The effect of ethanol on paracetamol absorption and activated charcoal efficacy, in a simulated human paracetamol overdose

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OBJECTIVE

• This study evaluated if ethanol in two different strengths affected the gastric emptying time, and if activated charcoal efficacy was altered in the presence of ethanol, in humans; Previous data on ethanol influence are conflicting

RELEVANCE?

• In vitro results gave an indication (Hoegberg et al. 2002)
• Highly relevant hence ~ 10% of drug poisonings included ethanol (Danish figures, Boegevig et al. 2011)
HYPOTHESIS

• The adsorption capacity of activated charcoal is decreased, and drug absorption increased, if gastric content includes ethanol
  – We might treat drug intoxications with an insufficient amount of activated charcoal when ethanol is involved

• Ethanol slow down gastric emptying
  – Activated charcoal dosing might be effective late compared to no alcohol
RESULTS

<table>
<thead>
<tr>
<th>Study day</th>
<th>Activated charcoal (50 g)</th>
<th>AUC (min*mg/L)</th>
<th>Tmax (min)</th>
<th>Cmax (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water, 1068 ml</td>
<td>No</td>
<td>9197 [1752]</td>
<td>53 [42]</td>
<td>50 [18]</td>
</tr>
<tr>
<td>Beer, 1068 ml (7.2% v/v ethanol)</td>
<td>At 1 h</td>
<td>6949 [2375]</td>
<td>59 [14]</td>
<td>41 [13]</td>
</tr>
<tr>
<td>Liquor, 205 ml (37.5% v/v ethanol + 150 ml juice)</td>
<td>At 1 h</td>
<td>8375 [2749]</td>
<td>39 [18]</td>
<td>51 [18]</td>
</tr>
</tbody>
</table>

Pharmacokinetic parameters for paracetamol. **Mean** [SD].

**AUC**
- Water vs. Beer: p<0.05
- Beer vs. Beer+AC: p<0.01
- Beer+AC vs. Liquor+AC: p<0.05

**Tmax**
- Water vs. Beer: p<0.01
- Beer vs. Beer+AC: p<0.01
- Beer+AC vs. Liquor+AC: p<0.01

**Cmax**
- Water vs. Beer: NS
- Beer vs. Beer+AC: NS
- Beer+AC vs. Liquor+AC: p<0.05
RESULTS

- serum-Ethanol concentrations peaked at 60 min

10 mmol/L = 0.46‰

Blood alcohol content (BAC) limits worldwide:
- DK 0.5‰
- Europe 0.0-0.9‰
- Australia 0.5‰
- Canada/USA 0.8‰
- Swaziland 1.5‰

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METHODS
Volunteers...
METHODS

Real-life mechanism:
Cause triggering action (e.g. depressive state) → Drinking →
Overdose (emptying the tablet container) → Say goodbye → Hospital

Simulated mechanism/Model:
Continous alcohol consumption (5 units = 60 g ethanol, in 45 min) →
Model drug intake, high dose, many tablets (paracetamol, 50 mg/kg bodyweight as 125 mg paracetamol/tablet) → Wait (1h) → Hospital intervention (activated charcoal, 1x50g).
METHODS

Challenge:

• Moderate alcohol ingestion
  – we could not exceed the maximal daily intake as recommended by the Danish board of Health

• Drug ingestion
  – we could not load with toxic doses
  – we needed a drug easy to measure in blood samples
**METHODS**

- Volunteers are their own control
- 4 study days
- Randomised to sequence 1-4

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Study day 1</th>
<th>Study day 2</th>
<th>Study day 3</th>
<th>Study day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>D</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>A</td>
<td>D</td>
<td>B</td>
</tr>
<tr>
<td>4</td>
<td>D</td>
<td>C</td>
<td>B</td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Water (0% v/v ethanol), in 45 min</th>
<th>Beer (7.2% v/v ethanol), in 45 min</th>
<th>Liquor (37.5% v/v ethanol in 150 ml fruit juice), in 45 min</th>
<th>Activated charcoal (50 g)</th>
<th>Paracetamol (50 mg/kg)</th>
<th>Blood sampling, for 7 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day A/ Control: Beer:</td>
<td>1068 ml</td>
<td>1068 ml *</td>
<td>When water was finished</td>
<td>1 hour after paracetamol ingestion</td>
<td>When liquor was finished</td>
<td>Yes</td>
</tr>
<tr>
<td>Day B/ Beer:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Day C/ Beer +AC:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Day D/ Liquor +AC:</td>
<td></td>
<td></td>
<td>205 ml *</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Correlates to 60 g ethanol or 5 units each of 12 g ethanol.
DISCUSSION - Limitations

Study:
• *Design*
  – Real-life mechanisms of drug overdose are possibly much more complex than our simplified simulated mechanism
  – The prolonged gastric emptying time from beer might be caused by nutrient components
• *Missing*
  – Water +AC; Liquor ÷AC days

Extrapolation:
• *The drug*
  – Paracetamol is a model drug, other drugs might behave differently
• *Ethanol*
  – Ingested units might differ in real-life poisonings; from the present model it is difficult to tell if absorption and adsorption were affected by volume or concentration
DISCUSSION - Conclusion

What did we learn:

• Activated charcoal stopped the drug absorption in both alcohol groups
• Beer prolonged gastric emptying time, and increased drug absorption
• Liquor (high ethanol conc.) increase gastric emptying compared to Beer (low ethanol conc.)

• We have no reason to believe that present activated charcoal dosing strategies should be changed when the patient co-ingested alcohol
STUDY GROUP

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...for providing serum-Ethanol analysis
Thank you...