Interaction of paracetamol in chronic alcoholic patients. Importance for odontologists

Gerardo Gómez-Moreno 1, Javier Guardia 2, Antonio Cutando 3

(1) Professor of Clinical Odontology for Special Patients. Professor responsible for Pharmacological Interactions in Odontological Patients with Systemic Pathology
(2) Bachelor of Odontology. Collaborator of Pharmacological Interactions in Odontological Patients with Systemic Pathology
(3) Professor of Clinical Odontology for Special Patients. Department of Odontology. University of Granada. Spain

Correspondence:
Dr. Gerardo Gómez-Moreno.
Facultad de Odontología, Universidad de Granada.
Colegio Máximo s/n, Campus de Cartuja.
E-18071, Granada. Spain
E-mail: ggomez@ugr.es

Received: 21/07/2007
Accepted: 13/02/2008

Abstract
For social, cultural and historical motives alcohol (ethanol or isopenthanol) is considered to be just a beverage rather than a liquor. However, from a pharmacotherapeutic point of view alcohol is a depressor of the central nervous system. The effects of alcohol consumption can range from raised loquacity to drunkenness, loss of consciousness and death as a result of insufficient respiration. Probably the most frequent pharmacological interaction is the combination of alcohol with other depressors of the central nervous system which increases the depression even further. Some medicaments which more frequently produce an interaction are antihistamines, analgesics, antidepressants and medicaments for coughs, common cold and influenza.

Paracetamol or acetaminophen is an analgesic medicament similar to acetylsalicylic acid lacking anticoagulatory properties and gastric irritation. However, its major drawback is hepatic toxicity as a result of a toxic metabolite produced in the liver by cytochrome P-450, principally cytochrome CYP2E1, which is detoxified under normal conditions by hepatic glutathione. Ethanol is also detoxified by CYP2E1, which is an inducer of ethanol such that chronic ingestion increases the level of this enzyme. When the ingestion of alcohol is stopped, CYP2E1 is greatly increased and only metabolises the paracetamol giving rise to high quantities of hepatotoxic metabolites so that the hepatic glutathione is unable to detoxify resulting in irreversible hepatic damage. Therefore for odontologists it is important that in chronic alcoholic patients the consumption of alcohol should not be suspended on prescribing paracetamol.

Key words: Alcohol, paracetamol, hepatotoxicity.

Introduction
According to the 2004 data of the World Health Organisation (1) there are 76.3 million people with disorders produced by consuming alcoholic drinks resulting in 1.8 million deaths. In Spain 62.3% of adults, predominantly men, are alcohol consumers (Table 1). The consumption of pure alcohol in litres per head in Spain is 12.25%, much higher than in countries like Italy, the United States or Russia (Table 2). The major drawback of paracetamol is the effect on the liver after excessive consumption which can be fatal if adequate measures are not taken. Of all the pharmacological interactions of paracetamol, one of the most important for the odontologist is the combination with alcohol. Due to the easy accessibility of paracetamol and high levels of alcohol consumption it is important to be aware of this interaction which has gained notoriety over the last few years because of legal implications. For example, a court decreed in favour of a patient who...
consumed alcohol and was prescribed paracetamol for influenza. He later developed liver failure and required a liver transplant (2).

For this review references were obtained from studies published in indexed journals, in MEDLINE databases up to June 2007, which show the importance, for the odontologist, to be aware of the interaction of paracetamol in chronic alcoholic patients.

Metabolism of paracetamol and alcohol

The CYP2E1 enzyme (pertaining to the oxidative enzymes of cytochrome P-450) plays an essential role in the metabolism of paracetamol. When this enzyme metabolises paracetamol a highly hepatotoxic compound called NAPQI (N-acetyl-p-benzoquinoneimine) is formed which is rapidly detoxified by hepatic glutathione (Figure 1). The CYP2E1 enzyme of cytochrome P-450 also intervenes in the metabolism of ethanol. It has been demonstrated that there is a risk of hepatic alteration when paracetamol and alcohol are ingested within short intervals of time because alcohol consumption induces CYP2E1 increasing its concentration. Alcohol is the principal substrate for this enzyme which inhibits other substrates such as paracetamol. Consequently metabolism of ethanol has an influencing role inhibiting the non toxic metabolism of paracetamol and the detoxification of NAPQI (3). As a result of this combination a single intake of 600mg/kg of paracetamol in rats produces significant hepatic lobular necrosis, hemorrhagic congestion and erythrocyte infiltration but without damaging the hepatic parenchyma. Ingestion of 300mg/kg of paracetamol in combination with ethanol produces lesions in the parenchyma and endothelium similar to a single ingestion of 600mg/kg of paracetamol (4). Together with the alterations cited, the combination of these two substances, at the hepatic level, gives rise to stenosis and ischemic changes (5) accompanied by a considerable increase of hepatic proteins and transaminases (ALT, AST and SGOT) (5-8) producing liver failure or death by hepatic coma (7). Even so, the induction of the CYP2E1 enzyme does not appear to be sufficient to explain the magnitude of these adverse effects on the assumption that they influence other enzymes like CYP3A or mitochondrial glutathione (GSH). The toxicity of paracetamol shortly after alcohol consumption results from the induction of the CYP2E1 enzyme. However, if the ingestion is spaced out over time then the toxicity is due to the induction of CYP2E1 and a selective depletion of mitochondrial GSH (9).

CYP2E1 is an enzyme induced by alcohol and has a great affinity for paracetamol. This enzyme is a potent inhibitor as is triacetyloleandomycin (TAO). The application of TAO protects against the hepatotoxicity of paracetamol in rats that have been administered paracetamol and alcohol and was able to reduce the serum levels of ALT but not of AST (10). All these data could suggest that in the interaction, the CYP2E1 enzyme is not exclusively implicated (11,12). At the immune system level the combination of paracetamol and alcohol produces a progressive reduction of circulatory leucocytes, the relative weight of the liver, spleen and thymus in comparison with the consumption of alcohol alone. There is also a significant reduction of platelets, in the haemoglutination of sheep erythrocytes and IgG antibodies in response to bovine serum albumen. Therefore there is a tendency for phagocyte suppression when both substances are combined (6). At the renal level, and in experimental animals, paracetamol induces an increased effect on the cells of the proximal tubules as a result of the association of both substances.

On the other hand, the activity of the urinary N-acetyl-glucuronidase, a lysosomal enzyme located preferentially in the proximal renal tubules and which catalyses the hydrolysis of glucuronosides to glucuronates and alcohols,

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Total (%)</th>
<th>Men (%)</th>
<th>Women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom</td>
<td>2000</td>
<td>12.0</td>
<td>9.0</td>
<td>14.0</td>
</tr>
<tr>
<td>United States</td>
<td>2002</td>
<td>33.9</td>
<td>29.3</td>
<td>38.2</td>
</tr>
<tr>
<td>Spain</td>
<td>2003</td>
<td>37.7</td>
<td>26.9</td>
<td>48.7</td>
</tr>
<tr>
<td>France</td>
<td>1999</td>
<td>6.7</td>
<td>4.3</td>
<td>8.9</td>
</tr>
<tr>
<td>Italy</td>
<td>2000</td>
<td>25.0</td>
<td>36.4</td>
<td>12.8</td>
</tr>
<tr>
<td>Russia</td>
<td>1996</td>
<td>23.1</td>
<td>9.0</td>
<td>35.0</td>
</tr>
<tr>
<td>Canada</td>
<td>1998-1999</td>
<td>22.1</td>
<td>17.8</td>
<td>26.1</td>
</tr>
</tbody>
</table>

Table 1. Percentage of teetotallers in the adult population.

Table 2. Consumption of pure alcohol in litres per head (over 15 years of age).

<table>
<thead>
<tr>
<th>Country</th>
<th>Total</th>
<th>Country</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iran</td>
<td>0.00</td>
<td>United Kingdom</td>
<td>10.39</td>
</tr>
<tr>
<td>Egypt</td>
<td>0.10</td>
<td>Finland</td>
<td>10.43</td>
</tr>
<tr>
<td>Morocco</td>
<td>0.41</td>
<td>Russia</td>
<td>10.58</td>
</tr>
<tr>
<td>Maldives</td>
<td>1.72</td>
<td>Spain</td>
<td>12.25</td>
</tr>
<tr>
<td>Mexico</td>
<td>4.62</td>
<td>Portugal</td>
<td>12.49</td>
</tr>
<tr>
<td>United States</td>
<td>8.51</td>
<td>Luxembourg</td>
<td>17.54</td>
</tr>
<tr>
<td>Greece</td>
<td>9.30</td>
<td>Uganda</td>
<td>19.47</td>
</tr>
</tbody>
</table>

Table 2. Consumption of pure alcohol in litres per head (over 15 years of age).
is significantly higher (13). It has been observed that, via maternal milk in alcoholic mothers who ingest paracetamol, a renal effect could be produced in the offspring and even result in a reduction of weight gain (13).

**Importance of the interaction of paracetamol in chronic alcoholics for odontologists**

In Spanish society alcohol is considered to be a beverage without placing any importance on the pharmacological effects which could arise, above all, in the central nervous system. The ease of obtaining alcoholic drinks and paracetamol (which does not require a medical prescription in Spain) obliges odontologists and other medical professionals to be very aware of the interaction when prescribing paracetamol to chronic alcoholic patients.

In odontology clinics it is very difficult to identify chronic alcoholic patients. Generally the patients do not recognise their addiction and naturally none of them consider their consumption as being excessive. Even so, we should investigate their clinical history and look for suspicious signs of excessive alcohol consumption. On the other hand the primary reason for an odontological consultation is pain, which obliges the odontologist prescribe analgesics daily. The fact that paracetamol does not have any adverse gastric effects makes this medicament attractive and is generally overprescribed.

The importance of the interaction between paracetamol and chronic alcoholic patients for the odontologist is that it is not advisable to suspend the consumption of alcohol in the patients that are prescribed paracetamol because suddenly stopping alcohol consumption could result in serious hepatic failure which would then be the responsibility of the odontologist. This is because the metabolism of paracetamol and alcohol both use the same cytochrome P-450 enzyme, CYP2E1. Under normal conditions 5% of the paracetamol is metabolised by CYP2E1 producing a metabolite called NAPQI which is rapidly detoxified by glutathione to avoid hepatic damage (Figure 1).

Ethanol, the principal component of alcoholic drinks, is an inducer of the CYP2E1 enzyme, which in chronic alcoholics, increases the concentration of this enzyme. Consequently in chronic alcoholics the CYP2E1 enzyme is used almost exclusively in the metabolism of ethanol relegating the conjugation with other medicaments such as paracetamol to a secondary level.

The concentration of the enzyme rises with increased time of ethanol ingestion. Because of this, when there is a sudden stoppage of alcohol consumption the CYP2E1 enzyme (which is greatly increased) only metabolises paracetamol (which is the only substrate with which it can combine). This results in large concentrations of the hepatotoxic metabolite (NAPQ1) which cannot be totally detoxified by hepatic glutathione. This could provoke irreversible liver damage leading to liver failure requiring a transplant (14).

What is more important for the odontologist is the necessity to explain to these patients that they should not suddenly stop drinking alcohol while on pharmacological treatment with paracetamol. If the maximum dose of paracetamol of 4g/day is too high for alcoholic patients then a reduction of the dose is recommended. For safety and effectiveness, N-acetylcysteine (mucolytic and expectorant) is the antidote of choice in patients with paracetamol overdose and who have chronically consumed alcohol (15,16). Administration of this compound should be made as soon as possible to minimise the adverse effects on the liver. Hepatic protection in rats by administration of Cassia occidentalis leaves after combination of alcohol and paracetamol has also been described (17).

---

**Fig. 1. Metabolism of paracetamol and ethanol.**
References


