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Hepatotoxicity induced by acute and chronic paracetamol overdose in adults. Where do we stand?

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ABSTRACT

Paracetamol (Acetaminophen) poisoning data can reveal the potential deficiencies of paracetamol poisoning management guidelines. We conducted a retrospective cohort study of patients >18 years who were attended in the emergency department (ED) of a Spanish tertiary hospital, from 2005 to 2010 for suspected paracetamol overdose and who had measurable paracetamol concentrations. 208 patients suspected of paracetamol poisoning were identified. The annual incidence in the ED increased from 2.0 (95%-CI: 0.2–7.2) cases per 10,000 patients in 2005 to 3.4 (95%-CI: 1.1–8.8) in 2010. Only 7 of 98 patients (7.14%) with acute poisoning at toxic doses showed hepatotoxicity signs, 4 (57.1%) of whom presented acute liver failure (ALF) criteria, while 8 of 10 patients (80%) with chronic paracetamol poisoning at toxic doses presented hepatotoxicity and 3 (37.5%) with ALF criteria. The time required to find medical care was 9.0 h for acute poisoning and 49.6 h for chronic poisoning ($p < 0.001$). We conclude that the incidence of suspected cases of paracetamol poisoning at our hospital is increasing. The majority of toxicity cases, including ALF, associated with the ingestion of paracetamol were due to chronic poisoning. This finding constitutes an important warning regarding paracetamol chronic poisoning, and clinicians should have a higher index of clinical suspicion for this entity.

1. Introduction

Paracetamol is the most widely used analgesic in the world. In most Western countries, including the UK (ÒGrady et al., 1989) and USA (Schiødt et al., 1999), it is the leading cause of acute liver failure (ALF). Accurately and rapidly predicting the risk of hepatotoxicity after a paracetamol overdose is essential because the clinical and biochemical signs of organ toxicity are not detectable until about 24 h after overdose, well past the optimum time for antidote therapy.

Unintentional overdosing from self-medication for pain or fever that leads to daily doses exceeding 4 g is usually only recognized after the symptoms have developed. Delays in seeking medical attention and delays in initiating N-acetylcysteine (NAC) therapy are associated with a greater risk of morbidity and mortality (Dargan and Jones, 2002; Chun et al., 2009).

Although the recommended doses of 4 gr/day is generally safe, Watkins et al. found that even with the ingestion of this dose for several days, it is possible to develop an asymptomatic ALT elevation in healthy volunteers (Watkins et al., 2006). In patients with impaired liver function there are no uniform criteria for recommending an appropriate dose of paracetamol. Along these lines, a meta-analysis concluded that among participants who consumed ethanol just prior to or during the trial and ingested 4 g/day of paracetamol, there was no evidence of elevation of ALT on day four (Rumack et al., 2012). Lewis et al. recommend that the dose of paracetamol for cirrhotic patients should be reduced to a maximum of 2–3 g/day (Lewis and Stine, 2013). Rossi et al. assessed healthcare providerś recommendations on how over-the-counter analgesics should be used in patients with Chronic Liver Disease (CLD) and concluded that physicians recommend against the use of paracetamol more than NSAIDs in patients with CLD (Rossi et al., 2008).

For nearly 20 years, it has been recognized that hepatotoxicity develops in about 6% of patients with a serum paracetamol concentrations above 200 μg/ml at 4 h from ingestion who are treated with NAC within 10 h of the overdose (Smilkstein et al., 1988).

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Patients with higher serum paracetamol concentrations, longer delays to NAC, and other risk factors (such as alcoholism) are at higher individual risk. Zyoud et al. (2011) also found that abdominal pain at presentation, the presence of psychiatric illness, and delays in NAC administration were associated with a prolonged hospital stay.

In a substantial proportion of cases, the patient has concomitantly overdosed one or more drugs in addition to paracetamol; such drugs may affect the outcome of the paracetamol intoxication as a result of pharmacokinetic interaction or through independent toxic or hepato-protective properties. Suggested mechanisms of interaction include an increased or reduced rate of absorption of paracetamol, reduced conjugation of paracetamol, depletion of glutathione and inhibition of cytochrome P450-mediated metabolism (Bhattacharya et al., 2012) or an intrinsic inflammatory stimulus (Roth and Ganey, 2010). Schmidt and Dalhoff (2002) reported concomitant drug overdosing in 31%; (95% CI 27–34%) of patients (207/671) between 1994 and 2000. Benzodiazepines, opioid analgesics, acetylsalicylic acid (ASA), and nonsteroidal anti-inflammatory drugs (NSAIDs) predominated.

The aim of this study was to analyze the incidence and outcome of acute paracetamol overdosing compared with chronic overdosing among adults in a tertiary hospital in Spain.

2. Material and methods

This was an observational, longitudinal, retrospective cohort study conducted at La Paz University Hospital (LPUH) in Madrid, a tertiary teaching hospital with 1,365 beds that serves a population of 868,138 inhabitants. Using LabTrack (a database of an Integrated Laboratory System, development version; TrackHealth, Woolloomooloo, Australia), we identified all patients over 18 years of age whose paracetamol serum concentrations were measured by the Clinical Pharmacology Laboratory between 2005 and 2010. We then reviewed the patients' medical records (electronic and paper) to document the study variables in a case report form (CRF) designed for this purpose. We conducted a causality analysis on those cases with impaired hepatic function with or without hepatic failure. The needed sample size was determined to be 198 patients (margin of error ±7%, 95% CI, 50% of distribution of response). The sample size for univariate logistic regression showed that accepting an alpha risk of 0.05 and a beta risk of 0.2, for a proportion of chronic overdose between 8 and 10%, between 196 and 179 subjects were needed to recognize a statistically significant odds ratio greater than or equal to 2. The study was approved by the Clinical Research Ethics Committee of LPUH, whose members are accredited by the Spanish Ministry of Health.

The patients were classified according to the reason for requesting serum paracetamol serum concentrations: accidental ingestion, attempted suicide, and the study of impaired hepatic function for those with a history of paracetamol ingestion. Similarly, we classified the patients according to the type of ingestion: acute or chronic.

2.1. Study population

The population consisted of all patients over 18 years of age for whom a determination of paracetamol serum concentration was requested from the Clinical Pharmacology Laboratory between 2005 and 2010. According to clinical protocols, paracetamol concentration tests are performed for all patients with suspected acute paracetamol poisoning (PAP) but not necessarily for chronic poisoning. In the latter case, the request was at the discretion of the attending physician and was based on clinical and laboratory variables.

2.2. Definition of variables

The following information was recorded in the CRF: demographic and hospital variables, medical history, concomitant medication, reason for the request for paracetamol concentration test, laboratory findings, time elapsed since overdose and type of regimen (acute, chronic).

Acute toxic doses of paracetamol were considered to be a single ingestion of paracetamol of more than 4 g, while chronic poisoning was defined as the repeated consumption of a dosage greater than 4 g/day for one or more days.

Based on the Food and Drug Administration classification, we considered significant hepatotoxicity an increase in glutamic-pyruvic transaminase (GPT), also know alanine aminotransferase (ALT), concentrations >3 times the upper limit of normal (ULN) with or without >2 times the ULN in total bilirubin (FDA, Pre-marketing Guidance, 2009). Patients were considered to have ALF if they had an increased concentration of transaminases with acute onset of impaired coagulation (INR >1.5 or prothrombin activity <50%), with encephalopathy (Jiménez-Gómez et al., 2010).

The final causality assessment of liver toxicity from paracetamol was established based on a history of potentially toxic paracetamol ingestion prior to the request for determining serum concentrations of this drug. The presence of liver enzyme disorders and a lack of an alternative cause that might explain the condition were also assessed. The assessment of causality followed the Spanish PharmacoVigilance System (SPVS) (Capellá and Laporte, 1993) and the RUCAM (Roussel Uclaf Causality Assessment Method). Both algorithms evaluate similar parameters: the chronology, which refers to the interval between drug administration and the effect, the literature defining the degree of knowledge of the relationship between the drug and the effect, the evaluation of drug withdrawal, the rechallenge effect, and the presence of alternative causes. SPVS and RUCAM include assessing the presence of other diseases and/or other drugs. In addition, in the RUCAM scale, a history of hepatitis adds an extra point. The final evaluation was classified as not related, possibly related, probably related and definitive or highly probable.

2.3. Statistical analysis

The frequency results are expressed in absolute terms, such as percentages and confidence intervals. The continuous variables are expressed as means (±SD) or median (range) according to the normality test (Kolmogorov Smirnov test). The discrete variables are expressed as median (range). We used the chi-squared test, Fisher's exact test, Student's *t*-test or the equivalent non-parametric test, as appropriate, to calculate the differences between the variables. To estimate the risk factors associated with chronic poisoning, we performed a univariate logistic regression analysis.

We calculated the incidence of suspected paracetamol poisoning for 2007 in the adult population served by LPUH. The numerator was the number of patients with paracetamol serum concentration requests to the Clinical Pharmacology Laboratory in 2007, and the denominator was the adult population count in 2007. We calculated the incidence per year during the study period in the LPUH ED using, as the numerator all cases with paracetamol serum concentrations recorded during the year and as denominator the total number of patients attended in the ED during the same period.

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