Original Article

Fulminant Hepatic Failure and Paracetamol Overuse with Therapeutic Intent in Febrile Children

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ABSTRACT

Objective. To evaluate the risk of fulminant hepatic failure in relation to paracetamol overuse with therapeutic intent in febrile children.

Methods. It was a case control study. Paracetamol ingestion for the current febrile illness was compared between 25 cases of fulminant hepatic failure and 33 hospital age matched controls.

Results. Supra-therapeutic doses of paracetamol (mean 145 mg/kg/day) were consumed by all 25 cases compared to none in the control group. Mean paracetamol level in the cases and controls were, respectively, 26.84 µg /dl and 0.051 µg /dl ($p<0.001$). The mean duration of paracetamol intake prior to admission in cases was 3. 45 days compared to 1.85 days in the control group. Nineteen, 5 and 3 were, respectively, graded as hepatic encephalopathy grade 1, 2 and 3. All six patients in grade 2 and 3 had hepatomegaly compared to 78% in the grade 1. Four had jaundice and all were in grade 2 or 3. Mean alanine aminotransferase was 2781 U/L None of the randomly selected cases (6) had serological evidence of Hepatitis A, Hepatitis B or Dengue. Three cases died.

Conclusion. Exposure to multiple supratherapeutic doses of paracetamol is a risk factor to develop fulminant hepatic failure in children with an acute viral like febrile illness. **[Indian J Pediatr 2006; 73 (10) : 871-875]**
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Paracetamol (acetaminophen) was discovered 100 years ago, but its use as an over – the- counter (OTC) medication began only in the 1960s and is now the most frequently used OTC medication in children.[1] With the withdrawal of aspirin for pediatric use in 1980s owing its association with Reye's syndrome, the World Health Organization and American Association of Pediatrics recommend paracetamol as a first line antipyretic.[1] In Sri Lanka the pharmaceutical industry, took this opportunity to widely advertise paracetamol as a safe drug over the media and press. Parents and patients therefore, consider paracetamol as a child safe and "friendly" medication.

Clinical Pharmacologists on the other hand will agree that there is no safe drug and in many instances only the dose differentiates a drug from a poison and this was soon evident in the case of paracetamol when hepatotoxicity associated with acute paracetamol overdose was recognised. But, the evidence at that time supported children, to be less susceptible to hepatotoxicity in acute paracetamol overdose due to differences in the hepatic metabolic pathway.[2]

However, its safety in children is now been challenged with the recent concerns of hepatotoxicity associated with prolonged use of paracetamol for antipyresis in children with viral fevers.[3-10] But a definite cause-effect relationship was not available from these studies as most were either case reports or case series. We earlier reported a case of fulminant hepatic failure leading to death associated with the use of multiple supratherapeutic doses of paracetamol.[11] This case control study was designed to determine the cause-effect relationship between multiple supratherapeutic doses of paracetamol and hepatotoxicity in children with acute viral fever.

MATERIAL AND METHODS

Study settings and population: The study was carried out

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at Lady Ridgeway Hospital for children (LRH) and Colombo South Teaching Hospital. Cases and controls study were from the children admitted to the pediatric medical wards to these two hospitals for a period of three months from January 1st 2001. Approval of the study was obtained from the institutional ethics committee.

Definition of cases and controls: Cases belonged to three types, *(i)* children admitted with fever, developed liver disease while in the ward, and then went into encephalopathy, *(ii)* children admitted with liver disease and then developed encephalopathy while in the ward, and *(iii)* children admitted with encephalopathy (usually transferred from small hospitals). Controls were selected from children admitted with fever, and had an uneventful recovery without developing liver disease or any other complications. We defined fulminant hepatic failure as acute liver disease complicated by hepatic encephalopathy occurring within eight weeks of the onset of the liver disease.[12] Liver disease was defined as presence of fever, nausea and vomiting with increased alanine aminotransferase more than 3 times of the reference value. Fulminant hepatic failure was graded as follows, Grade I as minor disturbances of consciousness or motor function, Grade II drowsy, but responsive to commands, Grade III stuporous but responsive to pain, and Grade IV as unresponsive to pain.[12]

Identification of cases and controls: Identification of children with a diagnosis of fulminant hepatic failure was based on clinical diagnosis by the paediatrician and biochemical criteria. One investigator from the research team visited the wards daily. All cases in which the diagnosis of fulminant hepatic failure was questioned were excluded. The controls were selected from children admitted with uncomplicated viral fever. Up to two controls were selected for each case, matched according to centre, time of admission (within 2-7 days of hospitalisation of their matched cases), age and gender. Controls were observed throughout their stay in the hospital and those who developed any complications were excluded. All cases and controls whose parents could not be reliably interviewed were excluded. Investigations to rule out other possibilities as the cause of fever were carried out if the fever was persisting, and clinicians caring for these children chose the appropriate investigations depending on the clinical presentation. Hepatitis E was not tested for as it is uncommon in Sri Lanka. Malaria and Enteric fever were excluded on history.

Exposure definition: The recommended antipyretic dose of paracetamol for children is 15/mg/Kg/dose and a maximum of 60 mg/Kg/day.[13] A dose above 60 mg/Kg/day was considered as supratherapeutic.

Data collection: A structured pre - tested questionnaire was used to obtain the following information from both cases and controls; demographic data, details of paracetamol intake, concurrent ingestion of other medications, presence of other risk factors for hepatic toxicity, clinical features, development of complications, results of laboratory investigations and outcome. The required information was obtained from interviewing the parents and doctors and from going through the case notes. Data collected on potential confounding factors included, medication history, and past or family history of liver disease. Also randomly selected six samples from both cases and controls were tested for common infective causes of fulminant hepatic failure in our region.

Lab investigations: Paracetamol levels were estimated by fluorescence polarization immunoassay technology. The results of other laboratory investigations were obtained from the case notes.

Data analysis and Statistics: The data were analysed using Statistical Package of Social Sciences. Cases were compared with controls for factors contributing to toxic effects of paracetamol on liver such as *(i)* exposure to paracetamol, *(ii)* intake of supratherapeutic doses, *(iii)* average amount ingested in a day (mg/Kg/day), *(iv)* duration of ingestion, *(v)* total amount ingested during the current illness (mg/Kg), and (vi) the type of paracetamol (adult or pediatric). Also, plasma paracetamol levels in the cases were compared with that of controls. Toxic range described for acute ingestion of paracetamol was used to interpret the plasma paracetamol levels of cases and controls.[14]

For further analysis, Grade II, III & IV hepatic encephalopathy were grouped together as severe form and Grade I as mild. Cases with mild forms of hepatic encephalopathy were later compared with the severe forms to identify the clinical features which predict the severity. These included, (i) hepatomegaly, (ii) jaundice, (iii) hypoglycemia, and (iv) prothrombin time. Also, comparison was made between mild and severe forms of hepatic encephalopathy to determine the predisposing factors for the development of severe grades of hepatic encephalopathy. These included, *(i)* daily dose of paracetamol, *(ii)* duration of paracetamol, *(iii)* total dose of paracetamol ingested during the current illness, and (iv) type of paracetamol. Statistical methods used were chi-square and t test; p value < 0.05 was considered significant

RESULTS

During the study period, 33 children with suspected fulminant hepatic failure were identified. Eight were excluded because there was no convincing clinical and biochemical evidence of fulminant hepatic failure. Finally, 25 cases and 33 controls were included in the study. Their mean age was 3.56 years (range 1 – 12 years) with male: female ratio of 1.4:1.

Exposure to paracetamol: All 25 cases (100%) and 11 (33%) controls had consumed paracetamol during the current illness. Table 1 shows that all 25 cases gave a history of exposure to supratherapeutic dose (> 60 mg/

TABLE 1. Average Daily dose of Paracetamol Given to Children with Fulminant Hepatic Failure (N=25) and to Their Matched Controls (N=33)

Daily dose range (mg/kg/day)	Patients	
	Cases	Control
Not given	Nil	22
< 60	Nil	11
60-90	02	Nil
91-120	10	Nil
121-150	05	Nil
151-180	05	Nil
181-250	03	Nil
>250	Nil	Nil
Total	25	33

Kg/day) of paracetamol during each day of the illness compared to none in the controls. The mean daily paracetamol dose in cases was 145 mg/Kg/day (SD = 57.8) compared to 40 mg/Kg/day (SD = 8.3) for the control ($p < 0.001$). The mean duration of paracetamol intake prior to admission in cases was 3. 45 (SD = 1.3) days compared to 1.85 (SD = 1.2) days for the control group.

All cases received the adult form of paracetamol as opposed to 66% of the controls. Adult form of paracetamol contain 500 mg paracetamol in a tablet as opposed to pediatric preparations such as syrup containing 120 mg paracetamol in 5 ml, or chewable tablets containing 80 mg in a tablet. 3% of the cases were given more than one brand of paracetamol compared to none in the control group; 60% of cases were prescribed paracetamol by their general practitioner. The cases have ingested a mean total dose (daily dose multiplied by duration) of 468. 36 mg/Kg (SD = 206.52) paracetamol during the current illness.

Plasma paracetamol level: All (100%) cases and 19 (57.5%) controls showed presence of paracetamol in their plasma at the time of testing. Mean plasma paracetamol level in the cases and controls were, respectively, 26.84 µg /dl (SD=3.8) and 0.051 µg /dl (SD = 0.03) ($p< 0.001$). 11 cases had levels greater than the hepatotoxic range described for acute ingestion.[14] Fig 1 shows the plasma paracetamol level in the cases compared to the total dose of paracetamol administered during the current illness.

Clinical manifestations: All cases and controls were previously healthy with no history of liver disease. All had symptoms of a presumed viral fever which included fever and rhinnorhea. The other clinical features of cases and controls are given in Table 2. Of the 25 cases, 19 (76%), 5 (20%) and 1 (4%) were, respectively, graded as hepatic encephalopathy Grade I, II and III respectively.

Lab investigations: Mean alanine aminotransferase was 2781 IU/L (SD = 934) (Normal range 0-40 IU/L) in the cases. Prothrombin time was done in 19 cases; 15 (79%) had elevated levels above the standard value for the laboratory. Hyperbilirubinaemia was observed in four

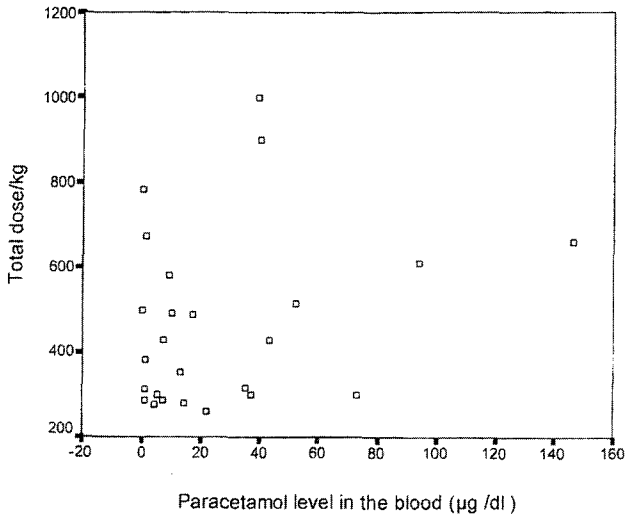

Fig. 1. Plasma Paracetamol Level in Cases (N=25) Compare with the Total dose of Paracetamol Administered During the Current Illness

TABLE 2. Clinical Manifestations in Children with Fulminant Hepatic Failure (N=25) and in Their Matched Controls (N=33)

Clinical Feature		Cases (N = 25)	Controls (N=33)
Vomiting		18 (72%)	8(24.2%)
Coffee ground vomitus		11 (44%)	Nil
Melena		3 (12%)	Nil
Hepatomegaly		21 (84%)	Nil
Hypoglycemia		10 (40%)	Nil
Renal failure		2 (8%)	Nil
Hepatic encephalopathy	1	19 (76%)	05 (20%)
	2	01 (4%)	Nil
	3	Nil	Nil
Jaundice		04 (16%)	Nil
Spontaneous bleeding		3 (12%)	Nil

cases; 10 had hypoglycemia. None of the randomly selected cases (6) had serological evidence of Hepatitis A, Hepatitis B or Dengue.

Treatment and outcome: Seventeen (68%) cases were given N Acetylcysteine. Others were managed symptomatically. Ten were treated for hypoglycemia. Three (12%) cases died and in two of them liver biopsy showed evidence of massive centrilobular necrosis compatible with paracetamol poisoning.

Clinical manifestations seen in different grades of hepatic encephalopathy: Twenty one of the 25 cases had hepatomegaly; 100% in patients with severe hepatic encephalopathy and 78% in the mild form. Four had jaundice and all were in the severe form. Prothrombin time was done in 14 patients with mild hepatic encephalopathy and in 5 with severe. Of which 78% (11 out of 14) in mild hepatic encephalopathy and 80% in severe had elevated levels. However, hypoglycemia was observed more in mild hepatic encephalopathy (42%) compared to severe (33%).

Exposure to paracetamol in different grades of hepatic encephalopathy: Table 3 shows the dose and duration of paracetamol ingestion in patients with mild hepatic encephalopathy compared to that of patients in severe grades. 83% (5/6) of the patients with severe hepatic encephalopathy gave a history of total paracetamol ingestion of more than 400 mg/Kg over a period greater than three days during the current illness. On the other hand, 57.8% (11/19) of the patients with mild hepatic encephalopathy gave a history of total paracetamol ingestion of more than 400 mg/kg and of them only 31.5 % (6/19) had taken it for a period grater than 3 days. When the daily dose of paracetamol alone is considered, none with severe hepatic encephalopathy had ingested < 90 mg/Kg/day. The details of which are shown in Table 3.

TABLE 3. Details of History of Paracetamol Ingestion in Children with Different Grades of Hepatic Encephalopathy (N=25; Grade 1=19, Grade 2 & 3=6)

Exposure to paracetamol	Grades of hepatic encephalopathy	Grade 1	Grade 2 & 3
Daily dose (mg/Kg/day)	< 60	Nil	Nil
	60-90	02	Nil
	91-120	07	03
	121-150	04	01
	151-180	03	02
	181-250	03	Nil
	>250	Nil	Nil
	Total	**19**	**06**
Duration (days)	Nil	Nil	Nil
	1-3	13	01
	>3	06	05
	Total	**19**	**06**
Total dose (mg/Kg)	<250	Nil	Nil
	250-400	08	01
	401-800	09	05
	> 800	02	Nil
	Total	**19**	**06**

DISCUSSION

In this case control study, we have identified the probable risk factors which predispose children with suspected viral fever to develop hepatotoxicity when they are exposed to multiple supratherapeutic doses of paracetamol. The risk factors were; daily dose of paracetamol (> 90 mg/day), duration of exposure (> 3 days), total dose ingested during the illness (> 400 mg/Kg) and exposure to adult preparations of paracetamol.

Paracetamol was detected in the plasma of all cases and in 19 (57.5%) controls; the mean paracetamol level in cases was statistically greater than that of the controls. Although only 11 controls gave a history of exposure to paracetamol, 19 had paracetamol in their plasma. Paracetamol intake data reported in our study, as in previous published reports relied on history alone.[4,7,8] Hence it is possible that prescriptions given to cases may also have had "hidden" paracetamol.

Although the nomogram described by Rumack and Matthews [14] for single overdose was not designed to predict toxicity in multiple doses, studies indicate that it may have a place in the management of multiple supratherapeutic overdoses.[7] Our findings support this as 11 of the 25 cases had paracetamol levels greater than the toxic range as described in Rumack and Matthews nomogram, despite a mean time lag of about 14 hours between ingestion and testing and an average last dose of 135 mg/Kg. Neither the published studies nor ours were able to determine the serum levels likely to predict hepatic failure after multiple supratherapeutic doses.

A distinct clinical pattern has been described in children developing fulminant hepatic failure with definite or presumed exposure to multiple supratherapeutic doses of paracetamol as opposed to other causes of fulminant hepatic failure.[8] The pattern includes prodromal viral fever like illness, often with fasting and/or vomiting followed by severe synthetic failure associated with hypoglycaemia, coagulopathy and mild encephalopathy, but with low bilirubin levels. Clinical finding seen in our cases are in agreement with this distinct clinical pattern.

Two questions which need to be addressed are the factors which push a proportion of children who were exposed to multiple supratherapeutic does of paracetamol into fulminant hepatic failure and within this group of children which factors contribute to the severity of fulminant hepatic failure. The first question has been addressed in previous studies and our findings are in agreement with them.[4,7,8] In most multiple overdoses, children are of young age (< 2 years), febrile, acutely malnourished and exposed to higher daily doses over a period of more than 3 days resulting in exposure to a high total dose during the illness.

As the numbers are limited, it is difficult to answer the second question from our findings. Most cases were mild (Grade I) hepatic encephalopathy. However, when clinical manifestations were analysed, hepatomegaly and jaundice were more in the severe grades of hepatic encephalopathy and hence could be considered as the warning signs.

Although the majority of cases in all grades of hepatic failure gave a history of ingestion of an average daily dose of 91 - 180mg/kg/day, there were three cases who gave a history of having ingested 181-250 mg/kg/day but with mild hepatic failure. In two of these three it may be possible to relate this finding to the duration of ingestion (two days: total dose 430 and 516 mg), whereas most cases categorized as severe had ingested supratherapeutic doses for over 3 days. However it is difficult to explain as to how a child who gave a history of ingestion of a total dose of 998 mg over a period of 4 days had only symptoms of mild liver failure. It could be due to a good nutritional state of the child which we did not assess.

Owing to constraints in the laboratory facilities, we couldn't do the prothrombin time in all the cases, also only limited number of cases were tested for the common infectious causes for their clinical picture with none showed positive results.

In conclusion, considering both history of exposure to paracetamol and serum paracetamol levels, our study despite some limitations, provides evidence to support that exposure to supratherapeutic doses of paracetamol contributes to the development of fulminant hepatic failure in febrile children. Our findings also strengthens the already available information in the literature about this risk associated with the use of an OTC medication which is perceived as a very safe and child friendly medicine by doctors and parents.

In tropical countries, some infections such as Malaria, Hepatitis E, and Enteric fever can also present with features of viral fever which is subsequently complicated with fulminant hepatic failure. However, none of the cases were clinically suspected of having any of those diseases. As pointed out earlier, Hepatitis E is not a common disease in Sri Lanka and Malaria has become an uncommon cause for childhood fever in the Province where the study was carried out. Clinicians are well experienced in identifying Enteric Fever, and none of the cases or controls was clinically suspected of having Enteric Fever. So possibility of these infections masquerading as the cause of the fulminant hepatic failure in the cases is highly unlikely.

These identified risk factors are preventable and easy to rectify. We recommend that certain national decisions should be taken, such as (i) enforcing generic prescribing and informing of parents that the product contains paracetamol (ii) limiting the number of registered products and preparation of paracetamol. Availability of many brands of paracetamol results in confusion over names and doses. Presently we have over 39 registered products of paracetamol under different brand names and a community based study on prescribing in children in Sri Lanka has shown that over 80% of medicines are prescribed in brand name.[15] (iii) re-looking the advertisement privileges given to OTC medicines, (iv)amending the current labeling instructions given in paracetamol preparations (v) educating parents and health professionals on dosing of paracetamol and substitution of adult preparations in children under 5years (vi) re-looking at the pricing of paediatric syrups. Five hundred milligrams of paracetamol in the form of syrup is about 15 times more expensive than an equal amount taken as an adult tablet; the syrup is therefore, not within the reach of a Sri Lankan daily paid labourer.

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REFERENCES

1. Cranswick N, Coghlan D. Paracetamol efficacy and safety in children: the first 40 years. *Am J of Ther* 2000; 7: 135-141.
2. Miller RP, Roberts RJ, Fisher LJ. Kinetics of acetaminophen elimination in newborns, children and adults. *Clin Pharmacol Ther* 1976; 19 : 284-294.
3. Blake KV, Bailey D, Zientek GM *et al.* Death of a child associated with multiple overdoses of acetaminophen. *Clin Pharm* 1988; 7 : 391-397.
4. Rivera-Penera T, Gugig R, Davis J *et al.* Outcome of acetaminophen overdose in pediatric patients and factors contributing to hepatotoxicity. *J Pediatr* 1997; 130 : 300-304.
5. Pershad J, Nichols M, King W. 'The silent killer': chronic acetaminophen toxicity in a toddler. *Pediatr Emerg Care* 1999; 15: 43-46.
6. Morton NS, Arana A. Paracetamol-induced fulminant hepatic failure in a child after 5 days of therapeutic doses. *Pediatr Anaesth* 1999; 9 : 463-465.
7. Heubi JE, Barbacci MB, Zimmerman HJ. Therapeutic misadventures with acetaminophen: hepatoxicity after multiple doses in children. *J Pediatr* 1998; 132 : 22-27.
8. MilesFK, Kamath R, Dorney SF *et al.* Accidental paracetamol overdosing and fulminant hepatic failure in children. *Med J Aust* 1999; 171 : 472-475.
9. Eriksson LS, Broome U, Kalin M *et al.* Hepatotoxicity due to repeated intake of low doses of paracetamol. *J Intern Med* 1992; 231 : 567-570.
10. Smith DW, Isakson G, Frankel LR *et al.* Hepatic failure following ingestion of multiple doses of acetaminophen in a young child. *J Pediatr Gastroenterol Nutr* 1986; 5: 822-825.
11. Ranganathan SS, Fernandopulle BM, de Silva MV, Fernandopulle M. Fulminant hepatic failure in a child following paracetamol overdosing. *Ceylon Med J* 2001; 46(2) : 72-73.
12. Mowat AP. *Liver disorders in childhood.* 3rd ed. United Kingdom: Butterworth-Heinemann; 1994
13. Royal College of Paediatrics and Child Health. *Medicines for Children.* London: RCPCH Publications Ltd; 1999
14. Rumack BH, Matthews H. Acetaminophen poisoning and toxicity. *Pediatrics* 1975; 55: 871-876.
15 Fernandopulle BMR, Nirmalie MI. Survey of prescribing patterns of paediatric preparations. *Proceedings of the Sri Lankan Medical Association 115th Anniversary Academic sessions;* 21 – 24 March 2002.