Absorption of Alcohol Hand Disinfectants

Prof. Axel Kramer, Greifswald, Germany

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propan-2-ol after excessive hygienic and surgical hand disinfection (alcohol based rubs)

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Aim of our study

Determination of alcohol absorption after excessive hygienic or surgical hand disinfection with hand rubs based on ethanol, propan-1-ol and/or propan-2-ol at identical test conditions and with the same volunteers to evaluate the safety/risk of alcoholic hand disinfection

We chose high exposure, because

- no exact absorption rates following hand disinfection are published
- for chemical analysis concentrations about the detection limit are necessary

Setting in our study

- Hand rubs were applied in a room of 37 m³ with two open windows and an open door
- no controlled air exchange during application
- between applications volunteers went to another room in which no one was allowed to use an alcohol-based hand rub
- blood samples were taken in a third room

Volunteers

All hand rubs were tested on the same 6 male and 6 female

Inclusion criteria
- ≥ 18 years
- ability to perform the applications

Exclusion criteria
- visible skin lesions on hands or forearms
- skin disease
- intake of ethanol in any form within 48 h before hand rub
- pregnancy or lactation
- participation at a clinical trial during 30 d before beginning of this study

Study was approved by the Ethics Committee of the Board of Physicians Mecklenburg-West Pomerania at the University of Greifswald

Trial of hygienic hand disinfection

On 5 consecutive days for each application 4 ml were applied to both hands in the test room and rubbed in for 30 s according to the standard rub-in procedure of EN 1500

After a break of 1 min outside the test room the procedure was repeated 20 times resulting in a total exposure time with each hand rub of 10 min over 30 min

At the end of each test day cosmetic hand cream was applied to the treated skin areas

The CDC-guideline for hand hygiene clearly favours the use of alcohol-based hand rubs in hospitals, because antimicrobial soaps have significant disadvantages such as

- lower efficacy
- worse dermal tolerance
- higher potential for impaired efficacy due to an incorrect performance of the procedure
- the necessity of a wash basin


K a m p f G ,  K r a m e r  A .   E p i d e m i o l o g i c  B a c k g r o u n d  o f  H a n d  H y g i e n e  a n d  E v a l u a t i o n  o f  t h e  M o s t
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Relation to „worse case“ events in hospital practice
- On our intensive care unit we observed that at least 15 min will pass between hygienic hand disinfections
- Voss and Widmer1 assumed ~20 hand disinfections per shift and HCW


Trial of surgical hand disinfection
- Start 7 d after the trial of hygienic hand disinfection on 5 consecutive days for each application 4 ml of a hand rub were applied to the hands and distributed on hands and forearms, which was repeated 5 times with the aim to keep hands and forearms wet with the hand rub for the recommended application time of 3 min
- After a break of 5 min outside the test room, a total of 10 surgical hand disinfections were performed
  - resulting in a total exposure time with each hand rub of 30 min over 80 min
- At the end of each test day a cosmetic hand cream was applied to the treated skin areas

Blood samples
- Prior to blood sampling, skin antisepsis was performed with an alcohol-free skin antiseptic
- Blood samples of 5 ml were taken through a venflon before the first daily disinfection (baseline) and 2.5, 5, 10, 20, 30, 60 and 90 min after the last application by hygienic hand disinfection resp. 5, 10, 20, 30, 60 and 90 min after the last application by surgical hand disinfection. Only for hand rub C an additional sample was taken after 120 min.
- Blood samples were stored before analysis at 4 °C for up to 12 h.

Analysis of alcohols, acetaldehyde, aceton and propionaldehyde
- Gas chromatography (modification of Römhild1) by head-space injection (CombiPal-Autosampler, CTC Analytics) with flame-ionisation detection (GC 5890 Hewlett Packard) and DB 624 column for separation (60 m x 0.32 mm x 1.8 µm; J&W).
- Conditions: 150 °C injector temperature, 250 °C detector temperature, column temperature programme 40 °C (8min), 3 °C/min to 120 °C (0 min), 30 °C/min to 230 °C (5 min). Nitrogen (5.0) served as carrier gas with 1.45 ml/min (21.9 cm/s).
- 1 ml sample or standard and 0.5 g glowed Na2SO4 were filled in 1.5 ml head space vials, incubated 45 min at 75 °C, and 2.5 ml were injected splitless
- Calibration with external or self made standard, if the sample concentration did not lie in the calibration level (ethanol) or is commercially not available (acetaldehyde).

Detection thresholds
<table>
<thead>
<tr>
<th>Compound</th>
<th>limit (mg/ml) of detection determination</th>
<th>recording</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>0.14</td>
<td>0.28</td>
</tr>
<tr>
<td>Propan-1-ol</td>
<td>0.13</td>
<td>0.26</td>
</tr>
<tr>
<td>Propan-2-ol</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>Acetaldehyd</td>
<td>0.07</td>
<td>0.15</td>
</tr>
<tr>
<td>Aceton</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Propionaldehyd</td>
<td>0.02</td>
<td>0.05</td>
</tr>
</tbody>
</table>

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Calculation of absorbed alcohols

- Median ethanol concentration was calculated at each time point.
- The proportion of absorbed ethanol and acetaldehyde was determined for each hand rub and type of application by the method of Wittmann:
  
  \[
  \text{Absorbed amount (mg)} = \text{body mass (kg)} \times r \times \text{max. serum level (mg/l)}
  \]

  \[r = 0.7 \text{ for male resp. 0.6 for female}\]


Part I: Absorption of ethanol

Use of three hand rubs with different ethanol content to prove the statement, that ethanol at a concentration between 55% and 95% is considered to be safe\(^1\) for topical use on hands


No data in literature on ethanol absorption by hand disinfection

Despite the worldwide use of ethanol-based hand rubs only few studies have addressed the issue of absorption of ethanol when used on skin with the result

no rise of ethanol in serum was found even after excessive exposure by using dressings for 3 h soaked with 200 ml ethanol


Tested hand rubs

Three blinded ethanol-based hand rubs:

A = 95% w/w ethanol (solution)

B = 85% w/w ethanol (gel)

C = 55% w/w ethanol (solution)

Baseline values in volunteers

- Baseline data for ethanol 0.01-10 mg/l\(^{1,2}\); for acetaldehyde 0.31\(^{1,2}\)
- In 83.8% of samples (57 of 68) the baseline of ethanol concentration was below the limit of detection with median of 0.7 mg/l and highest baseline concentration of 1.7 mg/l
- For acetaldehyde 5.9 % of the baseline values (4 of 86) were below the limit of detection. The median was 0.2 mg/l, the highest baseline concentration was 1.95 mg/l


Baseline values in volunteers

Results indicate the abstinence of volunteers from ethanol before beginning the experiments

Origin of endogenous ethanol is mainly the metabolism of normal intestinal flora which is then absorbed by the host\(^{1,2}\)


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Exposure by hygienic hand disinfection

During 20 hygienic hand disinfections, volunteers were exposed for a contact time of 10 min within a period of 30 min to 80 ml (20 x 4 ml) of hand rub, corresponding to
- 60 g ethanol with hand rub A
- 56.2 g ethanol with hand rub B
- 39.6 g ethanol with hand rub C

Ethanol absorption by hygienic hand disinfection

Highest serum levels (median) of ethanol was found 30 min after the last application:
- 20.9 mg/l with hand rub A (equivalent to 0.02‰ ethanol)
- 11.45 mg/l with hand rub B (equivalent to 0.011‰ ethanol)
- 6.9 mg/l with hand rub C (equivalent to 0.007‰ ethanol)

Total amount of absorbed ethanol:
- 1356 mg with hand rub A (95 % ethanol content)
- 630 mg with hand rub B (85 % ethanol content)
- 358 mg with hand rub C (55% ethanol content)

Based on the total amount of applied ethanol, the proportion of absorbed ethanol was:
- 2.3 % for hand rub A
- 1.1 % for hand rub B
- 0.9 % for hand rub C

Blood concentration of acetaldehyde (mg/l) after hygienic hand disinfection

<table>
<thead>
<tr>
<th>Hand rub</th>
<th>Before first application</th>
<th>30 min</th>
<th>90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.06</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>B</td>
<td>0.08</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>C</td>
<td>0.1</td>
<td>0.6</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Interpretation of acetaldehyde levels

all values are within physiological range

Exposure by surgical hand disinfection

During 10 surgical hand disinfections, volunteers were exposed for a contact time of 30 min within a period of 80 min to a total of 200 ml of hand rub, corresponding to
- 150 g ethanol with hand rub A
- 140 g ethanol with hand rub B
- 99 g ethanol with hand rub C

Absorption by surgical hand disinfection

Highest serum levels (median) of ethanol was found 30 min after the last application:
- 17.5 mg/l with hand rub A (equivalent to 0.017‰ ethanol)
- 30.1 mg/l with hand rub B (equivalent to 0.029‰ ethanol)
- 8.8 mg/l with hand rub C (equivalent to 0.008‰ ethanol)

Total amount of absorbed ethanol:
- 1067 mg with hand rub A (95 % ethanol content)
- 1542 mg with hand rub B (85 % ethanol content)
- 477 mg with hand rub C (55% ethanol content)

Based on the total amount of applied ethanol, the proportion of absorbed ethanol was:
- 0.7 % for hand rub A
- 1.1 % for hand rub B
- 0.5 % for hand rub C

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Blood concentration of acetaldehyde (mg/l) after surgical hand disinfection

<table>
<thead>
<tr>
<th>Hand rub</th>
<th>Before first appl.</th>
<th>30 min after last application</th>
<th>90 min after last application</th>
<th>120 min after last application</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.8</td>
<td>3.6</td>
<td>2.6</td>
<td>not done</td>
</tr>
<tr>
<td>B</td>
<td>0.6</td>
<td>3.3</td>
<td>1.3</td>
<td>not done</td>
</tr>
<tr>
<td>C</td>
<td>0.4</td>
<td>0.9</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Interpretation of acetaldehyde levels

All values are within physiological range

- with all hand rubs concentration of acetaldehyde was significantly above baseline of 0.2 mg/l throughout the observation period (p < 0.05)
- after 30 to 60 min, levels of acetaldehyde began to go down slowly

Assessment of exposure

- In our test model as well as in practise its not possible to distinguish between dermal and pulmonary absorption, so we described the overall absorption by practical hand disinfection.
- Some of the observed absorption is certainly explained by pulmonary uptake. If for example 200 ml of hand rub A is applied within 80 min, a total of 190 g ethanol is going to evaporate into the air from the skin. If no air exchange takes place it would have resulted in an ethanol concentration in air of 4.1 g/m³ which is almost three times above the maximum occupational exposure concentration of ethanol (1.9 g/m³).
- But the increase of blood levels after the last application up to 30 min could be explained only by dermal absorption.

Risk assessment for determined ethanol absorption

- Under the extreme test conditions, which will not be found in hospitals, only 0.5 % to 2.3% of applied ethanol is absorbed, and nearly independent of ethanol concentration in the disinfectant
- Calculation under real conditions: At 3 surgical hand disinfection with hand rub A with the highest ethanol concentration (95%) over 6 h, exposition is 15.1 g ethanol every 2 h. Approx. 0.7% of the applied ethanol will be absorbed (~ 106 mg ethanol). The average man/woman has a body weight of 70/60 kg with 40.6/28.8 l total body water. Systemic availability of ethanol after surgical hand disinfection is therefore in man approx. 0.0025‰ (= 2.61 mg/l), in woman 0.0035‰ (= 3.68 mg/l).
  both ethanol levels are systemically safe, there are only 2 fold higher than the baseline in our study and are distinctly lower than the maximum of physiological value of 0.01

Risk assessment for determined ethanol absorption

The average metabolisation rate of ethanol is 150 mg/l/h or 0.15‰/h

As consequence, in real time intervals between hand disinfections, the effective resulting level of Ethanol in blood would be remarkably lower than in our model


Part II: Absorption of propan-1-ol and propan-2-ol

Origin of baseline levels

- **Ethanol**: intestinal flora, fruit juices, antiseptic mouth washes
- **Propan 1**: no baseline levels known
- **Propan 2**: reduction of aceton

Knowledge on absorption of propan-1-ol

- no data in literature on absorption of propan-1-ol
- on isolated human epidermis the constant of permeability is
  - ethanol: $0.8 \times 10^{-3}$ cm/h
  - propan-1-ol: $1.2 \times 10^{-3}$ cm/h
  - propan-2-ol: $1.35 \times 10^{-3}$ cm/h


Knowledge on absorption of propan-2-ol

- Study1 on 10 volunteers: hand disinfection every 10 min over 4 hours (52.6 % w/w propan-2-ol)
  - 0.5-1.8 mg/l (1 = no detectable level)
- Conclusion: 500 mg/l are associated with mild absorption1, further studies are necessary1


Metabolism of alcohols

- **Ethanol**: linear elimination rate (to acetaldehyde)
  - $0.1-0.2‰$ /h
- **Propan-1-ol** (to propionaldehyde) and **propan-2-ol** (aceton) exponential elimination rate
  - half life time/human for ethanol: 2-6 h
  - half life time/rat for propan-1-ol: ~ 45 min
  - half life time/rat for propan-2-ol: ~ 1-4 h
  - half life time/man for propan-2-ol: ~ 170 min

1. www.ma.uni-heidelberg.de/inst/ikc/ikc-normbereiche_kc.html - 387k

Consequences

- no risk of accumulation to blood levels about 0.1‰ by usual hand disinfection

References

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Tested hand rubs

Blinded rubs:
D = propan-1-ol 30 % w/w + propan-2-ol 45 % w/w  (solution)
E = propan-2-ol 70 % w/w  (solution)

Baseline values for trial with propan-1-ol based rub

Baseline data for propan1-ol < 0.05 mg/l1, for aceton 0.2-14.4 mg/l2, for propionaldehyde no data in literature – see our results:
- Propan-1-ol: in the first trial (hygienic hand rub) all volunteers < 0.1 mg/l were detectable, in the second trial only one volunteer (0.07 mg/l), for the other the concentrations were below the limit of detection
- Aceton: 5.9 % of the baseline values (4 of 86) were below the limit of detection. The median was 0.2 mg/l, the highest baseline concentration was 1.95 mg/l
- Propionaldehyde: 0.1mg/l

Our median baseline values indicate abstinence of volunteers from alcohol (congeners) before beginning the experiments.

Interpretation of baseline values

Exposure by hygienic hand disinfection

During 20 hygienic hand disinfections, volunteers were exposed for a contact time of 10 min within a period of 30 min, using 80 ml (20 x 4 ml) of hand rub, corresponding to
- 18.9 g propan-1-ol with hand rub D
- 28.4 g propan-2-ol with hand rub D
- 43.7 g propan-2-ol with hand rub E

propan-1-ol absorption by hygienic hand disinfection

Highest serum levels (median) of propan-1-ol was found 30 min after the last application for hand rub D:
- 12.6 mg/l (equivalent to 0.012‰)

The total amount of absorbed propan-1-ol:
- 599.8 mg

Based on the total amount of applied propan-1-ol, the proportion of absorbed propan-1-ol was:
- 3.2 %

propan-2-ol absorption by hygienic hand disinfection

Highest serum levels (median) of propan-2-ol was found 60 min after the last application:
- 6.6 mg/l with hand rub D (equivalent to 0.006‰)
- 7.8 mg/ml for hand rub E (equivalent to 0.0075‰)

Total amount of absorbed propan-2-ol:
- 309.5 mg with hand rub D (45 % propan-2-ol content)
- 309.5 mg with hand rub E (70 % propan-2-ol content)

Based on the total amount of applied propan-2-ol, the proportion of absorbed propan-2-ol was:
- 1.1 % for hand rub D
- 0.7 % for hand rub E

Blood concentration of aceton (mg/l) after hygienic and surgical hand disinfection

<table>
<thead>
<tr>
<th>Hand rub</th>
<th>before first appl.</th>
<th>30 min after last application</th>
<th>90 min after last application</th>
<th>120 min after last application</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pygienic surgical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td>3.4</td>
<td>4.4</td>
<td>not determined</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>2.6</td>
<td>4.7</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>1.7</td>
<td>4.2</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>hygienic surgical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.7</td>
<td>4.4</td>
<td>5.0</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Exposure by surgical hand disinfection

During 10 surgical hand disinfections, volunteers were exposed for a contact time of 30 min within a period of 80 min to a total of 200 ml of hand rub, corresponding to:
- 47.3 g propan-1-ol with hand rub D
- 71.0 g propan-2-ol with hand rub D
- 109.2 g propan-2-ol with hand rub E

Propan-1-ol absorption by surgical hand disinfection

Highest serum levels (median) of propan-1-ol was found min after the last application for hand rub D:
- 23.2 mg/l (equivalent to 0.022‰)

The total amount of absorbed propan-1-ol:
- 918.2 mg

Based on the total amount of applied propan-1-ol, the proportion of absorbed propan-1-ol was:
- 1.9 %

Propan-2-ol absorption by surgical hand disinfection

Highest serum levels (median) of propan-2-ol was found min after the last application:
- 12.7 mg/l for hand rub D (equivalent to 0.012‰)
- 10.1 mg/l for hand rub E (equivalent to 0.0097‰)

Total amount of absorbed propan-2-ol:
- 598.6 mg for hand rub D
- 471.6 mg for hand rub E

Based on the total applied amount of propan-2-ol, the proportion of absorbed propan-2-ol was:
- 0.8 %
- 0.4 %

Conclusion

The absorption and the metabolisation rate of the three alcohols is nearly the same, but ethanol is less toxic than the propanols

<table>
<thead>
<tr>
<th>agent</th>
<th>oral LD50 (mg/kg) for rat</th>
<th>total absorbed amount (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ethanol</td>
<td>14000</td>
<td>22.0</td>
</tr>
<tr>
<td>propan-1-ol</td>
<td>5400</td>
<td>13.1</td>
</tr>
<tr>
<td>propan-2-ol</td>
<td>5840</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Risk assessment by LD50 and absorption

Quotient of LD50 and total absorbed amount at unrealistically high test exposure!

- ethanol 636.4
- propan-1-ol 412.2
- propan-2-ol 720.0

Obviously no toxic risks
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Risk assessment by acceptable daily intake (ADI)
- WHO: Recommendation for ethanol = 7 g/d
- EFSA1: ADI for propan-2-ol 2.4 mg/kg = 144 mg/60 kg

Conclusion
- Absorption of the three alcohols is low < 0.03.
- The possibility of systemic toxic effects can be effectively ruled out.
- Our recommendation: For skin antisepsis on newborns, ethanol-based preparations are preferred because dermal absorption and inhalative properties are more tolerable than propanols. For premature newborns non-absorbable antiseptics should be used (i.e. octenidine).

Conclusion
- A hand rub must be safe and effective
- The exposure to a hand rub should be only as long as necessary to ensure the required efficacy, tolerance and compliance
- recent data suggest that 1.5 min application time for surgical hand antisepsis is as effective as 3 min application of the reference 60% propan-1-ol

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