 and 79.1 ± 42.5 µg/L at the end of smoking (low and high dose, respectively) and decreased to less than 1 µg/L during 6 h with elimination half-lives of 1.4 ± 0.1 h calculated from 1 to 6 h, which is shorter than reported previously. The elimination half-lives of THC-OH (2.0 ± 0.3 h) and THCA (3.4 ± 0.9 h) were significantly higher. The THC concentrations in oral fluid were highest with 900 ± 589 and 1041 ± 652 µg/L (low and high dose, respectively) in the first sample collected at 0.25 h and decreased to 18 ± 12 µg/L over 6 h with elimination half-lives of 1.5 ± 0.6 h. The elimination half-life of THC in serum and oral fluid and between the two doses did not significantly differ. Oral fluid/serum ratios were 46 ± 27 and 36 ± 20 (low and high dose, respectively), which are higher than previously reported and might be based on sample collection and/or analytical issues. In conclusion, despite similar elimination rates of THC in serum and oral fluid, which appear incidental, the high differences in oral fluid/serum ratios are not a reliable basis for correlating THC concentrations in oral fluid and serum. The oral compartment and its kinetics for drugs, particularly THC, are not yet satisfactorily understood.

Introduction

Cannabis use is the most prevalent illegal drug in traffic offenses in European countries (1). Interpretation of serum cannabinoid concentrations is, therefore, important for evaluating driving impairment. With the aim to establish oral fluid as biological specimen for roadside testing, knowledge of the pharmacological properties of this alternative body fluid in comparison with serum is of great importance. Only one study providing information on the correlation of THC concentrations in plasma and oral fluid exists (2). In other studies, positive oral fluid cannabis tests have been found to correlate with THC in serum (3), and a positive urine test result is not a proof of recent cannabis consumption (4,5).

In a study on the effects of cannabis smoking on the performance of recreational users (6), 20 participants were given a low (18.2 ± 2.8 mg, mean ± SD) and a high dose (36.5 ± 5.6 mg) of THC in marijuana cigarettes (13%). Paired blood and oral fluid samples were obtained from 10 of these participants up to 6 h after smoking. These samples were analyzed for cannabinoids and were evaluated for THC concentrations and its elimination comparing serum and oral fluid.

Experimental

Chemicals and reference standards

Δ^9-Tetrahydrocannabinol (THC, 1 mg/mL); 11-hydroxy-THC (THC-OH, 1 mg/mL); 11-nor-9-carboxy-THC (THCA, 1 mg/mL); and the deuterated analogues THC-d_3, THC-OH-d_3, and THCA-d_3 (each 0.1 mg/mL) were purchased from Cerilliant (Promochem, Wesel, Germany). The derivatization reagent *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (MSTFA) was from Macherey & Nagel (Düren, Germany), and methyl iodide and all other reagents and organic solvents were of analytical grade and from Merck (Darmstadt, Germany).

Study design

The data presented here supplement data from the study by Ramaekers et al. (6,7) on the influence of cannabis on cognition, impulse control and psychomotor function. From 10 of the 20 participants in the study, in addition to blood samples, oral fluid samples were taken using the Intercept DOA Oral

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Specimen Collection Device (OSCD) from OraSure Technologies (Bethlehem, PA) without intentional stimulation of saliva flow. To exclude an influence of cannabis use by the participants on their own prior to the experiments, urine and oral fluid samples were obtained and absence of THC was confirmed in all cases. The subjects (9 male and 1 female, aged 19 to 21 years) received THC doses in marijuana cigarettes prepared from batches containing 13% THC, a standard potency for marijuana sold at Dutch pharmacies for medical use (Dutch Bureau for Medicinal Cannabis, www.cannabisbureau.nl). The cigarettes were prepared for each individual in proportion to body weight (BW) and contained 250 µg THC per kg BW as a low dose (13.8 to 22.3 mg) and 500 µg THC per kg BW as a high dose (27.5 to 44.5 mg). After smoking the entire cigarette according to a fixed procedure (7) during 10 min, blood samples and oral fluid samples were collected at the end of smoking (0 min) and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, and 6 h. Blood was immediately centrifuged for serum separation, and the supernatant was stored at –20°C and shipped to the laboratory in Stuttgart. Oral fluid samples were stored in preservation buffer at –20°C after collection and shipped to the forensic toxicological laboratory in Frankfurt/Main

Analysis of serum samples by gas chromatography–mass spectrometry (GC–MS)

Extraction of the serum samples and derivatization was performed following a previously published procedure (8). GC–MS analyses were performed on a Finnigan PolarisQ GC–MSn from Thermo Electron (Egelsbach, Germany) using a Trace GC equipped with a Programmable Temperature Vaporizer and a factorFour VF-5 MS capillary column (30 m × 0.25-mm i.d., 0.25-µm film thickness, and 5-m EZ-guard), carrier gas was helium with a flow rate of 1 mL/min. The MS conditions were 275°C transfer line temperature and 70 eV ionization energy. Data analyses were performed using Xcalibur 4.0 software from Thermo Electron. The quantification was done basing on the ion trap MS–MS technique using 328/331 at 1V, 313/316 at 1V, and 357/360 at 1V as precursor ions for the methyl-derivatives of THC/THC-d_3, THC-OH/THC-OH-d_3 and of THCA/THCA-d_3, and (313/316, 297/300), (247/250, 231/234) and 297/300 as fragment ions for quantification (quantifier ions underlined). The limits of detection (LOD) for THC, THC-OH, and THCA were 0.2, 0.1, and 1.9 µg/L, the limits of quantification (LLOQ) were determined to be 0.5, 0.3, and 6.2 µg/L, and the upper limits of quantification (ULOQ) were 10, 10, and 40 µg/L, respectively. The interday precisions (n = 8) of serum controls of THC and THC-OH (0.25 and 2 µg/L) and THCA (5 and 40 µg/L) were 9.2% and 8.1% for THC, 15.1% and 2.9% for THC-OH, and 3.2% and 2.8% for THCA.

Analysis of oral fluid by GC–MS

The assay of THC in oral fluid samples was performed as described previously (7). Sample preparation for oral fluid samples was performed by addition of 2 mL methanol to each sample tube and incubation for 15 min with shaking and collecting the liquid by centrifugation. From the weight of each recovered liquid, the weight of 0.8 mL buffer and 2 mL methanol was subtracted in order to determine the amount of original oral fluid. A portion (2.5 mL) of each sample, concentrated at 40°C to approximately 1 mL and then diluted with deionized water to 5 mL, was used for analysis. After addition of 50 µL internal standard solution (0.25 ng/µL of THC-d_3 in methanol) the mixture was vortex mixed and centrifuged for 10 min at 2000 × g. Automated solid-phase extraction was performed as described previously using the robot RapidTrace (Caliper LifeSciences, Rüsselsheim, Germany) equipped with 3-mL Bakerbond C_{18} 500-mg cartridges (Baker, Griesheim, Germany). The extracts were evaporated at 60°C, and the dry residues were derivatized using MSTFA. One microliter was analyzed using a GC–MS system (6890N GC, 7683 series injector, 5973 MSD) from Agilent (Waldbronn, Germany) with Varian (Darmstadt, Germany) factorFour VF-1MS capillary column (30 m × 0.25-mm i.d., 0.25-µm film thickness) and helium carrier gas with a flow rate of 1.0 mL/min. The MS conditions were 280°C transferline temperature and 70 eV ionization energy. Data analysis was performed using Agilent ChemStation software version B.01.00.

Quantification of the trimethylsilyl derivatives was performed in the SIM mode using the following fragment ions (quantifiers underlined): *m/z* 389, 374, and 306 for THC-d_3 (internal standard) and *m/z* 386, 371, and 303 for THC. For calibration a matrix was used that was similar to the analyzed samples (equalling a mixture of 0.5 mL drug-free oral fluid, 0.8 mL preservation buffer, and 2 mL methanol). Calibration standards were prepared from the oral fluid mixture spiked with THC (0, 1, 3, 5, 10, 25, 50, 100, 500, and 1000 µg/L oral fluid) and processed in the same way as the samples. For quality assurance, calibration samples were analyzed twice, before and after the samples exhibiting less than 2% deviation. The limits of detection (LOD) and quantification (LLOQ) were assayed to be 0.5 and 2.4 µg/L, respectively. Samples with analysis results above the ULOQ (1000 µg/L) were diluted and reanalyzed. Additional samples were prepared and analyzed for the determination of precision and accuracy using two concentrations (10 µg/L and 75 µg/L). Precision and accuracy were determined to be 7.2% and 2.2% (10 µg/L, n = 5) and 2.5% and –7.5% (75 µg/L, n = 5), respectively. Accuracy tests were also performed using serum containing 2.3 µg/L THC (BTMF 1/04-A S-plus reference material, Medichem Diagnostica GbR, Steinenbronn, Germany).

Evaluation of the data

The quantitative data were evaluated with model-independent methods using Microsoft Excel 2003. From the concentration-time curves it was assumed that distribution processes (α phase) were in a steady state after 1 h after smoking. The elimination half-lives ($t_{½}$ β) were calculated from the result of exponential regression of the data where only samples taken one hour or more after smoking were considered. Concentrations that were lower than the LOQ were omitted in the calculations. For regression analyses only data sets with six points were used. The areas under the curves (AUC) were estimated using the trapezoidal rule. Because the mean values did not differ markedly from median values, a normal distribution was assumed, and Student's t-test was used to test significant differences.

Results and Discussion

The analysis of samples collected after the consumption of cannabis by occasional users provided data enabling the correlation of cannabinoid concentrations in serum and oral fluid. The highest concentrations (C_{max}, Table I) of THC in serum observed were 110 µg/L (low dose) and 134 µg/L (high dose), on average the C_{max} values were 47.8 µg/L (low dose) and 79.1 µg/L (high dose). The increment by the factor of 1.7 correlates with an increase in THC dose but was not statistically significant. Similar results were obtained for the AUC which was significantly ($p < 0.05$) higher in the high dose group by a factor of 1.8. Accordingly the concentrations and AUCs of THC-OH and THCA were increased with the dose (factors 1.5–1.7); however, only the increase of THC-OH AUC was significant ($p < 0.05$). It is known that the bioavailability of THC after cannabis smoking is variable and influenced by individual technique and experience (10). The high coefficients of variation for C_{max} (53% to 75%) indicate that this was also observed in the present study. Participants 2 and 3 especially absorbed only a small fraction of the THC dose, which is indicated by very low C_{max} and AUC values in comparison to the other eight participants. A marked intraindividual variability can also be demonstrated in subject 11 who exhibited higher C_{max} and AUC values for THC in serum in the low dose than in the high dose experiment, whereas THC-OH and THCA concentrations in serum and the THC amount in oral fluid were in accordance with the dose. In general, the concentrations and AUCs of oral fluid were higher after using the high dose, but the increase was not significant exhibiting factors below 1.5. Some notable variations were observed in subjects 1, 7, and 14, who showed higher C_{max} and AUC values in their samples obtained during the low-dose experiment.

The maximum serum concentrations of THC (t_{max}) were measured directly after smoking (0 h), while the metabolite concentrations increased, reaching their maximum about 0.25 h after smoking (Table I). In all but four cases, THC was still detectable in serum 6 h after smoking. THC concentrations then were less than 1 µg/L even after the higher dose except in subjects 4 and 6 (1.4 and 1.0 µg/L, respectively), which is in accordance with previous results (11). In oral fluid the first sample after smoking was taken at 0.25 h where the THC concentration was highest in 16 of the 20 experimental sessions confirming previous results (4). Overall, concentrations were higher in oral fluid than in serum (up to 300-fold). Accordingly, concentrations at 6 h post smoking were much higher than in serum with a mean of 13.8 and 22.3 µg/L for the low and high dose, respectively. This confirms previous reports that THC can be detected longer in oral fluid than in serum (12,13). The concentration range corresponds to the concentrations found in another study where a THC dose of 11 mg was used (14). In the studies of Niedbala et al. (4,15), much lower concentrations of THC were observed in oral fluid (less than 230 µg/L) after smoking cannabis cigarettes containing 12.75 mg or 20–25 mg of THC, which might be due to the lower doses used and analytical issues (9,16). Despite the almost similar THC doses applied in the study by Huestis and Cone (2), the oral fluid concentrations determined were much lower in general than those reported in the present study except the very high concentrations of their first samples. This difference can be explained by the different oral fluid collection methods. Huestis and Cone (2) used sour candy to stimulate saliva flow and collected the samples by expectoration, yielding up to 5–10 mL, whereas in the present study, a collection device was placed in the mouth and only up to 1.25 g was sampled.

Elimination of cannabinoids from serum or oral fluid

Inspection of the concentration-time curves in serum (Figure 1) shows a marked decrease in the first hour after smoking which is equivalent to the distribution phase (17). To estimate the elimination half-lives of THC, THC-OH and THCA in serum exponential regressions were performed on the data from 1 to 6 h after cessation of smoking (Table I, median of all regression coefficients was 0.99). The derived half-lives indicate a low variation among the subjects which is less than 10% for THC, less than 20% for THC-OH and less than 30% for THCA. The mean half-lives determined for the two dose groups are not significantly different. For THC the elimination half-life is 1.4 h, which is significantly shorter than 2.0 h determined for THC-OH ($p < 0.01$) and 3.4 h for THCA ($p < 0.01$). In accordance with previous results (18), the elimination rate of the metabolites is slower than that of the parent compound (19). The elimination half-life of THC from serum has been reported to be in the range of 20–30 h (20), except for two studies (19,21) where half-lives below 2 h were determined. For pharmacokinetic modelling of THC concentrations in serum, up to four distinct compartments have been used (18,20). Therefore, the marked discrepancy of the data might be explained by different observation times. However, the elimination pattern found in the present study appears to be applicable to THC concentrations above 1 µg/L, rather than the much longer terminal elimination phases observed in other studies.

For THC in oral fluid similar profiles were observed as in serum (Figure 1) consisting of a steep decline during the first 1–2 h after smoking followed by a slower decrease. This biphasic pattern confirms previous reports (2,14,15) where the first phase lasted about 1 h (14,15). The exponential regression of the oral fluid concentrations in the time range of 1 to 6 h exhibited lower regression coefficients than those obtained for the serum data (median 0.92 for both doses of THC in oral fluid). Also substantial variation in the derived half-lives of THC was observed among the subjects (44% and 35% for low and high dose, respectively) which has been noted before (4). In the present study, the mean elimination half-life of THC in oral fluid is 1.5 h (range 1.0 to 3.0 h), which is in accordance with a previous report (15). Significant differences between the elimination of THC in oral fluid and serum was not found, which confirms results of Huestis and Cone (2), who determined 0.80 and 0.78 h as half-lives in oral fluid and plasma, respectively. A good correlation between the detectability of THC in serum and oral fluid has also been found in authentic cases (3), and it has been suggested that THC in oral fluid is influenced by THC in serum or vice versa (2,4). It has also been reported that the sublingual application of THC leads to significant plasma concentrations (20). However, it is widely accepted that THC in oral fluid results

Table I. Evaluation Results of the Quantitative Data Obtained from Serum and Oral Fluid Samples*

	250 µg/kg BW (13.8–22.3 mg)					500 µg/kg BW (27.5–44.5 mg)				
THC (S)	C_{max} [µg/L] (t_{max} [h])	$C_{6\,h}$ [µg/L]	$t_{C \geq LOD}$ [h]	$AUC_{0\rightarrow 6\,h}$ [µg/L * h]	$t_{½}$ β [h]	C_{max} [µg/L] (t_{max} [h])	$C_{6\,h}$ [µg/L]	$t_{C \geq LOD}$ [h]	$AUC_{0\rightarrow 6\,h}$ [µg/L * h]	$t_{½}$ β [h]
1	45.0 (0.0)	0.6	6	21.9	−1.48 (0.958)	51.0 (0.0)	0.5	6	27.8	−1.39 (0.980)
2	9.2 (0.0)	< LOQ	6	7.0	−1.60 (0.997)	25.0 (0.0)	n.d.	4	15.5	
3	11.0 (0.0)	n.d.	5	6.3		36.0 (0.0)	n.d.	5	17.2	
4	47.0 (0.0)	< LOQ	6	26.5	−1.32 (0.989)	127.0 (0.0)	1.4	6	74.9	−1.33 (0.990)
7	50.0 (0.0)	< LOQ	6	20.1	−1.61 (0.974)	97.0 (0.0)	< LOQ	6	37.3	−1.35 (0.888)
8	26.0 (0.0)	0.6	6	15.8	−1.71 (0.975)	132.0 (0.0)	1.0	6	65.7	−1.35 (0.994)
9	23.0 (0.0)	n.d.	5	11.0		32.0 (0.0)	0.8	6	25.1	−1.60 (0.996)
11	110.0 (0.0)	0.9	6	45.8	−1.55 (0.974)	74.0 (0.0)	0.8	6	35.8	−1.42 (0.996)
14	53.0 (0.0)	0.5	6	30.5	−1.32 (0.986)	83.0 (0.0)	0.9	6	43.2	−1.39 (0.976)
23	104.0 (0.0)	0.7	6	39.9	−1.43 (0.981)	134.0 (0.0)	0.8	6	60.6	−1.13 (0.976)
Mean ± SD	47.8 ± 35.0			22.5 ± 13.4	−1.5 ± 0.1	79.1 ± 42.5			40.3 ± 20.6	−1.4 ± 0.1
High vs. low dose						1.7 (n.s.)			1.8 ($p < 0.05$)	0.9 (n.s.)
THCOH (S)	C_{max} [µg/L] (t_{max} [h])	$C_{6\,h}$ [µg/L]	$t_{C \geq LOD}$ [h]	$AUC_{0\rightarrow 6\,h}$ [µg/L * h]	$t_{½}$ β [h]	C_{max} [µg/L] (t_{max} [h])	$C_{6\,h}$ [µg/L]	$t_{C \geq LOD}$ [h]	$AUC_{0\rightarrow 6\,h}$ [µg/L * h]	$t_{½}$ β [h]
1	4.8 (0.00)	0.4	6	6.8	−1.97 (0.967)	3.7 (0.25)	0.4	6	8.5	−1.78 (0.988)
2	0.4 (0.25)	n.d.	3	1.0		0.8 (0.25)	n.d.	3	1.8	
3	0.4 (0.75)	n.d.	1	0.5		0.7 (0.25)	n.d.	5	2.6	
4	5.3 (0.00)	0.3	6	8.4	−1.77 (0.997)	4.9 (0.00)	0.5	6	10.6	−1.97 (0.993)
7	2.3 (0.00)	< LOQ	6	3.4	−2.55 (0.975)	1.3 (0.00)	< LOQ	6	3.9	−1.97 (0.948)
8	2.6 (0.00)	< LOQ	6	3.9	−2.71 (0.913)	6.7 (0.00)	0.5	6	11.3	−2.28 (0.981)
9	1.2 (0.00)	n.d.	4	2.4		2.6 (0.25)	0.3	6	6.7	−2.00 (0.996)
11	2.7 (0.25)	0.4	6	6.4	−2.53 (0.974)	4.1 (0.00)	0.4	6	8.6	−1.97 (0.989)
14	2.7 (0.00)	< LOQ	6	6.3	−1.73 (0.989)	5.4 (0.25)	0.6	6	11.8	−1.85 (0.985)
23	2.3 (0.50)	0.3	6	6.7	−1.88 (0.990)	6.0 (0.00)	0.5	6	14.3	−1.54 (0.992)
Mean ± SD	2.5 ± 1.6			4.6 ± 2.7	−2.2 ± 0.4	3.6 ± 2.2			8.0 ± 4.2	−1.9 ± 0.2
High vs. low dose						1.5 (n.s.)			1.7 ($p < 0.05$)	0.9 (n.s.)
THCA (S)	C_{max} [µg/L] (t_{max} [h])	$C_{6\,h}$ [µg/L]	$t_{C \geq LOD}$ [h]	$AUC_{0\rightarrow 6\,h}$ [µg/L * h]	$t_{½}$ β [h]	C_{max} [µg/L] (t_{max} [h])	$C_{6\,h}$ [µg/L]	$t_{C \geq LOD}$ [h]	$AUC_{0\rightarrow 6\,h}$ [µg/L * h]	$t_{½}$ β [h]
1	14.0 (0.50)	< LOQ	6	50.0	−3.60 (0.959)	27.0 (0.25)	7.8	6	88.3	−3.68 (0.995)
2	3.0 (0.25)	n.d.	2	10.4		11.0 (0.25)	n.d.	4	28.6	
3	2.7 (0.25)	n.d.	1	9.8		7.3 (0.25)	n.d.	5	21.3	
4	26.0 (0.25)	< LOQ	6	70.0	−2.95 (0.989)	38.0 (0.25)	8.0	6	107.0	−2.88 (0.989)
7	15.0 (0.25)	< LOQ	6	42.9	−4.09 (0.996)	16.0 (0.25)	< LOQ	6	53.0	−3.46 (0.936)
8	10.0 (0.00)	< LOQ	6	26.2	−5.81 (0.977)	27.0 (0.25)	< LOQ	6	59.8	−2.87 (0.966)
9	5.3 (0.25)	n.d.	3	16.2		16.0 (0.25)	< LOQ	6	50.8	−3.24 (0.994)
11	18.0 (0.25)	< LOQ	6	44.8	−2.39 (0.999)	24.0 (0.25)	< LOQ	6	59.3	−2.21 (0.997)
14	7.6 (0.25)	< LOQ	6	24.2	−3.37 (0.995)	20.0 (0.25)	< LOQ	6	61.9	−3.00 (0.997)
23	34.0 (0.25)	10.0	6	104.4	−3.94 (0.995)	48.0 (0.25)	9.9	6	138.3	−2.73 (0.998)
Mean ± SD	13.6 ± 10.2			39.9 ± 29.8	−3.7 ± 1.1	23.4 ± 12.4			66.8 ± 35.4	−3.0 ± 0.5
High vs. low dose						1.7 (n.s.)			1.7 (n.s.)	0.8 (n.s.)

THCA (S)	C_{max} [µg/L] (t_{max} [h])	$C_{6\,h}$ [µg/L]	$t_{C \geq LOD}$ [h]	$AUC_{0\rightarrow 6\,h}$ [µg/L * h]	$t_{½}$ β [h]	OF/S (mean ± SD)	C_{max} [µg/L] (t_{max} [h])	$C_{6\,h}$ [µg/L]	$t_{C \geq LOD}$ [h]	$AUC_{0\rightarrow 6\,h}$ [µg/L * h]	$t_{½}$ β [h]	OF/S (mean ± SD)
1	1075.0 (0.25)	8.0	6	642.0	−1.39 (0.902)	33.0 ± 26.5	247.5 (0.25)	8.9	6	283.4	−1.66 (0.920)	14.5 ± 4.5
2	371.1 (0.25)	14.6	6	295.2	−3.16 (0.934)	55.1 ± 32.6	841.4 (0.25)	25.4	6	717.8	−1.92 (0.922)	57.9 ± 22.5
3	305.0 (0.25)	5.5	6	337.1	−1.16 (0.985)	67.7 ± 28.8	528.3 (0.25)	21.9	6	747.8	−1.16 (0.903)	52.4 ± 20.9
4	244.7 (0.25)	2.7	6	267.8	−1.02 (0.974)	11.6 ± 5.5	572.4 (0.75)	31.3	6	547.4	−2.58 (0.755)	11.3 ± 6.8
7	774.8 (0.25)	7.3	6	511.9	−1.32 (0.854)	28.6 ± 26.5	821.5 (0.50)	8.4	6	404.2	−1.84 (0.896)	17.6 ± 16.5
8	1055.3 (0.25)	7.2	6	637.0	−1.28 (0.925)	45.7 ± 52.7	1468.4 (0.50)	18.9	6	1384.1	−1.00 (0.925)	24.8 ± 16.1
9	779.8 (0.25)	30.9	6	621.6	−1.94 (0.772)	104.6 ± 99.2	1454.5 (0.25)	17.2	6	1492.1	−1.02 (0.976)	63.9 ± 44.2
11	816.4 (0.25)	17.3	6	1053.3	−1.09 (0.979)	30.9 ± 15.4	948.3 (0.50)	32.6	6	1372.3	−1.26 (0.967)	49.6 ± 12.7
14	1352.6 (0.25)	6.9	6	824.3	−1.01 (0.924)	24.1 ± 23.1	983.4 (0.25)	11.0	6	748.4	−1.17 (0.885)	17.8 ± 11.3
23	ca. 2228 (0.25)	37.1	6	1795.8	−1.43 (0.877)	60.3 ± 27.5	ca. 2544 (0.25)	46.3	6	2456.3	−1.12 (0.809)	48.0 ± 26.0
Mean ± SD	900.3 ± 589.1	13.8 ± 11.6		698.6 ± 456.1	−1.5 ± 0.6	46.2 ± 27.0	1040.9 ± 651.8	22.2 ± 12.1		1015.4 ± 660.5	−1.5 ± 0.5	35.8 ± 20.3
High vs. low dose							1.2 (n.s.)			1.5 (n.s.)	1.0 (n.s.)	0.8 (n.s.)

* The results are given for THC, THC-OH, and THCA in serum (S) and for THC in oral fluid (OF) for the two doses. The maximum concentration (C_{max}) with the corresponding time (t_{max}) and the last concentration measured 6 h after smoking ($C_{6\,h}$) are given. Detection of analyte below the limit of quantitation is given as "< LOQ", analytes not detected as "n.d." and in two cases the oral fluid concentrations exceeded the upper limit of quantitation and are given as "ca." values. The duration of detection is given as the time of the last sample where the concentration was above the limit of detection ($t_{C \geq LOD}$). The areas under the curves are given for the time of measured concentrations ($AUC_{0\rightarrow 6\,h}$) without further extrapolation. Elimination half-lives ($t_{½}$ β) are calculated from exponential regression of 6 valid concentration-time data (1 to 6 h) and are given together with the regression coefficient in parentheses. For oral fluid the ratios of THC concentrations in oral fluid and serum (OF/S) are given as mean ± SD over the time course of each experiment ($n = 9$ at most). Below the data for the 10 study participants (1–23), their mean ± SD is given and also the ratio of high dose value versus low dose value with the respective statistical significance.

from contamination of the oral cavity (22,23), and the mechanisms of deposition and elimination have not been elucidated. It is suggested that when THC is smoked, it is predominantly delivered to the lungs and only a small fraction remains in the oral cavity. Therefore, a contribution of this small depot to plasma concentrations even if complete absorption is assumed appears to be neglectable.

Correlation of THC concentrations in oral fluid and serum

An interesting aspect of oral fluid analysis is to correlate oral fluid THC concentrations to those of serum relating to impairment of cognition and motor control (e.g., driving performance). In one study a good correlation between THC concentrations in oral fluid and intoxication symptoms was found (14). However, in addition to a study published recently (2), the present study is only the second investigation correlating THC concentrations in oral fluid and serum after the controlled smoking of THC containing cigarettes. Huestis and Cone (2) found that oral fluid mimicked plasma concentrations over a time range of 0.3 through 4.0 h with oral fluid/plasma ratios of 1.18 ± 0.62 (mean ± SD). Similar ratios were also observed by Samyn and van Haeren (24) in drug users. In the present study it was expected that the markedly higher oral fluid concentrations determined would also lead to much higher oral fluid/serum ratios. The ratios calculated were 46.2 ± 27.0 and 35.8 ± 20.3 (mean ± SD, OF/S in Table I) with interindividual variations of 58.5% and 56.9% (coefficients of variation) for the low and high dose, respectively, no significant differences between the OF/S ratios were found. The interindividual variation of the ratios was rather high as were the intraindividual variation, as seen in Table I. The combined coefficients of variation of both doses range from 25.5% to 115.4% with a median of 59.4%. The inter- and intraindividual variations of 50–60% are in the same range as observed in the study of Huestis and Cone (2), where a coefficient of variation of 52.5% was found. This high variation might be attributable to the variable saliva flow which is decreased after cannabis smoking (4) and increased during oral fluid collection.

In conclusion, the similar elimination rates of THC in serum and oral fluid are considered accidental and the mechanism of elimination from oral fluid can not be explained to date. The high differences in OF/S ratios, especially after using different collection procedures, are not a reliable base for correlating THC concentrations in oral fluid and serum, although it appears to contradict the conclusion of Huestis and Cone (2).

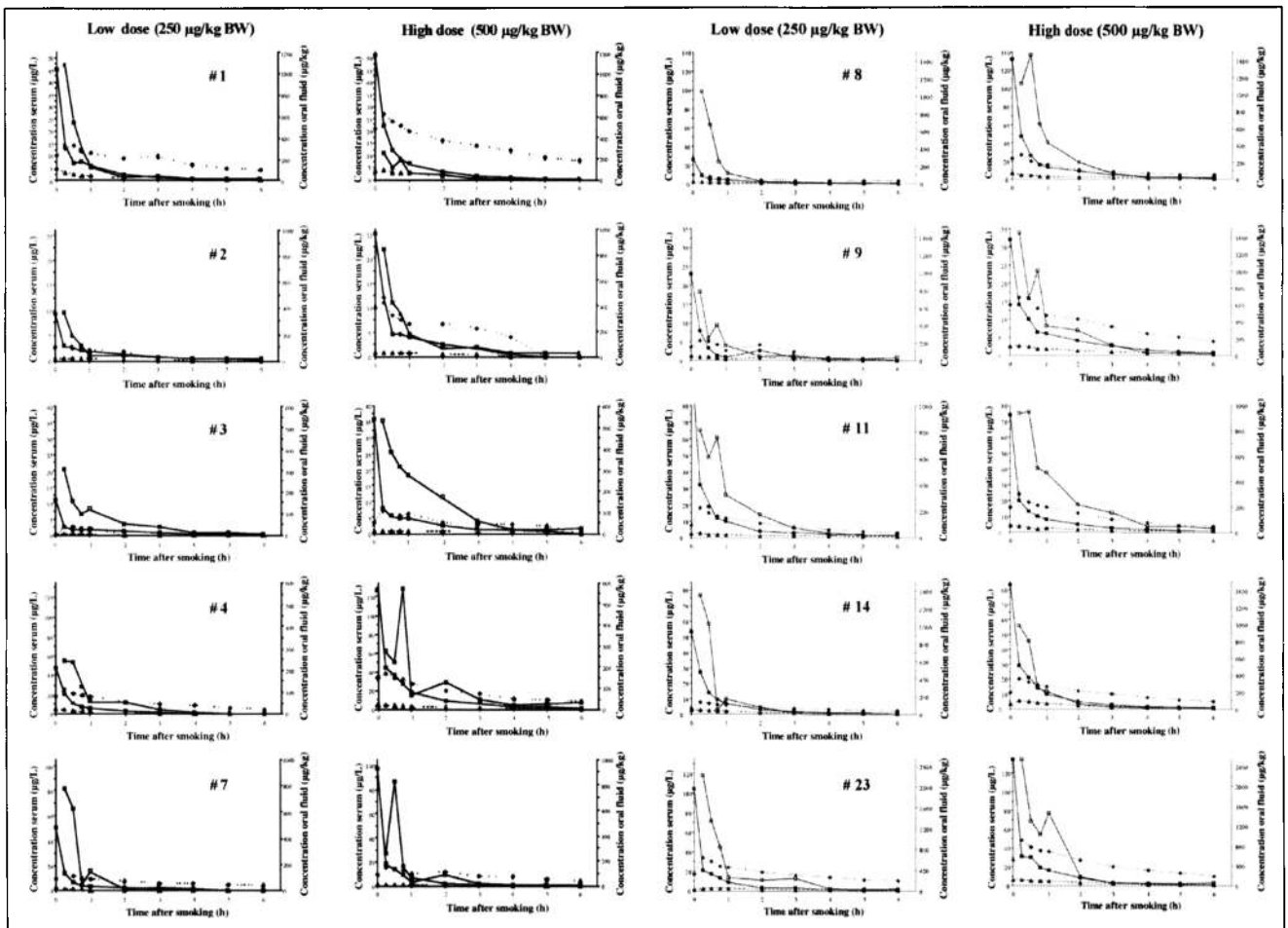

Figure 1. Concentrations of THC (■), THC-OH (▲), and THCA (♦) in serum (left y-axis) and THC in oral fluid (□, right y-axis) in correlation with the time after smoking. The data for each of the 10 individuals are presented in one line where the left graph shows the data for the low-dose experiment, and the right graph shows the data for the high-dose experiment.

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