13.8% of the so called 'unexplained fetal death' in their series of 9223 deliveries might in fact be due to fetomaternal haemorrhage[3].

The management depends on the gestational age of the fetus when the problem is detected. Viable fetuses are perhaps best served by immediate delivery. Neonatologists should be present at delivery and be alerted regarding the nature of the problem and be prepared to transfuse the babies promptly as otherwise, resuscitative attempts may prove ineffective.

## Conclusion

Occult fetomaternal haemorrhage should be considered in all unexpected cases of stillbirths or intrauterine death, and Kleihauser's test should be incorporated into the panel of investigations. Reduced fetal movements and presence of sinusoidal fetal heart tracing should alert the obstetrician on the possibility of this serious condition. This poorly studied disorder certainly warrants further research in future with regards to its pathogenesis and management.

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# Repeated Paracetamol Overdosage in Children

G L Kuan, MRCP, Department of Paediatrics, Malacca Hospital, Jalan Peringgit, 75400 Malacca


## Summary

Paracetamol (pcm) is widely used in children as a safe analgesic and antipyretic. Repeated pcm overdosage in children resulting in hepatotoxicity occurs when doses of pcm are given in excess of 150mg/kg/day for 2-4 days. This is a less well recognised entity and this paper reports 3 such cases in Malacca Hospital in the last 2 years.


Key Words: Paracetamol overdosage, Hepatotoxicity

## Introduction

Paracetamol is considered as a safe analgesic and antipyretic amongst children because of its wide toxic therapeutic ratio. However, paracetamol poisoning can occur as an acute overdosage or as a "chronic" ie repeated overdosage[1] when it is administered in doses exceeding 150mg/kg/day over a period of 2-4 days to children[2]. The recommended therapeutic dose of paracetamol is 10-15mg/kg/dose, whilst the maximum daily dose should not exceed 90mg/kg/day. Repeated paracetamol overdosage in children resulting in hepatotoxicity and mortality is a less well recognised entity when compared to acute paracetamol overdosage.

In a 2 year retrospective analysis (May 1995 - April 1997), there were 3 such cases admitted to the Malacca Hospital. The cases will be described in detail here.

## Case Reports

### Case 1

CLH a 6-year-old Chinese boy, weight 16kg was admitted to the Malacca Hospital on the 28/4/97 with a history of fever of 1 week's duration and progressive lethargy and vomiting for 3 days. He had been well until the 23/4/97 when he was seen by a GP for fever, who prescribed a 500mg/5ml paracetamol syrup. The patient was given 10mls 4 hourly ie 1gm 4 hourly for 4 days. This amounted to 400mg/kg/day for 4 days. On admission, he was found to be in stage 2 hepatic encephalopathy, mildly jaundiced, enlarged liver 4cm below MCL. Although vital signs were stable, he was hypoglycaemic (RBS 2.8micromols/L) and dehydrated. His SGOT>1000iu/L; PT was 61.1 secs; Hepatitis A, B & C serology were negative. The serum paracetamol was 14.5microgms/ml 40 hours after the last dose. With supportive management, his general condition improved by the second day and he was discharged well four days after admission.

### Case 2

FML a 3-year-old Chinese girl weight 12kg was referred from a private hospital on 19/3/96 for complaints of fever for 4 days and vomiting for 3 days. She was given a paracetamol suspension (500mg/5ml) purchased over the counter from a GP's clinic by her mother when she first presented with fever. The mother administered 10mls tds (6gms/day ie 500mg/kg/day) over the next 2 days before admission. On the 17/3/96, FML developed recurrent vomiting, persistent fever and patient was seen by a GP who prescribed more paracetamol (250mg/5ml) at a dosage of 5mls qid. However, the patient was only given 2 doses because of vomiting. By the 18/3/96, whe FML became drowsy, more irritable with worsening vomiting; she was admitted to a private hospital where she stayed for one day before being referred to us.

On admission, FML was in stage 3 hepatic encephalopathy, not jaundiced, midly dehydrated and her liver was 2.5cm below MCL. Her total bilirubin was 26micromol/l with SGOT>2000IU/L; SGPT>1000iu/l. PT was 57.4 secs. The serum paracetamol level was 19.2 microgm/ml 12 hours after the last dose. Serology for HAV, HBV and HCV was not done. The patient was closely monitored in ICU, and responded well to supportive care and was discharged 4 days after admission.

### Case 3

TCG a 2-year-old Chinese girl weight 13kg, was referred from a private hospital on the 20/5/95 for fever for 5 days and vomiting for 1 day. During the 5 days prior to admission, she had been seen by a GP for persistent fever, cough and runny nose. She was prescribed syrup paracetamol preparation (500mg/5ml) by a GP and was given 1 teaspoon 2 hourly for 2 days (300mg/kg/day).

Two days prior to admission, the child became drowsy, lethargic and irritable and she was sent to a private hospital where after correction for 7% dehydration, the liver increased in size from 3 to 6cm below MCL. As the child's drowsiness deteriorated and she developed hypoglycaemia (RBS 2.7micromols/L) she was referred to us. On admission, TCG was in established liver failure, in stage 4 hepatic encephalopathy, the liver was hard at 7cm below MCL, she was also in shock and had upper GIT bleed. She was ventilated in the intensive care unit, and given supportive care; she developed hepato renal failure on the following day.

Her serum paracetamol level was 7.44microgms/ml 72 hours after the last dose. Serum salicylate level was

normal. PT was 74.8secs the SGPT was on a rising trend from 148iu/l to 971iu/l. The total bilirubin was 112 micromol/L. Serology for HAV, HBV and HCV was negative. The serum creatinine was 204 micromol/l.

The patient died 3 days after admission and post mortem liver biopsy revealed extensive liver necrosis, with sinusoidal congestion and occasional foci of steatosis.

## Discussion

All 3 cases in our series, were Chinese, aged 2 years to 6 years. There was 1 male and 2 females. Only in 1 patient (case 2) was the syrup paracetamol puchased over the counter whilst in the other 2 cases, the paracetamol was prescribed by a GP.

Doses of paracetamol administered was 400gm/kg/day and 500mg/kg/day over a period of 4, 2 and 3 days respectively. This exceeded the recommended dose of 150mg/kg/day by 2-6 - 3.3 times. The preparation used in all 3 patients was the 500mg/5ml formulation.

Other than fever which all 3 had in common, they also presented with vomiting, drowsiness and lethargy approximately 1-2 days after ingestion of the high dose paracetamol. At the point of admission, all were in stage 2, 3 and 4 hepatic encephalopathy. In none of the 3 cases was N acetyl cysteine administered because of the delay in arriving at a diagnosis.

In all 3 cases, a clinical diagnosis of repeated paracetamol overdosage was made based on the history of paracetamol administration. Serum levels of paracetamol for all 3 patients were taken 12, 40 and 72 hours after the last dose, and all 3 had been suffering from vomiting for a duration of 1 to 3 days before admission. Therefore none of the levels were within the potential toxicity range on the normogram for acetaminophen intoxication[3]. The absolute values are probably of less importance in repeated paracetamol overdosage since the normogram is derived from experiences in single acute overdoses and serves primarily as a marker for significant paracetamol accumulation.

Two of the patients recovered completely 4 days after admission. The youngest patient TCG, aged 2 years however succumbed to the hepatotoxicity[2]. In a review of paracetamol poisoning in children, Penne and Buchanan described 8 children receiveing doses of paracetamol >150mg/kg/day for several days. Four of these patients receiving >300mg/kg/day died. It has been suggested that in young children on chronic therapy, the therapeutic index for paracetamol in relation to hepatotoxicity is low.

There are 117 paracetamol products in Malaysia from various manufacturers out of a total of 241 listed paracetamol products. There are syrup paracetamol formulations in various strengths : 120mg/5ml; 160mg/5ml; 250mg/5ml and 500mg/5ml. Do we need such a variety of strengths?

In Malaysia, Chinese parents culturally are anxious about persistent high fever in their offsprings. This results in doctors attending to these patients being pressured to bring the fever down rapidly and sustaining it. This phenomenon may explain the popularity of the higher paracetamol strength (500mg/5ml) which was used in all the 3 patients. Rather than submit to their anxiety, doctors should educate parents against excessive medication, and they should be aware that chronic ingestion (>150mg/kg/day) over 2-4 days can cause severe hepatotoxicity and even death. When confronted with a febrile child, doctors should prescribe paracetamol at a stat dose of 20mg/kg, followed by 10-15mg/kg/dose prn or not more frequently than four times a day; the maximum daily dose not exceeding 90mg/kg/day. Persistent vomiting or clinical deterioration in a febrile child given paracetamol for the last two to three days should prompt a review of the child. Finally, doctors working in hospitals should consider repeated paracetamol overdosage as a differential diagnosis in all young children being admitted with hepatic encephalopathy.

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