Hepatotoxicity induced by acute and chronic paracetamol overdose in children: Where do we stand?

Hoi Yan Tong, Nicolás Medrano, Alberto Manuel Borobia, José Antonio Ruiz, Ana María Martínez, Julia Martín, Manuel Quintana, Santos García, Antonio José Carcas, Elena Ramírez
Madrid, Spain

Original article

Background: **There are few data on hepatotoxicity induced by acute or chronic paracetamol poisoning in the pediatric population. Paracetamol poisoning data can reveal the weaknesses of paracetamol poisoning management guidelines.**

Methods: **We retrospectively studied the patients of less than 18 years old with measurable paracetamol levels, who were brought to the emergency department (ED) of La Paz University Hospital, Madrid, Spain, for suspected paracetamol overdoses between 2005 and 2010.**

Results: **Ninety-two patients with suspected paracetamol poisoning were identified. In 2007, the incidence of paracetamol poisoning in the pediatric population was 0.8 [Poisson-95% confidence interval (CI): 0.03-3.69] per 10 000 inhabitants aged less than 18 years. The incidence in the same year was 1.53 (Poisson-95% CI: 0.24-5.57) per 10 000 patients in the pediatric ED. The most common cause of poisoning was attempted suicide (47.8%) in teenagers with a median age of 15 years, followed by accidental poisoning (42.2%) in babies with a median age of 2.65 years. Difference was seen in the frequency of hepatotoxicity between acute and chronic poisoning cases. Only 1 of 49 patients with acute poisoning showed hepatotoxicity [acute liver failure (ALF)], whereas 7 of 8 patients with chronic poisoning showed hepatotoxicity (3 cases of ALF). The average time to medical care was 6.83 hours for acute poisoning and 52.3 hours for chronic poisoning (*P*<0.001).**

Conclusions: **Chronic paracetamol poisoning is a potential risk factor for hepatotoxicity and acute liver failure. Delays in seeking medical help might be a contributing factor. Clinicians should have a higher index of clinical suspicion for this entity.**

World J Pediatr 2017;13(1):76-83

Key words: **acute liver failure; hepatotoxicity; paracetamol; poisoning**

Introduction

Paracetamol (acetaminophen) is widely used in children and has a well-established safety profile and efficacy, especially when compared with other antipyretic drugs. The overall risk of developing hepatotoxicity from paracetamol appears to be lower in children than in adults.[1] In children, sulfation predominates over glucuronidation, resulting in a reduced formation of toxic intermediates. Children also have a greater capacity to synthesize glutathione than adults and are therefore capable of inactivating the toxic metabolites of paracetamol more efficiently than adults.[2-4]

Various studies on patients under 19 years of age have revealed that acute drug poisoning is among the primary reasons for visiting the emergency department (ED).[5] There appears to be no doubt about the relationship between acute paracetamol poisoning and hepatic damage. The Pediatric Acute Liver Failure Study analyzed 348 cases of acute liver failure (ALF) in a pediatric population.[6] In 21% of the cases, the cause of ALF in those over 3 years old was due to paracetamol acute poisoning (PAP). The key factors to assess in PAP are the ingested dose and the serum concentration of the drug. However, this relationship is not as clear when the drug is taken on a long-term basis at doses considered therapeutic (60 mg/kg per day).[7-10] The most important risk factor for liver damage and death after PAP is a delay of more than 8 hours in starting treatment with N-acetyl cysteine (NAC).[11] The increase in transaminase levels usually occurs within the first 24 hours; however, some patients show no evidence of liver damage until

Author Affiliations: Department of Clinical Pharmacology, Hospital Universitario La Paz, IdiPAZ, School of Medicine, Universidad Autónoma de Madrid, Madrid, Spain (Tong HY, Medrano N, Borobia AM, Ramírez E, Carcas AJ); Pediatric Emergency Department, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain (García S, Ruiz JA, Martín J); General Emergency Department, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain (Martínez AM, Quintana M)

Corresponding Author: Elena Ramírez, Department of Clinical Pharmacology, Hospital Universitario La Paz, IdiPAZ, School of Medicine, Universidad Autónoma de Madrid, Paseo de la Castellana, 261, Madrid 28046, Spain (Tel: +34 91 7277559; Fax: +34 91 7277559; Email: elena.ramirez@inv.uam.es)

doi: 10.1007/s12519-016-0046-6
Online First, July 2016

24 hours after ingestion.[12,13] James et al[14] suggested that all pediatric patients with an acute paracetamol overdose should be observed and treated with NAC for 48 hours after ingestion. However, emerging evidence shows that prolonged treatment with NAC might impair liver's recovery from PAP hepatotoxicity, possibly because NAC interferes in glucose and mitochondrial tricarboxylic acid metabolisms; thus, when massive hepatonecrosis occurred, NAC does not maintain the proliferation of primary hepatocytes.[15]

There are few data on acute or chronic paracetamol poisoning in the Spanish pediatric population. The primary objectives of this study were to estimate the incidence, describe the suspected cases of paracetamol poisoning, and determine the differences between the patterns of acute vs chronic ingestion in patients younger than 18 years who were treated at a tertiary hospital.

Methods

Study design

A retrospective cohort study was conducted at La Paz University Hospital in Madrid, Spain, a tertiary hospital that in 2007 attended approximately 223 558 children aged under 14 years, plus 29 100 teenagers aged between 14 and 17 years, of a global population of 868 138 habitants. We identified all patients younger than 18 years whose paracetamol serum concentrations were measured by the Clinical Pharmacology Laboratory between 2005 and 2010, using a LabTrack data management system (Integrated Laboratory System, development version; TrackHealth, Woolloomooloo, Australia). We then reviewed the medical records (electronic and hard-copy) of the patients to document the study variables in case report forms (CRF) with the information dissociated. The necessary sample size was determined to be 86 patients [margin of error 5%, 95% confidence interval (CI)]. The study was approved by the Institutional Review Board at La Paz University Hospital, whose members are accredited by the Ministry of Health.

Study population

The population consisted of all patients younger than 18 years for whom a determination of paracetamol levels was requested from the Clinical Pharmacology Laboratory between 2005 and 2010. According to clinical protocols, the paracetamol level tests are required for all patients with suspected PAP but not for chronic poisonings. In the latter case, the request is at the discretion of the physician and is based on clinical and laboratory variables.

The following information is recorded in the CRF: demographic and hospital variables, medical history, concomitant medication, reason for the request for paracetamol level tests (accidental ingestion, attempted suicide, liver function impairment), laboratory findings, time elapsed since overdose, and type of regimen (acute, chronic).

The paracetamol dose taken by the patients according to the medical history was adjusted for weight. For patients younger than 14 years who were attended in the pediatric emergency department (PED), we recorded their actual weight as listed in their medical records. For patients aged 14-17 years who were attended in the general ED, we used the 50th percentile of the weight-age ratio curves by sex in the Spanish population as the reference.[16]

The patients were classified according to the reason for requesting serum paracetamol levels: accidental ingestion, attempted suicide, and the study of impaired hepatic function for those with a history of paracetamol ingestion. Likewise, we classified the patients according to the type of ingestion: acute or chronic. We conducted a causality analysis on those patients with impaired hepatic function with or without hepatic failure.

Diagnostic definition

Acute poisoning was considered a single supratherapeutic ingestion of paracetamol, whereas chronic poisoning was defined as repeated supratherapeutic ingestion of paracetamol. An acute toxic dose of paracetamol was considered a single dose ingestion of paracetamol of more than 150 mg/kg or 100 mg/kg with risk factors.[17] A chronic toxic dose of paracetamol was defined as follows: in children younger than 6 years, intake above 200 mg/kg in a 24-hour period; or more than 150 mg/kg every 24 hours for the preceding 48 hours; or greater than 100 mg/kg in a 24-hour period in patients with risk factors. In patients older than 6 years, intake greater than 200 mg/kg or 10 g (whichever is less) in a period of 24 hours; or greater than 150 mg/kg or 6 g (whichever is less) every 24 hours for the preceding 48 hours; or greater than 100 mg/kg or 4 g/day (whichever is lower) in a 24-hour period in patients with risk factors.[18]

Based on the Food and Drug Administration classification, we considered significant hepatotoxicity to be an increase in glutamic-pyruvic transaminase (GPT) [also called alanine aminotransferase (ALT)] levels >3 times the upper limit of normal (ULN) and/or >2 times the ULN in total bilirubin.[19] Patients were considered to have ALF if they had increased levels of transaminases with acute onset of impaired coagulation (INR >1.5 or prothrombin activity <50%), with or without encephalopathy.[20]

The final causality assessment of liver toxicity from paracetamol was based on the paracetamol ingestion

prior to the request for determining plasma levels of this drug, the presence of liver enzyme disorders, and a lack of an alternative cause that might explain the condition. The assessment followed the Spanish Pharmacovigilance System's method for attributing causality.[21] We considered possible, probable, and definitive cases to be related.

Statistical analysis

The results for frequency are expressed in absolute terms and percentages. The continuous variables are expressed as means (standard deviation) or median (range) according to the normality test (Kolmogorov Smirnov test). We used the Chi-square test, Fisher's exact test, Student's *t* test, or the equivalent non-parametric test, as appropriate, to calculate the differences between the variables. We performed a univariate logistic regression to estimate the risk factors associated with chronic poisoning. We calculated the incidence of suspected paracetamol poisoning for 2007 in the population under 18 years old admitted to the emergency department. The numerator was the number of patients with paracetamol serum levels requested of the Clinical Pharmacology Laboratory in 2007, and the denominator was the under-18 population count in 2007. The cumulative incidence was calculated only for the PED. We used as numerator the number of cases less than 14 years with record of levels of paracetamol during the study period and as denominator, the total number of patients attended at the PED during the same period. The data were analyzed using IBM SPSS Statistics for Windows, Version 19.0 (Armonk, NY, USA).

Results

From January 1, 2005 to December 31, 2010, we registered 92 patients under the age of 18 years with measurable paracetamol serum levels; 2 patients were not evaluated due to lack of data in patients' medical

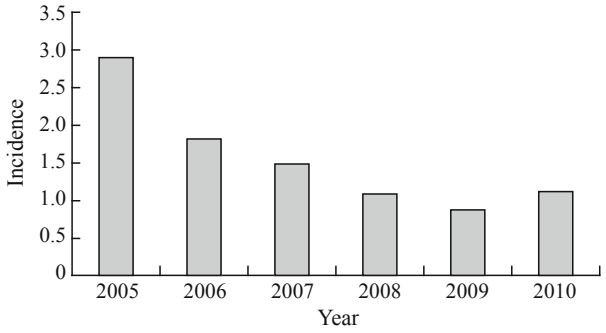

Fig. The yearly incidences of suspected paracetamol poisoning in patients with requested paracetamol serum level test at the emergency department of La Paz University Hospital.

Table 1. Demographic, diagnostic and hospitalization variables of patients with suspected paracetamol poisoning

Variables	Features	*n*	%
Median age (range), y	9.5 (0.003-17)	90	100
	<14	54	60
	≥14	36	40
Gender	Males	30	33.30
	Females	60	66.70
	Total	90	100
Origin	Spain	72	80
	Unknown	5	5.60
	Abroad	13	14.40
	Total	90	100
Liver disease	No	89	98.90
	Not indicated	1	1.10
	Total	90	100
Malnutrition	No	88	97.80
	Yes	1	1.10
	Not indicated	1	1.10
	Total	90	100
Other relevant medical history	None	73	81.10
	Psychiatric	10	11.10
	Cardiovascular system	1	1.10
	Dermatology	1	1.10
	Digestive system	1	1.10
	Neurological	1	1.10
	Obstetric and gynaecologic	1	1.10
	Respiratory system	1	1.10
	Trauma	1	1.10
	Total	90	100
Ingestion of other drugs	No	61	67.80
	Yes	25	27.80
	Unknown	4	4.40
	Total	90	100
Service requesting	Emergency Department	62	68.90
	Pediatrics/Internal	12	13.30
	Intensive Care	11	12.20
	Neonatology	1	1.10
	Nephrology	1	1.10
	Obstetric and Gynaecologic	1	1.10
	Pediatric Cardiology	1	1.10
	Pediatric Hepatology	1	1.10
	Total	90	100.00
Median days in ED, median (range)	1 (0-5)		
Hospitalization	No	59	64.40
	Yes	31	35.60
	Total	90	100.00
Admission service	Pediatrics/Internal	12	38.70
	Intensive Care	10	32.20
	Psychiatry	4	12.90
	Neonatology	1	3.20
	Nephrology	1	3.20
	Obstetric and Gynaecologic	1	3.20
	Pediatric Cardiology	1	3.20
	Pediatric Hepatology	1	3.20
	Total	31	100.00
Hospital stay in days, median (range)	3.5 (1-82)		
Outcome	Discharge from ED	59	65.60
	Discharge from ward	31	34.40
	Total	90	100.00
Reason for requested paracetamol serum level tests	Attempted suicide	43	47.80
	Accidental	38	42.20
	Liver enzyme disorder	9	10.00
	Total	90	100.00
Type of regimen	Acute	77	85.6
	Chronic	11	12.2
	Unknown	2	2.2
	Total	90	100.00
Treatment	N-acetyl cysteine	41	45.6
	Gastric lavage	37	41.1
	Activated carbon	50	55.6
	Hemodialysis	2	2.2
Number of therapies	None	20	22.2
	One	23	25.6
	Two	26	28.9
	Three	17	18.9
	Four	1	1.1
	Total	87	100.00

ED: Emergency Department.

Table 2. Variables according to reasons for requested paracetamol serum level test

Variables	Accidental (*n*=38)	Attempted suicide (*n*=43)	Liver enzyme disorder (*n*=9)
Age, y	2.65 (0.008-7)	15 (12-17)	1.57 (0.003-17)
Gender			
Female, *n* (%)	19 (50)	38 (90.5)	3 (33.3)
Male, *n* (%)	19 (50)	5 (9.5)	6 (66.7)
Origin			
Spain	38 (100%)	26 (60.5%)	8 (88.9%)
Abroad	0	12 (27.9%)	1 (11.1%)
Unknown	0	5 (11.6%)	0
Hours of Emergency Department (ED) care	2.3 (0.3-96)	4 (0.2-48)	38.5 (10-168)
Days in ED	1 (1-2)	2 (0-5)	1 (0-4)
Admission			
Yes	5 (13.2%)	18 (41.9%)	8 (88.9%)
Days in ward	2 (1-82)	3 (1-9)	7 (3-72)
Admission service	5 (100%)	18 (100%)	8 (100%)
Pediatrics/Internal	4 (80%)	4 (22.2%)	4 (50%)
Pediatric Cardiology	1 (20%)		
Intensive Care Unit		9 (50%)	1 (12.5%)
Obstetrics		1 (5.55%)	
Psychiatry		4 (22.2%)	
Neonates			1 (12.5%)
Nephrology			1 (12.5%)
Pediatric Hepatology			1 (12.5%)
Transaminase impairment due to paracetamol	1 (2.63%)	1 (2.33%)	6 (66.66%)
Outcome			
Discharge from ED	33 (86.8%)	25 (58.1%)	1 (11.1%)
Discharge from ward	5 (13.2%)	18 (41.9%)	8 (88.9%)
Type of regimen			
Acute	32 (84.2%)	43 (100%)	2 (22.2%)
Chronic	4 (10.5%)		7 (77.7%)
Unknown	2 (5.3%)		
Ingested dose			
Acute (mg/kg), median (range)	161.4 (13.8-381), *n*=32	136.1 (18.18-886.36), *n*=31	298.5 (97-500), *n*=2
Chronic (mg/kg/d), median (range)	144.8 (104.16-562.5), *n*=3	0, *n*=0	123.1 (72-192.3), *n*=6
Ingestion of other drugs			
Yes	1 (2.6%)	23 (53.5%)	1 (11.1%)
No	36 (94.7%)	17 (39.5%)	8 (88.9%)
Unknown	1 (2.6%)	3 (7%)	
Paracetamol level on admission, μg/mL	17.8±21.2	44.3±76.1	2.8±3.3
Time from ingestion to level test request (h)	4.5 (2-96), *n*=37	5 (1-48), *n*=28	30 (10-168), *n*=8
Treatment (yes/no)			
N-acetyl cysteine	18/19 (48.6/51.3%)	18/23 (42.9/54.8%)	5/4 (55.6/44.4%)
Gastric lavage	14/23 (37.8/62.2%)	22/19 (53.7/46.3%)	1/8 (11.1/88.9%)
Activated carbon	24/13 (64.8/35.1%)	24/17 (58.5/41.5%)	2/7 (22.2/77.8%)
Hemodialysis	0/37 (0/100%)	2/39 (4.7/95.1%)	0/9 (0/100%)
Unknown	1 (2.63%)	2 (4.65%)	0 (0%)

records, resulting in a total of 90 evaluated patients with suspected paracetamol poisoning. The incidence for 2007 in the PED was 1.53 (Poisson 95% CI: 0.24-5.57) per 10 000 patients who attended this department (Fig.). The incidence of suspected paracetamol poisoning for 2007 in patients younger than 18 years of age admitted to our hospital was 0.8 (Poisson 95% CI: 0.025-3.69) per 10 000 inhabitants.

The characteristics of the evaluated patients are shown in Table 1. The median age was 9.5 years (0.003-17), and the patients were predominantly female (66.7%); 31 patients (64.4%) were admitted to hospital wards and 32.2% were admitted to intensive care units. All the patients were discharged; there were no deaths and none required liver transplantation. Of the admitted patients, 27.8% consumed other drugs: among them, 52% were for musculoskeletal system disorders, 30% for nervous system diseases, 7% for alimentary tract and metabolism disorders, 7% for general anti-infections and 4% for systemic hormonal preparations.

The primary reasons for requesting paracetamol levels were attempted suicide (43 patients, 47.8%), accidental ingestion (38 patients, 42.2%), and elevated levels of liver enzymes with a history of paracetamol poisoning (9 patients, 10%). Table 2 shows the patient characteristics according to the reason for requesting paracetamol serum level tests. The accidental ingestion group was characterized by a median age of 2.65 years with no differences in sex. Approximately 13% of these patients were admitted to a hospital ward: 4 patients (10.5%) had chronic poisoning, 2 patients had no record of the type of ingestion, and the remainder had

acute ingestion. The mean paracetamol serum level at admission was 17.8±21.2 μg/mL, the median number of hours from ingestion to the request of serum levels was 4.5 hours (n=37), and the median time to arrival at the ED after ingestion was 2.33 (0.3-96) hours. In the attempted paracetamol suicide group, the median age was 15 years, and 90% of the patients were female. Of these patients, 41.9% required hospitalization and 100% involved acute ingestion. The mean paracetamol serum level was 44.32±76.1 μg/mL, the median time from ingestion to the request for serum level tests was 5 hours (n=28), and the time from ingestion to arrival at the ED was 4 (0.2-48) hours. Nine patients had liver enzyme impairment upon arrival at the ED, which prompted the request for paracetamol plasma level tests for having a history of ingesting this drug: 7 for chronic poisoning and 2 for acute poisoning. Following the causality assessment, 6 of the 7 patients with chronic poisoning presented liver impairment secondary to paracetamol. The median dosage was 123.1 mg/kg per day, the median paracetamol serum level at admission for these patients was 2.8±3.33 μg/mL, and the median time from ingestion to the request for serum level tests was 51 hours. The 2 patients with acute ingestion presented alternative causes.

In terms of the type of ingestion, 77 (85.6%) patients had acute paracetamol poisoning and 11 (12.2%) had chronic poisoning; 2 (2.2%) patients were of unknown type. The comparison of these groups is shown in Table 3. There were significant differences between acute and chronic poisoning in the mean of age (9.33 years *vs.* 4.86 years, P=0.033), in the hours of ED care (6.83 hours *vs.* 52.3 hours, P<0.001), in the percentage of admissions (29.9% *vs.* 72.2%), in the median of hospitalization days (3 days *vs.* 7 days, P=0.009), in the reasons for paracetamol level request (P<0.001), in the increase of transaminases >3ULN (1.3% *vs.* 63.6%, P<0.001), and in the percentage of ALF (1.3% *vs.* 27.3%, P<0.001). The most relevant difference between the acute and chronic cases of paracetamol toxicity was the frequency of hepatotoxicity. Only 1 of 49 patients with acute poisoning at toxic dose showed hepatotoxicity; this patient arrived at the ED within 48 hours, with ALF criteria and renal function impairment. With regard to chronic poisoning, 7 of the 8 patients with paracetamol poisoning at toxic doses presented hepatotoxicity, 3 of whom presented ALF criteria. The odds ratio (OR) for hepatitis in the group of chronic poisoning was 65.63 (95% CI: 10.16-423.99) compared with that of the group of acute poisoning, the OR for liver failure in the group of chronic poisoning was 28.50 (95% CI: 2.64-307.18, P<0.001) compared with that in the group of acute poisoning.

Discussion

Paracetamol is the drug most frequently involved in pediatric poisonings, and it is estimated that in the United States paracetamol is responsible for approximately 56 000 ED visits and more than 450 deaths per year in patients of all ages.[22] In Spain, poisonings by this drug are not as common, with an incidence in the PED of approximately 4 cases per 10 000 ED visits.[23,24] Our study measured an even lower incidence of 1.53 cases per 10 000 patients under 14 years of age who were treated in the PED of our hospital. It should be noted that our study only selected those cases in which serum level tests of this drug were requested. Although this might represent an underestimation of the actual number of cases, we believe that it is close to the actual number for 2 fundamental reasons: 1) patients with suspected acute paracetamol poisoning are sent to the hospital if the ingestion is considered at risk; and 2) the request for testing paracetamol levels is formalized and is a common practice for all cases of suspected PAP. In contrast, the request is not clearly formalized in cases of chronic poisoning, and therefore the approach depends on the discretion of the attending physician. We believe that these cases may cause an underestimation in our results.

Paracetamol represents the leading cause of ALF for all ages, and it is the most commonly drug involved in poisoning in countries such as the United States, the United Kingdom and Scandinavian countries.[25] A multicenter prospective study of patients younger than 18 years of age conducted in the United States between 1999 and 2004 found that of a total of 348 patients with ALF criteria, 14% were due to acute paracetamol poisoning.[6] The results are in contrast to data from a study conducted between 1992 and 2000 in 17 hospitals of 11 Spanish communities, which assessed 267 patients with ALF between the ages of 1 and 79 years. That study observed that only 2.2% of the patients were secondary to paracetamol.[26]

These differences between Spain and other countries in the incidence of paracetamol poisoning and its toxicity could be due to cultural differences or to the approach to attempted suicide. However, it is striking that the oral solution formulations marketed for children in Spain are more concentrated (100 mg/mL) than those marketed in the United States (32 mg/mL). Therefore, these differences in the complications from paracetamol poisoning might also be secondary to other factors, such as the time of arrival at the ED, greater genetic susceptibility, nutritional factors, the presence of risk factors (dehydration, alcoholism) or the concomitant use of other drugs (particularly enzyme inducers).

Table 3. Comparison of acute poisoning and chronic poisoning

Variables	Acute		Chronic		*P* [OR (95% CI)]
	n=77	*n*	*n*=11	*n*	
Age, mean (SD), y	9.33 (6.46)	77	4.86 (5.98)	11	0.033 [0.89 (0.79-0.99]
Gender, *n* (%)					
Female/Male	53/24 (68.8/31.2)	77	7/4 (63.6/36.4)	11	0.729 [0.79 (0.34-4.72)]
Hours of ED care	6.83 (9.8)	65	52.3 (54.37)	10	<0.001 [1.08 (1.03-1.13)]
Days in ED	1.6 (0.98)	77	1.36 (0.92)	11	0.450 [0.74 (0.34-1.63)]
Admission, *n* (%)					
Yes/no	23/54 (29.9/70.1)		8/3 (72.7/27.3)		0.005 [6.26 (1.52-25.74)]
Days in ward	3 (1-11)	20	7 (3-82)	8	0.009 1.36 (1.02-1.79)]
Outcome, *n* (%)					
Discharge from ED/Ward	54/23 (70.1/29.9)		3/8 (27.3/72.7)		0.005 [0.16 (0.04-0.66)]
Reason for request paracetamol levels, *n* (%)					
Accidental	32 (41.6)	32	4 (36.4)	4	
Attempted suicide	43 (55.8)	43	0	0	<0.001 [6.74 (2.83-16.01)]
Liver enzyme disorder	2 (2.6)	2	7 (63.6)	7	
Toxic dose ingested, yes/no, *n* (%)	49/28 (63.6/36.4)	77	8/3 (72.7/27.3)	11	0.555 [0.66 (0.16-2.68)]
Ingested dose, median (range)	156.25 (13.8-886.36)*	65	128.6 (72-562.5)*	9	0.304 [0.99 (0.99-1.01)]
Ingestion of other drugs, yes/no, *n* (%)	23/51 (29.9/66.2)	74	2/9 (18.2/81.8)	11	0.381 [0.49 (0.10-2.46)]
Paracetamol level at admission (μg/mL)	9.77 (0-336)	77	1.23 (0.89-28.23)	11	0.129 [0.94 (0.87-1.01)]
Liver function					
Transaminases >3 ULN, yes/no, (%)	1/76 (1.3/98.7)		7/4 (63.6/36.4)		<0.001 [65.63 (10.16-423.99)]
Maximum ALAT (UI/L), median (range)	34.5 (14-12412)	30	213 (82-14397)	8	<0.001 (NC)
Maximum ASAT (UI/L), median (range)	27 (15-16192)	30	144.5 (30-17671)	8	<0.001 (NC)
Maximum GGT (UI/L), median (range)	17.5 (2-79)	24	120 (22-502)	7	<0.001 [1.07 (1.01-1.12)]
Maximum total Bi (mg/dL), mean (SD)	1 (1.33)	27	3.7 (4.89)	8	0.344 [1.30 (0.89-1.89)]
ALF, yes/no, *n* (%)	1/76 (1.3/98.7)		3/8 (27.3/72.7)		<0.001 [28.50 (2.64-307.18)]
Treatment (yes/no), *n* (%)					
N-acetyl cysteine	35/40 (45.5/51.9)	75	6/5 (54.5/45.5)	11	0.824 [1.24 (0.37-4.11)]
Gastric lavage	37/38 (48.1/49.4)	75	0/11 (0/100)	11	0.002 (NC)
Activated carbon	49/26 (63.6/33.8)	75	1/10 (9.1/90.9)	11	<0.001 [0.053 (0.01-0.44)]
Haemodialysis	2/73 (2.6/94.8)	75	0/11 (0/100)	11	0.584 (NC)
Unknown	2 (2.6)	2	0	0	NC

*: dose: mg/kg; †: dosage: mg/kg/d. OR: odds ratio; CI: confidence interval; ULN: upper limit of normal; ALF: acute liver failure; Bi: bilirubin; GGT: glutamyl transpeptidase; ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase; NC: not calculated; SD: standard deviation; ED: Emergency Department.

In our study, the patients with accidental poisoning had a median age of 2.65 years, a finding reported in a North American study in which the mean age for presenting accidental ingestion was 28 months.[2] This type of ingestion usually occurs in small children and could be due to accidental ingestion by the child or by an error in medication, which might be due to a failure to understand the scheduled dose, confusion between the dosing of one antipyretic drug and another (for example, the frequent alternate use of paracetamol and ibuprofen), and the use of adult formulations with children.

On the other hand, poisoning due to attempted suicide tends to be more common in adolescents. In our study, this group had a mean age of 15 years, and there was a greater tendency for this type of poisoning among the female population, which was similar to that reported by Alander et al.[11] In contrast to accidental poisoning, this patient group had a higher frequency of hospitalization (41.9%) due to complications from the poisoning (half of the admissions to the ICU) or for psychiatric assessment of the suicide attempt. The ingestion of paracetamol in this patient group might be motivated by the fact that paracetamol is freely sold in pharmacies, is widely consumed by the general population, and is frequently found in home medicine cabinets.

A relevant aspect of our findings is that the majority of hepatotoxicity cases associated with paracetamol were caused by chronic poisoning (7 cases), whereas there was only 1 case of acute poisoning. We therefore found more cases of ALF in chronic poisoning than in acute poisoning. This led to a longer hospital stay for this patient group, that is involved in morbidity and financial costs. The increased severity observed in chronic poisoning might be due, among other factors, to the poor perception by parents/guardians of the high risk of hepatotoxicity associated with the repeated consumption of supratherapeutic doses. This lack of perception is evidenced by the delay in seeking medical help, a delay that is greater in chronic consumers than non-chronic consumers (52.3 *vs.* 6.83 hours; $P<0.001$), leading to a delay in starting treatment. Mahadevan et al[27] found that late arrival to the hospital following a paracetamol poisoning was a risk factor for developing severe

hepatotoxicity, thereby increasing mortality. The studies on the relationship between chronic ingestion and hepatic toxicity revealed that these episodes are less frequent than PAP, but the potential risk of liver damage is present (a significant OR of 65.93 for hepatitis and 28.50 for ALF). These studies recommended that the cumulative dosage should not exceed 60 mg/kg per day.[10,27,28] Our data indicated that from a pragmatic standpoint the chronic toxicity cases should be taken into greater consideration when treating these patients, not only in the ED but also during regular pediatric visits. We believe that PAP is easier to recognize, and the management is widely known. In our study, we determined that suspected PAP was treated with NAC, with a mean of 4.96 (±3.33) hours from ingestion. The administration of the antidote is especially effective in the first 8 hours following poisoning, thereby the risk of hepatotoxicity is reduced in this patient group, but it is not reduced in patients with chronic poisoning because NAC is less effective for late-presenting patients.[29,30] Although there are very few studies on chronic poisoning in children, there is a need to inform parents and guardians of this risk, to take measures to increase clinical suspicion by physicians, and to create clinical protocols for handling these types of poisonings.

The primary limitation of our study comes from the identification of cases based on the request for paracetamol serum level tests. If physicians did not suspect paracetamol poisoning enough to order paracetamol levels, the patient was not included in the study, and this fact could bias the results. However, we believe that the underestimation of acute poisoning cases is low. This problem would particularly affect cases of chronic poisoning in which the recognition of the risk, and therefore the degree of suspicion, could be lower. Otherwise, as a study with a retrospective design based on chart review, the quality of the data is weak. It is also a single-center study, thus the validity of the results needs to be confirmed in other hospitals. Moreover, a possible confounding factor is the ingestion of other concomitant drugs that did not allow us to rule out an interaction between them and the paracetamol.

In conclusion, the incidence of suspected paracetamol poisoning in our hospital was lower than that observed in other western countries. Most ALF cases were due to chronic poisoning of paracetamol. Clinicians should have a higher index of clinical suspicion for this entity.

Acknowledgements

We are grateful to ServingMed.com for the corrections to the English grammar and the academic style of the manuscript.

Funding: No funding to declare.

Ethical approval: This study was approved by the Ethical Committee of La Paz University Hospital.

Competing interest: No conflicts of interest are related to this sudy.

Contributors: Ramírez E and Tong HY conceived and designed the program. Borobia AM, Ruiz JA, Martínez AM, Medrano N, Martín J and García S analyzed and interpreted the data. Tong HY and Medrano N contributed to the critical writing. Ramírez E, Frías J, Carcas AJ, García S and Quintana M were in charge of the critical revision of the manuscript for important intellectual content. All authors contributed to the final approval of the version to be published.

References

1 Buckley N, Eddleston M. Paracetamol (acetaminophen) poisoning. Clin Evid 2007;12:2101.
2 Caravati EM. Unintentional acetaminophen ingestion in children and the potential for hepatotoxicity. J Toxicol Clin Toxicol 2000;38:291-296.
3 Miller RP, Roberts RJ, Fischer LJ. Acetaminophen elimination kinetics in neonates, children and adults. Clin Pharmacol Ther 1976;19:284-294.
4 Ji P, Wang Y, Li Z, Doddapaneni S, Hertz S, Furness S, et al. Regulatory review of acetaminophen clinical pharmacology in young pediatric patients. J Pharm Sci 2012;101:4383-4389.
5 Burillo G, Munné P, Dueñas A, Trujillo M, Jiménez A, Adrián M, et al. Acute poisoning: epidemiological and clinical profile, and analysis techniques used in digestive decontamination used in the Spanish Emergency Services in 2006-Study-HISPATOX. Emergencias 2008;20:15-26. [In Spanish]
6 Squires RH Jr, Shneider BL, Bucuvalas J, Alonso E, Sokol RJ, Narkewicz MR, et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. J Pediatr 2006;148:652-658.
7 Sabaté M, Ibáñez L, Pérez E, Vidal X, Buti M, Xiol X, et al. Paracetamol in therapeutic dosages and acute liver injury: causality assessment in a prospective case series. BMC Gastroenterol 2011;11:80.
8 Pershad J, Nichols M, King W. "The silent killer": chronic acetaminophen toxicity in a toddler. Pediatr Emerg Care 1999;15:43-46.
9 Heubi JE, Barbacci MB, Zimmerman HJ. Therapeutic misadventures with acetaminophen: hepatotoxicity after multiple doses in children. J Pediatr 1998;132:22-27.
10 Kozer E, Greenberg R, Zimmerman D, Berkovitch M. Repeated supratherapeutic doses of paracetamol in children – a literature review and suggested clinical approach. Acta Paediatr 2006;95:1165-1171.
11 Alander SW, Dowd MD, Bratton SL, Kearns GL. Pediatric acetaminophen overdose: risk factors associated with hepatocellular injury. Arch Pediatr Adolesc Med 2000;154:346-350.
12 Woo OF, Mueller PD, Olson KR, Anderson IB, Kim SY. Shorter duration of oral N-acetylcysteine therapy for acute acetaminophen overdose. Ann Emerg Med 2000;35:363-368.
13 Singer AJ, Carracio TR, Mofenson HC. The temporal profile of increased transaminase levels in patients with acetaminophen-induced liver dysfunction. Ann Emerg Med 1995;26:49-53.
14 James LP, Wells E, Beard RH, Farrar HC. Predictors of outcome after acetaminophen poisoning in children and adolescents. J

Pediatr 2002;140:522-526.
15 Yang R, Miki K, He X, Killeen ME, Fink MP. Prolonged treatment with N-acetylcystine delays liver recovery from acetaminophen hepatotoxicity. Crit Care 2009;13:55.
16 Sobradillo B, Aguirre A, Aresti U, Bilbao C, Fernández-Ramos C, Lizárraga A, et al. Growth curves and tables (longitudinal and transversal study), 1st ed. Bilbao, Spain: Fundación Faustino Orbegozo Eizaguirre, 2004: 11-21.
17 Noguera A, Martínez L, Luaces C. Acetaminophen poisoning. In: Mintegi S, Grupo de Trabajo de Intoxicaciones de la SEUP. Handbook of poisoning in Pediatrics, 2nd ed. Ergon: Madrid, 2008: 135-143.
18 Daly F, Fountain JS, Murray L, Graudins A, Buckley NA. Panel of Australian and New Zesland clinical toxicologists. Guidelines for the management of paracetamol poisoning in Australia and New Zealand. Med J Aust 2008;118:296-301.
19 CDER-PHRMA-AASLD Conference, 2000, clinical white paper, preconference study document before conference "Drug-Induced Liver Injury: A National and Global Problem." http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/ucm091457.pdf (accessed December 23, 2014).
20 Jiménez-Gómez J, Polo-Miquel B, Donat-Aliaga E. Acute hepatic failure. In: Spanish Society of Gastroenterology, Hepatology and Pediatric Nutrition, eds. Diagnostic-therapeutic protocols of gastroenterology, hepatology and nutrition pediatric, 1st ed. Madrid, Spain: ERGON, 2010: 197-205.
21 Capellá D, Laporte JR. La notificación espontánea de reacciones adversas a medicamentos. In: Laporte JR, Tognoni G. Principios de Epidemiología del Medicamento. Barcelona: Masson-Salvat, 1993: 147-170. [In Spanish]
22 Nourjah P, Ahmad SR, Karwoski C, Willy M. Estimates of acetaminophen (Paracetamol)-associated overdoses in the United States. Pharmacoepidemiol Drug Saf 2006;15:398-405.
23 Azkunaga B, Mintegi S, Del Arco L, Bizkana I, grupo de trabajo de intoxicaciones, Sociedad Española de urgencias de Pediatría. Epidemiological changes in poisonings treated in emergency pediatric services Spaniards between 2001 and 2010: Increase in alcohol intoxication. Emergencias 2012;24:376-379. [In Spanish]
24 Mintegi S, Fernández A, Alustiza J, Canduela V, Mongil I, Caubet I, et al. Emergency visits for childhood poisoning: a 2-year prospective multicenter survey in Spain. Pediatr Emerg Care 2006;22:334-338.
25 Murray KF, Hadzic N, Wirth S, Bassett M, Kelly D. Drug-related hepatotoxicity and acute liver failure. J Pediatr Gastroenterol Nutr 2008;47:395-405.
26 Escorsell A, Mas A, De la Mata M, Spanish Group for the Study of Acute Liver Failure. Acute liver failure in Spain: analysis of 267 cases. Liver transpl 2007;13:1389-1395.
27 Mahadevan SBK, McKiernan PJ, Davies P, Kelly DA. Paracetamol induced hepatotoxicity. Arch Dis Child 2006;91:598-603.
28 Spanish Agency for Medicines and Health Products. Intravenous (IV) paracetamol: Cases of dosing error. Spanish Agency for Medicines and Health Products (AEMPS). Information note MUH (FV), 05/2012, 2012. http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2012/NI-MUH_05-2012.htm (accessed December 23, 2014).
29 Whyte IM, Francis B, Dawson AH. Safety and efficacy of intravenous N-acetylcysteine for acetaminophen overdose: analysis of the Hunter Area Toxicology Service (HATS) database. Curr Med Res Opin 2007;23:2359-2368.
30 Kerr F, Dawson A, Whyte IH, Buckley N, Murray L, Graudins A, et al. The australasian clinical toxicology investigators collaboration. Randomized trial of different loading infusion rates of N-acetylcystine. Ann Emerg Med 2005;45:402-408.

Received September 29, 2014
Accepted after revision December 30, 2015