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Absorption, Pharmacokinetics, and Safety of Triclosan after Dermal Administration▽

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We evaluated the pharmacokinetics and safety of the antimicrobial agent triclosan after dermal application of a 2% triclosan-containing cream to six volunteers. Percutaneous absorption calculated from urinary excretion was 5.9% ± 2.1% of the dose (mean ± standard deviation). The amount absorbed suggests that daily application of a standard adult dose would result in a systemic exposure 890 times lower than the relevant no-observed-adverse-effect level. Triclosan can be considered safe for use in hydrophobic creams.

Triclosan is an antimicrobial agent with broad-spectrum activity against Gram-positive and Gram-negative bacteria as well as some molds and yeasts. It is bacteriostatic at low concentrations as it blocks lipid synthesis, whereas at higher concentrations (as reached in dermatological preparations) membrane destabilization and triclosan-induced K^+ leakage lead to a rapid bactericidal effect (9, 16). Furthermore, triclosan potently inhibits the growth of *Toxoplasma gondii* and *Plasmodium* (13, 20) and shows anti-inflammatory effects after topical administration (11, 19).

For more than 20 years, triclosan has been used widely worldwide in medical and consumer products (5, 21). In dermatological preparations, it is an effective topical antiseptic to reduce colonization with *Staphylococcus aureus* and to treat superinfected atopic dermatitis (2, 8, 10, 22). Despite the almost-ubiquitous occurrence of the substance, pharmacokinetic studies are sparse.

We evaluated the pharmacokinetics and safety of triclosan in a clinical study in six healthy Caucasians. The study was approved by the Ethics Committee of the University of Cologne and by the competent German authorities, and all participants gave their written informed consent. Demographic baseline characteristics are shown in Table 1. The study medication (provided by Infectopharm) was a hydrophobic cream containing 2% triclosan. Its composition corresponds to a dermatological standard preparation (NRF 11.122) which is listed in the *Neues Rezeptur Formularium* (German List of Recommended Standard Formulations). Approximately 60 g of the cream was massaged into the skin of the whole body except for the head and genitals. Exposure was ended by taking a shower 12 h after administration. The subjects were confined to the clinical ward under standardized conditions from 10 h prior until 48 h after study drug administration.

Urinary excretion during individual sampling intervals up to 168 h postdose was used for pharmacokinetic calculations (WinNonlin version 5.01). For quantification, the sum of free triclosan and its glucuronide and sulfate metabolites (after enzymatic hydrolysis) was determined using a specific and sensitive high-performance liquid chromatography-mass spectrometry approach based on published methods (15, 18). The lower and upper limits of quantification were 4.5 and 800 μg/ml, respectively. Quality control samples showed good precision and accuracy throughout the measurement of study samples.

In all individuals, the major fraction of absorbed triclosan was excreted within the first 24 h, and the lower limit of quantification was reached 48 h postdose. The mean amount excreted from 0 to 48 h (Ae_{0-48}) for triclosan was 57.3 mg, which is 4.9% of the administered dose (Table 2). The estimated mean $Ae_{0-\infty}$ was 68.7 mg, i.e., 5.9% of the dose (in the following discussion, the estimated mean $Ae_{0-\infty}$ is considered the dose absorbed). The mean apparent terminal elimination half-life ($t_{1/2\lambda z}$) was 10.8 h. This is consistent with the results of Sandborgh-Englund et al., who found a median urinary excretion half-life of 11 h after oral intake of triclosan (17). The maximal excretion rate, $t_{maxrate}$, was observed after 11.0 h. For a complete listing of pharmacokinetic data, see Table 2.

For all main pharmacokinetic parameters, the intersubject coefficient of variation (CV %) was >30%. This is also in agreement with data in the published literature for oral intake (17). This broad variability may be due to individual differences in the rate and extent of transdermal absorption and variations in distribution kinetics, metabolism, and renal clearance of triclosan. Moreover, the number of subjects in this trial was quite small.

The safety and tolerability checks (physical examination, electrocardiogram, vital signs, and clinical laboratory assessment) did not provide any evidence for health impairment caused by the study drug. Four mild adverse events occurred; two were located at the skin (irritation on chest after shaving, dry facial skin) and two were probably linked to slight virus

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TABLE 1. Baseline characteristics of all subjects[a]

Subject no.	Sex	Age (yr)	Body ht (cm)	Body wt (kg)
1	Female	34	171	58.3
2	Male	27	187	72.0
3	Female	38	168	57.3
4	Male	35	171	69.5
5	Female	32	181	70.6
6	Male	29	181	70.0
Arithmetic mean		32.5	175.6	66.3
Arithmetic SD		4.0	5.6	6.6

[a] Characteristics at prestudy examination ($n = 6$ study subjects).

infections (running nose, common cold). The good tolerability is consistent with safety and tolerability data on triclosan reported in both published and unpublished studies (4, 7).

For toxicology assessment, the individual systemic exposure was calculated as the dose absorbed/body weight and compared with the relevant no-observable-adverse-effect level (NOAEL) for triclosan. A NOAEL of 75 mg/kg of body weight was obtained from lifetime studies in hamsters; this species most closely reflects human metabolism and elimination pathways (J. R. Plautz, Ciba Specialty Chemicals, Basel, Switzerland, personal communication, 2007). The amount absorbed after whole-body application was approximately 81 times (range, 41 to 113 times) lower than the NOAEL (Table 3).

It can be concluded that the safety margin for therapeutic use of this agent is significantly higher. The recommended adult dose of 2 × 2.5 g of the investigational product would result in a systemic exposure of 0.084 mg/kg, which is approximately 890 times lower than the relevant NOAEL (assuming a body weight of 70 kg and a transdermal fraction absorbed of 5.9%). Hence, this trial did not reveal any toxicological concerns. This is supported by an extensive toxicology database in the literature (3, 4, 6, 7).

The conclusions regarding the pharmacokinetics and toxicology for triclosan are based on the assumption that the estimated total amount of triclosan excreted via urine, $Ae_{0-\infty}$, closely reflects the amount absorbed. As our data are based on urinary (not plasma) drug concentrations and could not be compared to those following intravenous administration, it cannot be excluded that the pharmacokinetic results of this study may have been confounded by incomplete renal excretion. After oral intake of triclosan, a mean amount excreted of approximately 50% of the dose is found (17), which could reflect accumulation, incomplete absorption and excretion via the feces, or poorly characterized metabolites. All this would result in the "true" amounts absorbed being higher than those calculated in this trial.

However, long-term multiple-application studies have shown no accumulation and similar mean area under the time-concentration curve values as those seen following a single-dose application (1, 12). In contrast to other species (for example,

TABLE 3. Toxicology following systemic exposure to triclosan and the calculated safety margin

Subject no.	Systemic exposure[a] (mg/kg)	Safety margin[b]
1	1.81	41.4
2	0.82	91.1
3	0.66	113.3
4	1.03	72.8
5	0.70	107.2
6	1.27	59.3
Mean	1.05	80.85
SD	0.44	28.07
CV %	41.6	34.7
Median	0.93	81.97
Minimum	0.66	41.4
Maximum	1.81	113.3

[a] Calculated as the estimated $Ae_{0-\infty}$/kg of body weight.
[b] Calculated as the NOAEL divided by the estimated systemic exposure, assuming a NOAEL of 75 mg/kg.

TABLE 2. Individual pharmacokinetic variables for triclosan following administration of approximately 60 g of a hydrophobic dermatological preparation containing 2% triclosan[a]

Subject no.	Dose administered[b] (mg of triclosan)	Ae_{0-48}		Estimated $Ae_{0-\infty}$ (dose absorbed)[c]		$t_{maxrate}$ (h)	$t_{1/2\lambda z}$ (h)
		In mg	As % of dose	In mg	As % of dose		
1	1,164	61.0	5.2	105.6	9.1	10.0	22.1
2	1,154	57.7	5.0	59.2	5.1	19.9	3.3
3	1,150	34.0	3.0	37.9	3.3	10.0	10.9
4	1,170	66.2	5.7	71.6	6.1	10.0	11.6
5	1,170	38.6	3.3	49.4	4.2	10.0	8.2
6	1,186	86.4	7.3	88.6	7.5	6.0	8.5
Mean	1,166	57.3	4.9	68.7	5.9	11.0	10.8
SD	13	19.1	1.6	25.2	2.1	4.7	6.3
CV %	1.1	33.4	32.5	36.7	36.2	42.6	58.2
Median	1,167	59.3	5.1	65.4	5.6	10.0	9.7
Minimum	1,150	34.0	3.0	37.9	3.3	6.0	3.3
Maximum	1,186	86.4	7.3	105.6	9.1	19.9	22.1

[a] Calculated based on urinary drug excretion. Ae, amount excreted; $t_{maxrate}$, time to reach maximum urine excretion rate; $t_{1/2\lambda z}$, apparent terminal elimination half-life.
[b] Calculated from the individual amount administered dermally and the strength of the cream (~60 g × 2%).
[c] The estimated $Ae_{0-\infty}$ is assumed to closely reflect the percutaneously absorbed triclosan.

the rat), excretion of triclosan in humans is predominantly urinary (1, 7, 18). Regarding fecal excretion in humans, to our knowledge no data have been published up to now. The extent of a possible contribution of fecal excretion to the elimination of dermally administered triclosan is supposed to be negligible. No oxidative metabolites were detected in the urine *in vivo* or after absorption through the skin *in vitro*, and the concentration of triclosan in urine (as the sum of conjugated and unconjugated substance) can be used as a biomarker of exposure to triclosan (5). Thus, the chosen study concept was considered suitable for the determination of the percutaneous absorption of triclosan.

As shown in Table 2, the dose absorbed was less than 10% in all individuals (mean, 5.9% of the dose). This corresponds to the absorption of triclosan from dermal spray and soap preparations in humans, which has been reported to be less than 10% of the dose administered (12). The *in vitro* absorption studies with human skin showed a penetration of 6.3% of the dose by 24 h and formation of glucuronide and sulfate metabolites (14).

Limitations of this study are the small number of participants and the inability to assess the absolute bioavailability based on intravenous data and blood sampling as discussed above. However, the calculated amount absorbed is in agreement with data reported in the literature, and given the large safety margin it can be concluded that triclosan is safe for therapeutic use in dermatological preparations.

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