Absorption, pharmacokinetics and safety of triclosan after dermal administration

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Running title:
Triclosan: absorption, pharmacokinetics and safety
Abstract

We evaluated pharmacokinetics and safety of the antimicrobial agent triclosan after dermal application of a 2% triclosan containing cream to 6 volunteers. Percutaneous absorption calculated from urinary excretion was 5.9% ± 2.1% of the dose (mean ± SD). The amount absorbed suggests that daily application of a standard adult dose would result in a systemic exposure of 890 times lower than the relevant NOAEL. 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 mould and yeasts. It is bacteriostatic at low concentrations by blocking 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, 17). Furthermore, triclosan potently inhibits the growth of *Toxoplasma gondii* and *Plasmodium* (13, 21) and shows anti-inflammatory effects after topical administration (11, 20). For more than 20 years, triclosan is being used widely worldwide in medical and consumer products (5, 22). In dermatological preparations, it is an effective topical antiseptic to reduce colonisation with *Staphylococcus aureus* and to treat superinfected atopic dermatitis (2, 8, 10, 23). Despite the almost ubiquitous occurrence of the substance, pharmacokinetic studies are sparse.

We evaluated pharmacokinetics and safety of triclosan in a clinical study in 6 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% of triclosan. Its composition corresponds to a dermatological standard preparation (NRF 11.122) which is listed in “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 head and genitals. Exposure was ended by taking a shower 12 hours 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 hours post-dose was used for pharmacokinetic calculations (WinNonlin version 5.01). For quantification, the sum of free triclosan and its glucuronide and sulphate metabolites (after enzymatic hydrolysis) was
determined using a specific and sensitive HPLC-MS method based on published methods. 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 hours, and the lower limit of quantification was reached 48 h post-dose. The mean amount excreted $A_e$ (0-48 h) for triclosan was 57.3 mg, which is 4.9% of the administered dose (Table 2). Estimated mean $A_e$ (0 - $\infty$) was 68.7 mg, i.e. 5.9% of the dose (in the following, estimated mean $A_e$ (0 - $\infty$) is defined as “dose absorbed”). The mean apparent terminal elimination half-life ($t_{\frac{1}{2}\lambda z}$) 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 (18). 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 literature data for oral intake (18). This broad variability may be due to individual differences in 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, ECG, vital signs, 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 infections (running nose; common cold). The good tolerability is consistent with safety and tolerability data on triclosan obtained in both published and unpublished studies (4, 7).

For toxicology assessment, the individual systemic exposure was calculated as dose absorbed / body weight and compared with the relevant NOAEL (No Observable Adverse Effect Level)
for triclosan. A NOAEL of 75 mg/kg was obtained from lifetime studies in hamsters; this species most closely reflects human metabolism and elimination pathways (15). The amount absorbed after whole body application was approx. 81 (41-113) times lower than the NOAEL (see Table 3).

It can be concluded that the safety margin for therapeutic use is significantly higher. The recommended adult dose of 2 x 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 concern. This is supported by an extensive toxicology database in literature (3, 4, 6, 7).

The conclusions regarding pharmacokinetics and toxicology are based on the assumption that the estimated total amount of triclosan excreted via urine $A_e (0 - \infty)$ closely reflects the amount absorbed. As our data are based on urinary (not plasma) concentrations and could not be compared to intravenous administration, it cannot be excluded that the pharmacokinetic results of this study might be confounded by incomplete renal excretion. After oral intake of triclosan, a mean amount excreted of approximately 50% of the dose was found (18), which could reflect accumulation, incomplete absorption and excretion via the faeces or as poorly characterized metabolites. All this would result in “true” amounts absorbed being higher than those calculated in this trial.

However, long-term multiple application studies showed no accumulation and similar mean AUC values as following single dose application (1, 12). In contrast to other species (for example rat) excretion of triclosan in humans is predominantly urinary (1, 7, 19). Regarding faecal excretion in humans, to our knowledge no data has been published up to now. The extent of a possible contribution of faecal 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 concentrations of...
triclosan in urine (as sum of conjugated and unconjugated substance) can be used as biomarkers 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 was reported to be less than 10% of the dose administered (12). In vitro absorption studies with human skin showed a penetration of 6.3% of the dose by 24 hours 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 i.v. data and blood sampling as discussed above. However, the calculated amount absorbed is in agreement with literature data, and given the large safety margin it can be concluded that triclosan is safe for therapeutic use in dermatological preparations.

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References


Table 1: Baseline characteristics of all subjects (pre-study examination; n = 6)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Body height (cm)</th>
<th>Body weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>female</td>
<td>34</td>
<td>1.71</td>
<td>58.3</td>
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<tr>
<td>2</td>
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<td>27</td>
<td>1.87</td>
<td>72.0</td>
</tr>
<tr>
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<td>38</td>
<td>1.68</td>
<td>57.3</td>
</tr>
<tr>
<td>4</td>
<td>male</td>
<td>35</td>
<td>1.71</td>
<td>69.5</td>
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<tr>
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<td>female</td>
<td>32</td>
<td>1.81</td>
<td>70.6</td>
</tr>
<tr>
<td>6</td>
<td>male</td>
<td>29</td>
<td>1.81</td>
<td>70.0</td>
</tr>
</tbody>
</table>

Arithmetic Mean  
Arithmetic SD
Table 2: Individual pharmacokinetic variables of triclosan following administration of approx. 60 g of a hydrophobic dermatological preparation containing 2% triclosan (calculated from urinary excretion)

<table>
<thead>
<tr>
<th>Volunteer No.</th>
<th>Dose administered* [mg triclosan]</th>
<th>Ae (0-48 h) [mg] [% of dose]</th>
<th>Estimated Ae (0 - ∞) [mg] [% of dose]</th>
<th>t\text{maxrate} [h]</th>
<th>t(\frac{1}{2}) (\lambda_z) [h]</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1164</td>
<td>61.0 [5.2]</td>
<td>105.6 [9.1]</td>
<td>10.0</td>
<td>22.1</td>
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<tr>
<td>2</td>
<td>1154</td>
<td>57.7 [5.0]</td>
<td>59.2 [5.1]</td>
<td>19.9</td>
<td>3.3</td>
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<tr>
<td>3</td>
<td>1150</td>
<td>34.0 [3.0]</td>
<td>37.9 [3.3]</td>
<td>10.0</td>
<td>10.9</td>
</tr>
<tr>
<td>4</td>
<td>1170</td>
<td>66.2 [5.7]</td>
<td>71.6 [6.1]</td>
<td>10.0</td>
<td>11.6</td>
</tr>
<tr>
<td>5</td>
<td>1170</td>
<td>38.6 [3.3]</td>
<td>49.4 [4.2]</td>
<td>10.0</td>
<td>8.2</td>
</tr>
<tr>
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<td>1186</td>
<td>86.4 [7.3]</td>
<td>88.6 [7.5]</td>
<td>6.0</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Mean 1166 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 1167 59.3 5.1 65.4 5.6 10.0 9.7
Minimum 1150 34.0 3.0 37.9 3.3 6.0 3.3
Maximum 1186 86.4 7.3 105.6 9.1 19.9 22.1

Ae: amount excreted; t\text{maxrate}: time to reach maximum urine excretion rate; t\(\frac{1}{2}\) \(\lambda_z\): apparent terminal elimination half-life.

*: Calculated from the individual amount administered dermally and the strength of the cream (~ 60 g x 2%).

**: Estimated Ae (0 - ∞) is supposed to closely reflect the percutaneously absorbed triclosan.
Table 3: Toxicology: systemic exposure to triclosan and calculated safety margin

<table>
<thead>
<tr>
<th>Volunteer No.</th>
<th>Systemic exposure * [mg/kg]</th>
<th>Safety margin**</th>
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<tr>
<td>1</td>
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<td>41.4</td>
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<td>0.82</td>
<td>91.1</td>
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<tr>
<td>3</td>
<td>0.66</td>
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<td>1.03</td>
<td>72.8</td>
</tr>
<tr>
<td>5</td>
<td>0.70</td>
<td>107.2</td>
</tr>
<tr>
<td>6</td>
<td>1.27</td>
<td>59.3</td>
</tr>
<tr>
<td>Mean</td>
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<td>80.85</td>
</tr>
<tr>
<td>SD</td>
<td>0.44</td>
<td>28.07</td>
</tr>
<tr>
<td>CV %</td>
<td>41.6</td>
<td>34.7</td>
</tr>
<tr>
<td>Median</td>
<td>0.93</td>
<td>81.97</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.66</td>
<td>41.4</td>
</tr>
<tr>
<td>Maximum</td>
<td>1.81</td>
<td>113.3</td>
</tr>
</tbody>
</table>

*: calculated as estimated Ae (0 - ∞) / body weight

**: calculated as NOAEL / systemic exposure, assuming a NOAEL of 75 mg/kg