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Paracetamol and acute liver injury

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Abstract
Background: Acute liver injury (ALI) induced by paracetamol overdose is a well-known cause of emergency hospital admission and death. However, there is debate regarding the risk of ALI after therapeutic dosages of the drug. The aim is to describe the characteristics of patients admitted to hospital with jaundice who had previous exposure to therapeutic doses of paracetamol. An assessment of the causality role of paracetamol was performed in each case.
Methods: Based on the evaluation of prospectively gathered cases of ALI with detailed clinical information, thirty-two cases of ALI in non-alcoholic patients exposed to therapeutic doses of paracetamol were identified. Two authors assessed all drug exposures by using the CIOMS/RUCAM scale. Each case was classified into one of five categories based on the causality score for paracetamol.
Results: In four cases the role of paracetamol was judged to be unrelated, in two unlikely, and these were excluded from evaluation. In seven of the remaining 26 cases, the RUCAM score associated with paracetamol was higher than that associated with other concomitant medications. The estimated incidence of ALI related to the use of paracetamol in therapeutic dosages was 0.4 per million inhabitants older than 15 years of age and per year (99%CI, 0.2-0.8) and of 10 per million paracetamol users-year (95% CI 4.3-19.4).
Conclusions: Our results indicate that paracetamol in therapeutic dosages may be considered in the causality assessment in non-alcoholic patients with liver injury, even if the estimated incidence of ALI related to paracetamol appears to be low.
Results: Up to December 31 1999, total follow up was 17,616,592 person-years and 126 patients fulfilling the inclusion criteria of ALI were identified. Drug exposures among these patients with ALI and comparative risks associated with various commonly used drugs have been reported on [12]. The RUCAM scale was applied to 32 cases exposed to paracetamol. In four cases paracetamol exposure started on the day the first symptoms of ALI (fever, abdominal pain, marked weakness, skin rash and/or pruritus, jaundice or choluria) appeared, and they were therefore classified as unrelated to paracetamol. In two cases the RUCAM score for paracetamol was < or = 2 and they were classified as unlikely. Of the remaining 26 cases, the score for paracetamol was higher than that for other concomitant drugs (7 cases). In 19 additional cases that took drugs that are known to be hepatotoxic agents, these drugs scored equal or higher than paracetamol. The different scores between the cases classified as "probable" and those classified as "possible" were mainly due to the differences in three items: time to onset, the course of the reaction after cessation of the drug, and previous information on the association between paracetamol exposure and liver injury, which in one case with a mixed pattern scored one point less. Several features for the 7 cases (4 probable and 3 possible) with a paracetamol score higher than that of concomitant drugs are provided in table 1. The median daily dose of paracetamol was 650 mg (range 650-3,250). The median duration of the exposure period, i.e. the period between the first and the last day of use was 10 days (range 1-77) in five patients. The other two patients had taken the drug for at least one year. The median alcohol consumption was 13.43 g per day (range 0-42.67). In six patients the pattern of liver injury was hepatocellular. Five cases showed symptoms of hypersensitivity (fever, rash, eosinophilia, thrombocytopenia or arthralgia). All cases except one were taking other drugs. Hypersensitivity reactions have been described for metamizol, dextromethorphan, indapamide, indomethacin, corticosteroids, metoclopramide, bisacodyl, budesonide, carbocysteine, ambroxol, benzocaine, chlorhexidine [2].

Keywords: paracetamol, liver, injury, overdose, emergency

1. Introduction
Paracetamol is the most important pharmacological cause of acute liver failure (ALF) [1–5] and is the primary cause of overdose in the Indian subcontinent. It is thought to be safe in recommended doses, up to 4 g per day in adults. The public health impact of a paracetamol overdose has been evaluated in several epidemiological studies [1] In a multicentric survey of ALF including hospitals attending approximately half the Spanish population, paracetamol was considered to be the cause of ALF in only 2.6% of 267 cases identified between 1992 and 2000, and the estimated incidence of ALF during the study period was of 1.4 cases per million inhabitants per year [7]. In contrast, liver injury after therapeutic dosages appears to be highly unusual and the mechanism accepted for the overdose liver injury has in fact been under discussion [10]. In a clinical trial in healthy volunteers who received 4 g of paracetamol daily, significant increases in alanine aminotransferase (ALT) were recorded [11]. The clinical significance of these results is unknown. In an epidemiological study a relative

Methods
A collaborating network including 12 hospitals covering a population of 2.7×10^6 inhabitants of 15 years of age or older was set up. To avoid any selection bias the patients were selected on the basis of their condition, rather than on

the basis of suspected exposures. Cases of ALI were defined as jaundice with a total bilirubin level of ≥ 3 mg/dl and an acute increase in ALT of at least five times the upper limit of the normal range and/or an increase in alkaline phosphatase (AP) of at least twice the upper limit of the normal range. Patients with alcohol consumption greater than 50 g per day and/or with other possible causes of liver injury were excluded (the principal causes were serologically proven viral hepatitis, alcoholic liver disease, processes causing obstruction of bile flow and drug overdoses). The pattern of ALI was classified as hepatocellular, cholestatic or mixed, according to the International Consensus Meeting designations of ALI [12]. The patients were interviewed, after informed consent was given, using a structured questionnaire covering their past medical history, clinical course of the present condition, and detailed information on the use of medicines and exposure to environmental toxins in the previous three months. Clinical and laboratory data were also recorded. As described, this was a population-based study, and thus allowed us to estimate the incidence of ALI related to paracetamol based on the cases defined as probably or possibly related to paracetamol exposure. The incidence on paracetamol users was estimated on the basis of drug consumption data. Confidence limits at 95% were used to obtain an approach to the precision of the estimated incidence.

Table 1: Values Are Expressed As Mean + Sd, Ast Is Aspartate Aminotransferase, Alt Is Alanine Aminotransferase, Alp Is Alkaline Phosphatase, Total Serum Bilirubin, Sd Is Standard Deviation

Treatments	AST (U/L)	ALT (U/L)	ALP (IU/L)	Total Bilirubin (MG/L)
Control	11.5+3.14	6.5+1.87	39.6+21.8	0.3+0.14
Paracetamol	32+7.98	17.9+8.7	75.9+27.9	0.87+0.38
Carvedilol	17.9+5.76	10.7+11.21	42.98+2190	0.9+0.25
Prazosin	12.9+3.12	7.16+3.12	46.98+17.7	0.9+0.10
Metoprolol	18.9+11.8	13.87+8.76	41.87+16.98	0.7+0.32
Prazosin + Metoprolol	19.9+8.76	12.9+5.5	40.87+4.89	0.34+0.14

Table 2: Effect of Esh and Paracetamol on Liver Enzymes

Design of treatment	SGPT U/L	SGOT U/L	ALP U/L	Total Bilirubin MG/DL
Normal control	40.98=2.12	90.87+1.98	109.87+0.76	0.65+0.32
Paracetamol control	86.76+0.87	154+2.98	132.98+2.1	1.32+0.43
Silymarin (100mr/kg/day)	56.87+0.98	123+4.76	121.87+1.54	0.61+0.21
Esh (200mmg/kg/day)	63.98+0.99	132.78+1.87	122.65+0.76	0.76+0.32
Esh (400mmg/kg/day)	78.43+O.65	143+1.987	132+0.65	0.92+0.011

Discussion

Paracetamol in high single doses (typically 15 g or more) causes liver injury through a toxic metabolite, NAPQI (N-acetyl-p-benzoquinone imine). Alcohol consumption and possibly starvation induce cytocrome P-450 and therefore increase NAPQI synthesis. These factors also contribute to glutathione depletion, [2, 4] thus enhancing paracetamol hepatotoxicity. Therefore, heavy drinkers would be at high risk of liver toxicity with paracetamol taken in relatively high doses [8, 9]. Acute liver failure has also been reported after doses up to 5 g per day, particularly in alcoholic patients, as well as in fasting patients and patients with underlying liver disease [8]. Those seven cases reported low alcohol consumption, except case number 1. This patient underwent a liver transplant, and we cannot rule out that paracetamol probably enhanced alcohol toxicity. No patient turned up with a wasting disease or with signs of starvation. Liver injury after therapeutic dosages of paracetamol has been described in several case reports, but the patients had concurrent potentially contributing conditions, such as asymptomatic HIV infection, hepatitis B or hepatitis C virus infection, heavy alcohol consumption (more than 50 g per day), and/or fasting and nutritional impairment [3,6]. In this study patients with these conditions were excluded. In a randomized controlled trial, 31% - 44% of healthy young participants experienced an ALT level greater than 3 times the upper limit of the normal range (ULN) and more than 19% of participants experienced ALT more than five times the ULN during treatment with paracetamol at a dose of 4 g per day for 14 days, although none developed symptoms or laboratory evidence of hepatic failure [11]. Hypersensitivity to paracetamol is rare, although a few cases of paracetamol-induced idiosyncratic hepatic injury [3] have been described. One case recurred on drug rechallenge, and showed symptoms of hypersensitivity [3]. Paracetamol seldom produces allergic skin reactions or respiratory symptoms, [4] and anaphylactic shock also occurs very rarely [4, 2]. Thrombocytopenia related to paracetamol has also been described even though in one case it can be explained by the use of other drugs (non-steroidal anti-inflammatory drugs) taken by the patient. In our series, three of the four patients with the highest causality scores for paracetamol had symptoms of hypersensitivity, suggesting that an immunological mechanism could be involved. This mechanism may explain the presence of ALI in cases with a short period of exposure. This study contributes to completing the information about drug-induced liver injury, especially about liver toxicity and paracetamol at therapeutic dosages, a topic that has not been studied from a prospective design up to now as far as we know. In fact its incidence is unknown and we provide an estimation where paracetamol is one of the most widely used analgesics. There has also been some controversy about its importance since the publication of a RCT [11] where the increase in transaminases seems more frequent than had previously been thought. This study has several strengths. Stringent clinical inclusion criteria were applied, case ascertainment was prospective, and the case definition depended on strict clinical criteria rather than on exposure to any particular drug. Additionally, intensive systematic ascertainment of all patients fulfilling the study criteria was performed within the study area. The exclusion of patients with alcohol

consumption greater than 50 g per day and/or with other possible causes of liver injury (the principal causes were serologically proven viral hepatitis, alcoholic liver disease, processes causing obstruction of bile flow and drug overdoses) allows us to focus on a more selected population where other causes of ALI have been discarded. In order to avoid selection bias, only serious forms of acute liver disease, usually with jaundice, were included. In addition, details on previous use of medicines (including over the counter drugs and herbs) and alcohol consumption were carefully recorded by asking patients using a detailed structured questionnaire about symptoms, specific indications that covered the use of medicines most frequently associated with liver disease, and by showing them pictures of the major medications of interest. Patients with other known causes of liver disease were excluded. A standardized method of causality assessment was used which may overcome some of the disadvantages of expert opinions in causality assessment of drug reactions. This study also has several limitations. Causality assessment was based on algorithms which are relatively simple to apply but where the weighting of each criterion can be somewhat arbitrary. Even though the RUCAM scale is considered at present as the best method for assessing causality in drug-induced liver disease, [4] the scale has some limitations, such as the poor definition of the items to be answered and the scarce diagnostic capability when two drugs are administered at the same time. This algorithm awards higher scores to the known hepatotoxic medications, and therefore it may tend to underestimate the causative role of any medication previously unknown to be hepatotoxic. However, not only recently marketed but also old drugs still not incriminated in hepatotoxicity could be to blame [5]. On the other hand, the RUCAM scale does not take into account symptoms of hypersensitivity, while nearly one third of acute hepatic drug reactions are mediated by immunoallergic mechanisms. In addition, very late onset of ALI is awarded lower scores, while several drugs are known to cause liver injury after latency periods of more than 90 days [7]. Finally, the algorithm does not take into account the indication of the suspected medication, which in turn may actually have been prescribed to alleviate early symptoms of liver disease.

Conclusion

The data from the present case series using detailed clinical and laboratory information indicate that paracetamol in therapeutic dosages may be considered a factor in the causality assessment in patients with liver injury in non-alcoholic individuals,(even if the estimated incidence appears to be low). However, the diagnosis of acute liver injury and the causality assessment to a particular drug remains a difficult task. Liver injury shows a hepatocellular pattern and concomitant symptoms of hypersensitivity in a proportion of cases suggest that the mechanism could be immune mediated. The threshold dose for paracetamol toxicity may vary among individuals, and it may depend on genetic as well as environmental factors. Further studies of the intrinsic mechanisms of hepatotoxicity and the research in biomarkers are needed for a better clinical management of those patients. The estimated population incidence and the incidence in paracetamol users were low and paracetamol use at therapeutic dosages may be considered safe enough regarding its potential liver toxicity.

Table 3: Patients classified as a probable or possible based on paracetamol score (Rucam Lgorithm).

Case	Sex/Age	Alcohol use (g/d)	ALT/AP	Bili	Hypersensitivity	Outcome	Indication	Daily dose (mg)	Rucam Score
1	F/58	43	15.85/1.74	1.36	No	Tx	OA		8
2	F/82	0	15.32/1.95	10.41	Thrombocytopenia	Recovered	Cold	650	7
3	F/85	0.5	22.21/1.27	12.32	Arthralgia, thrombocytopenia	Not recovered	OA	1950	7
4	F/25	24	383.33/2.35	3.64	Eosinophilia	Recovered	Cephalea	3250	7
5	M/18	13	5.27/1.24	5.88	Fever	Recovered	Cephalea	650	5
6	F/23	13	50.23/2.16	9.23	Fever, rash	Recovered	Cephalea	500	4
							Fever	1950	
							Fever	1950	
									Carbocysteine
									Ambroxol
									Benzocaine
									Chlorhexidine
7	F/35	20	61.10/0.64	22.43	No	Recovered	Dysmenorrhea	650	3

Alcohol Use Is Expressed As A Mean In Grams Per Day In The Last Year; Alt, Alanine Aminotransferase And Ap, Alkaline Phosphatase And Bili, Bilirubin, Expressed In Times The Upper Limit Of Normal Values; Outcome At 6 Months Of Follow-Up; Ali, Acute Liver Injury; Hc, Hepatocellular; M, Mixed; Tx, Liver Transplantation.

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