CASE REPORT

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Fulminant Liver Failure in a Young Child Following Repeated Acetaminophen Overdosing*

ABSTRACT: Acetaminophen (paracetamol), a widely used analgetic drug, is well tolerated at therapeutic doses, but may cause severe hepatotoxicity when ingested in large overdose. Self-poisoning is still very popular in adults and accidental ingestion of one single overdose occurs occasionally in children. In contrast, lethal intoxication in children after repeated administration of therapeutic doses is a very rare event. This case report describes an iatrogenic acetaminophen overdosing in a 5-year-old child receiving 8.5 g acetaminophen in 48 h. Fulminant liver failure developed within 60 h. Autopsy findings included panlobular liver cell necrosis. Acetaminophen serum levels were rather low compared to cases with ingestion of one single overdose. Postmortem diagnosis of chronic acetaminophen intoxication as cause of death should include the clinical history as well as, if available, the calculated drug serum half-life.

KEYWORDS: forensic science, forensic pathology, forensic toxicology, acetaminophen, paracetamol, intoxication, children, hepatotoxicity

Acetaminophen is a frequently used drug with mild antipyretic and analgesic effects, which, however, can cause severe hepatotoxicity in case of overdosage. Whereas suicidal ingestion of a high single dose in adults and accidental ingestion in children are common events, severe intoxication due to repeated acetaminophen overdosing in young children seems to be rare (1) despite the fact that this drug is sold over-the-counter in most countries; therefore, it sometimes may be severely underestimated. So little is known about the course of intoxication in young infants with chronic acetaminophen intoxication and about the criteria for postmortem diagnosis. Here, we describe a case of repeated overdosing in a young child with unusual rapid onset of liver failure.

Case Report

A 5-year-old girl was admitted for tonsillectomy because of chronic tonsillitis. The girl was treated with ampicillin and acetyl-

cysteine prior to hospitalization. On admission, physical examination and laboratory findings were largely normal (Hemoglobin 12.8 g/dL, GPT 12 IU/L, gamma GT 4 IU/L, Quick's test 93%). Surgery was performed without complications and with only little blood loss. Histological examination of the removed tonsils confirmed the diagnosis of chronic tonsillitis. For anesthesia methohexital (20 mg) and succinylcholine were used. For postoperative analgesia acetaminophen suppositories (500 mg) were given approximately every 3 h due to an misunderstanding between the responsible physician and the nurse staff. Within 48 h after surgery, the girl received 17 suppositories, totally 8.5 gram (222 mg/kg body weight/day). After 24 h, she began vomiting, showed stomach pain and obstipation and became lethargic. Again 24 h later, she was transferred to a pediatric intensive care unit.

There the following laboratory findings could be established: hemoglobin 7.9 g/dL (normal range: 12–16), WBC 15,600/μL (4.3-10), PTT 168 sec. (<40), GOT "out of range," after dilution 11,900 IU/L (<15), GPT 6850 IU/L (<17), gamma GT 22 IU/L (4–18), LDH 23850 IU/L (<240), bilirubin 3.6 mg/dL (<1.3). The liver was enlarged 3 cm below the right costal margin. The spleen was not palpable. Ecchymoses had developed in several body areas. Since the acetaminophen administration was not documented in the clinical records, the diagnosis of acetaminophen intoxication could only be established after considerable time loss. At this time, the status of the child had massively deteriorated, and antidote therapy with acetylcysteine was no longer regarded as useful. Preparations for an emergency liver transplantation were taken. The child, however, died in irreversible cardiac arrest 72 h after the first acetaminophen dose.

The autopsy showed a well-nourished, slightly dehydrated girl (body weight 19 kg) with extended skin bleedings. The liver was significantly enlarged (710 g, normal range in 5-year-old female children: 500 - 600 g). Beneath its capsule (Fig. 1) as well as on the cut surface, there were large areas with diffuse pale yellow tissue merged with small islets of pale tan color. Multiple submucous and subserous petechiae, diffuse muscular bleedings, extreme anemia of all organs, and moderate inflammation of trachea and bronchi were found. The histological examination showed massive panlobular liver cell necrosis without inflammation (Fig. 2), and acute tubular necrosis in both kidneys. Serological tests for hepatitis A, B, C, and for Cytomegalovirus were negative. For toxicological analysis, four frozen serum samples taken at different times during the treatment in the pediatric unit and a postmortem blood sample were used. Acetaminophen levels were measured by immunoassay (ADx-system®, Abbott) and confirmed by gas chromatography and
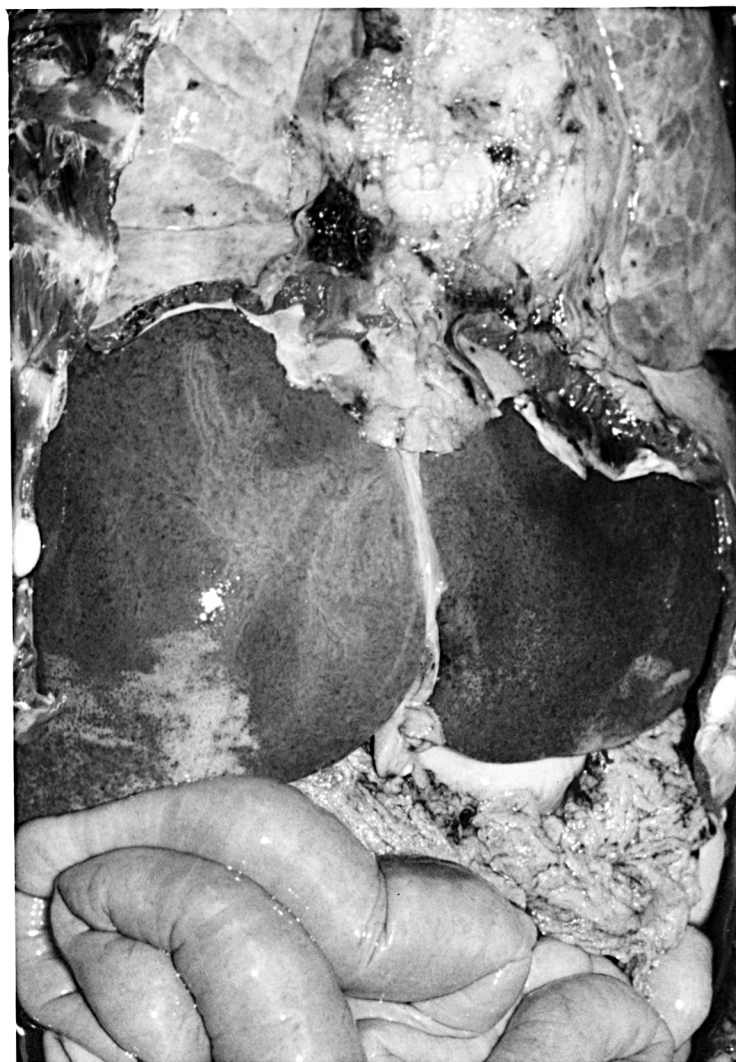
FIG. 1—*Autopsy situs showing liver surface with pale areas of necrotic tissue.*

mass spectroscopy (GC/MS), the half-life calculations based on the assumption of first-order kinetics. The time course of serum concentrations is shown in Fig. 3. No other exogenic substances could be found in blood. Urine was not available.

Discussion

Differential diagnosis of fulminant liver failure in children has to include a variety of conditions like virus infections, Wilson's disease, and Reye's syndrome. Some features of this case might suggest Reye's syndrome. The infant's age was appropriate, she suffered from mild respiratory tract infection and she was vomiting. However, the presence of jaundice, the extremely high GOT levels, and the massive liver necrosis are against the diagnosis of Reye's syndrome. Furthermore, children with this syndrome almost invariably die from raised intracranial pressure which was not present in this case. An underlying metabolic disease affecting the liver (e.g., Wilson's disease) is highly unlikely. The onset of Wilson's disease is very rare before six years of age. No history or physical findings suggestive of chronic liver disease were reported. Presurgical laboratory values indicative of liver function (GOT, gamma GT, and Quick's test) were normal.

The possibility that she had viral hepatitis must be considered. Severe hepatic necrosis is usually associated with hepatitis B. The infection of children mainly occurs at birth and presents with clinical symptoms during the first months of life. Hepatitis A rarely leads to fulminant liver failure. Other viruses (Cytomegalovirus, Epstein Barr virus) can affect the liver. In our patient, there were no signs of liver infection prior to surgery. Liver histology showed no evidence of viral infection with only slight, mainly polymorphonuclear infiltration of periportal zones. Serological studies excluded the presence of the most common hepatopathic viruses. Epstein Barr virus-induced hepatitis is typically associated with splenomegaly and atypical lymphocytes in peripheral blood smears. Both findings were not present in this case.

Finally, the liver disease may have been drug-induced. The list of drugs that can adversely affect the liver is long, but the only hepatotoxic drug administered to the child was acetaminophen. Halothane or enflurane which are known to cause liver necrosis in some cases were not used for narcosis. Furthermore, no other substances could be found in the blood sample taken before beginning of intensive care. The relative dose of acetaminophen in this case was sufficient to cause hepatic damage. The recommended maxi-
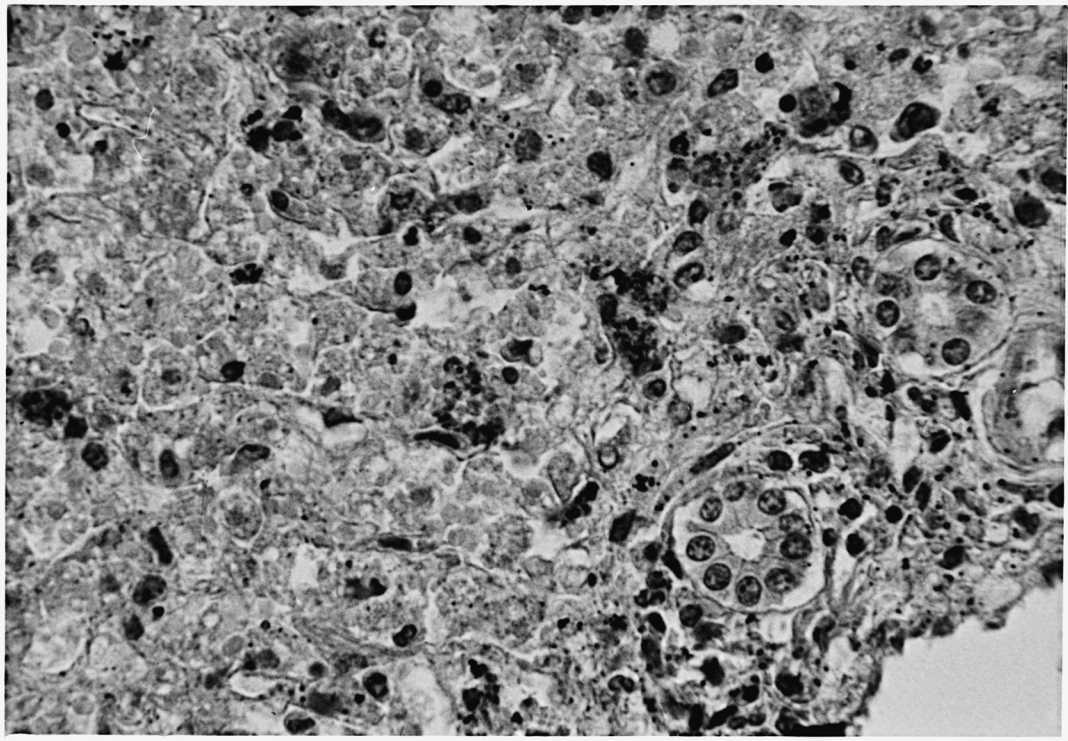
FIG. 2—*Liver lobule with massive necrosis of hepatocytes. The periportal zone (right lower corner) is intact and surrounded by a few surviving hepatocytes (hematoxylin-eosin; magnification ×250).*
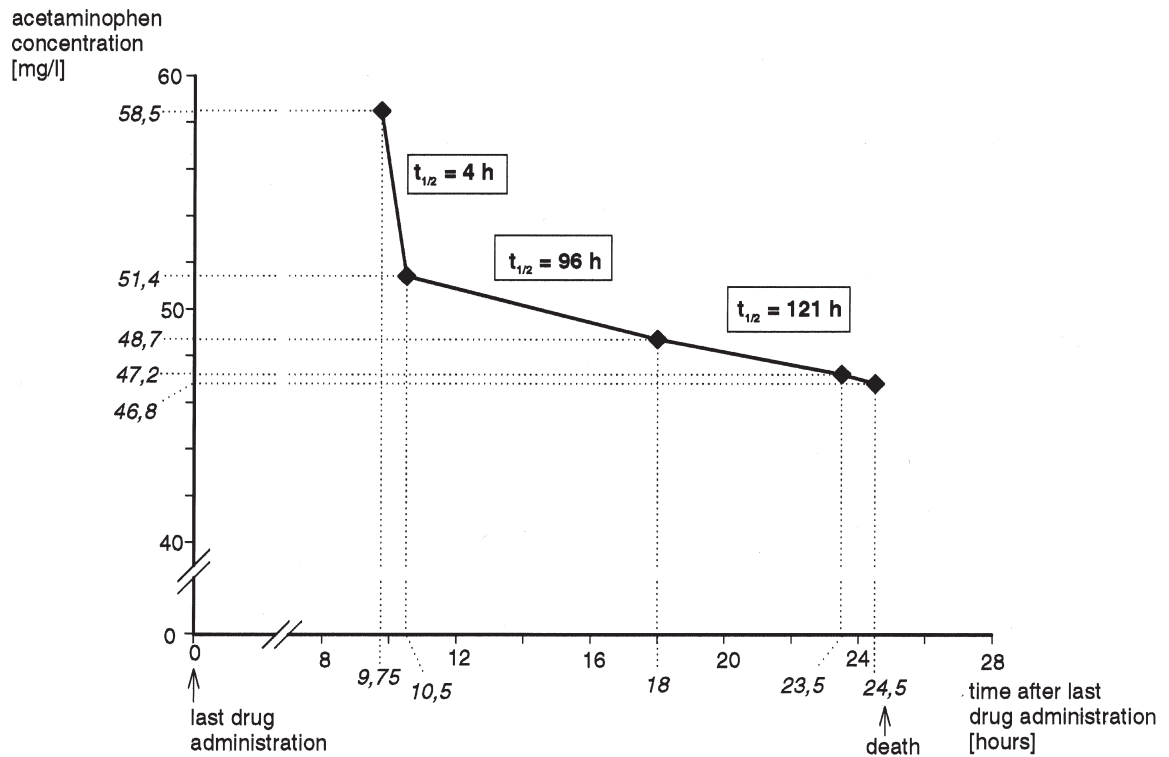

FIG. 3—*Paracetamol serum levels taken at different time points (◆) between last drug ingestion and death. The drug half-lives calculated for three time intervals are shown above the graph.*

mal dose is 50–70 mg/kg/day and the suggested limit of toxicity is at 150 mg/kg/day (2).

Autopsy findings after acetaminophen intoxication in adults include centrilobular liver necrosis which may extend to midzonal or panlobular hepatic necrosis in severe cases (3). Acute tubular necrosis is frequently present. Descriptions of the drug-induced liver pathology in children are sparse especially in cases with repeated overdosing. In three cases with ingestion of multiple overdoses who underwent successful liver transplantation, the explanted liver showed massive centrilobular necrosis (4). Focal centrilobular necrosis is described by another case report with complete recovery of the child (5). In cases with lethal outcome centrilobular necrosis was seen (6,7) as well as centrilobular and midzonal necrosis (8). No statements about autopsy findings were found in the case of de Nardo et al. (9). Panlobular hepatocellular necrosis with only few surviving hepatocytes with vacuolated cytoplasm and a central nucleus in some periportal areas was diagnosed in the case of Weber and Cutz (10) and in this case. Shock and ischemic cell damage cannot be regarded as major cause of hepatic necrosis since blood pressure was stable throughout the hospital treatment with values never falling below 100/70 mm Hg except during a short time period before death. The bleedings in skin, muscle, mucous, and serous membranes with significant hemoglobin decrease can be attributed to the destruction of hepatocytes with subsequent loss of blood clotting capacity. Disseminated intravascular coagulation (DIC) may have been present in the terminal phase and may have aggravated the bleedings, but external ecchymoses were already present without any concurrent shock symptoms at admission to the pediatric unit. Furthermore, histologically, no signs of DIC could be found.

In summary, all available data support the diagnosis of acetaminophen-induced hepatic necrosis as cause of death. Since it was the responsible physician, who recommended to give a suppository every 2 to 3 h, this death clearly was caused by malpractice. Obviously, the multiple administration of acetaminophen suppositories not adapted to the patient's body weight lead to a rapid and massive liver failure. The time interval between first acetaminophen administration and death in the previously reported cases was at least 5 days. In our case, death occurred only 3 days after beginning of acetaminophen administration and only 24 h after the last dose. This rapid onset of liver damage points to increased acetaminophen toxicity. A broad range of intersubject variation in the metabolic activation of acetaminophen was described (11), and there is certainly a host of factors which modulate the balance between bioactivation and detoxification. In this case, the concurrent influence of chronic infection (tonsillitis) (1) which may effect hepatic glutathione stores and therefore reduce the detoxification capacity of the liver has to be considered. However, at present, this is merely a hypothesis based on experimental data. Another possible explanation is the use of a short-acting barbiturate for narcosis. Barbiturates are known to act as potent enzyme inductors. Long term use can increase the formation of toxic acetaminophen metabolites. In mice, enhancement of acetaminophen hepatotoxicity occurs after one single dose of phenobarbital, which can be explained by interference of phenobarbital with acetaminophen glucuronidation (12). Hence, equivalent data in humans do not exist. Interestingly, N-acetylcysteine, the antidote in acetaminophen intoxication, was administered for mucolysis prior to surgery. However, for exerting a protective effect, the drug must be given during the time that metabolism of acetaminophen is maximal (3). Preventive administration is not possible.

Lethal acetaminophen intoxication after ingestion of multiple doses in young children is a rare event. Among 417 cases with ingestion of a potentially serious amount of acetaminophen, there were no deaths (13). As far as we know, only five case reports were published up to now (6–10). A recently published list of 47 cases with severe hepatotoxicity or death after multiple doses (2) compiled from published case reports and from clinical records contains only three additional cases with complete documentation of dosage, duration of therapy, histology and acetaminophen blood concentration. Fifteen deaths were regarded as due to acetaminophen intoxication but obviously not confirmed by autopsy.

In general, children below the age of six years are believed to be less susceptible to acute acetaminophen toxicity after accidental ingestion of one single dose because of probably higher activity of oxidative pathways in drug detoxification (14). After repeated therapeutic doses, available data point to a time-dependent decrease in acetaminophen clearance (15) with increased hepatotoxicity due to the depletion of cosubstrates required for detoxification (1).

For clinical and postmortem diagnosis, the drug blood level has to be determined. Under regular therapeutic conditions, the acetaminophen concentration should not exceed 10–20 mg/L (10). This therapeutic range, however, is of little value for diagnosis of intoxication since the interval between drug ingestion and taking of blood sample is of crucial importance. The Rumack-Matthew-Nomogramm (16) used to assess the likelihood of hepatic damage and the need of treatment in cases with ingestion of one single overdose cannot be applied here since the serum levels in chronic intoxication may remain below the line indicating a high risk of hepatotoxicity. According to this nomogram, the likelihood of hepatic damage would be high when the acetaminophen concentration is greater then 200 mg/L at 4 h or 50 mg/L at 12 h after ingestion. In our case, the acetaminophen serum levels would have been considered at low risk using the nomogram (Fig. 3). The risk of hepatotoxicity should, instead, be estimated by calculation of drug half-life as independent prognostic indicator (3). Since hepatic drug metabolizing enzymes are destroyed during the production of liver cell damage, the elimination half-life of acetaminophen exceeds the normal range of 2–4 h and increases progressively with further hepatic damage (17). In the present case, the calculated half-lives (Fig. 3) demonstrate the fulminant progression of liver failure. An increase of half-life from 4 to 96 h in a few hours indicates a nearly complete breakdown of drug metabolization and has to be regarded per se as adverse prognostic indicator. This was retrospectively confirmed by the rapid lethal outcome.

The therapeutic range of acetaminophen in cases with repeated drug administration seems to be rather small. The recommended maximum dose is between 50 and 70 mg/kg BW/day. The relative dose administered in (6) is only two-fold and the relative dose in this case only about four-fold higher. In children with recovery after liver damage, the relative acetaminophen doses were between 60 (1) and 420 mg/kg/day (1,2). Regarding the popularity of acetaminophen, it can be assumed that relative overdosing occurs frequently and may be responsible for some otherwise unexplainable deaths. In cases with liver failure in children, the possibility of repeated acetaminophen overdosing, therefore, should be included in differential diagnosis and should be the reason to obtain a detailed history and to perform toxicological analysis.

Therapy with paracetamol is safe and effective when the recommended instructions for the use of this drug are adhered to. However, this case, together with others (2), demonstrates that the full toxic potential of this drug is not recognized by all clinicians. Thus, information of parents and non-pediatricians treating children about the necessary dose limitation depending on the body weight

and not on the age should be intensified to prevent further fatalities. Furthermore, the risk of fulminant liver failure has to be kept in mind when dealing with acetaminophen-intoxicated children. The course of intoxication obviously cannot be predicted and the safety of acetaminophen therapy, especially after surgery in young children with concurrent chronic infection, should be reassessed.

Conclusion

Deaths after repeated acetaminophen overdosing are rare. In the case presented here, the amount of administered acetaminophen could be quantified exactly and for the first time the time course of blood levels between last drug ingestion, and death could be documented. The postmortem diagnosis of acetaminophen intoxication was based on the typical autopsy findings, on the history, and on the toxicological analysis. Postmortem acetaminophen serum levels can be low compared to intoxications after ingestion of one single dose and have to be interpreted carefully. Analysis of premortem blood samples, when available, and calculation of the drug half-life can be useful. In every case of liver failure without pre-existing liver disease, the possibility of acetaminophen poisoning with therapeutic intent should be considered.

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