TEACHING FILE (GRAND ROUNDS)

ACUTE LIVER FAILURE DUE TO ACETAMINOPHEN TOXICITY - HOW TO TREAT?

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Clinical Problem :

A 21 months old boy presented with fever, cough, cold for 4 days, drowsiness for 2 days and one episode of convulsion. He had been treated with oral paracetamol for the initial 2 days of fever every 4 hourly with intake of 150 mg/kg/day. There was no other drug ingestion. There was no jaundice. He was a full term delivery with birth weight of 3.5 kg. He was immunized till date and had normal milestones. On examination, he was comatose with Glasgow coma scale of 4/15. He had pallor, rickets and hepatomegaly. Other systems were normal. Investigations showed hemoglobin 10.2 gm/dl, white cell count 2,600/cumm (32% polymorphs, 62% lymphocyte), platelets 19,400/cumm, bilirubin 1.2 mg/dl, SGOT 1645 IU/L, SGPT 2190 IU/L, serum albumin 2.7 gm/dl, prothrombin time 11.5 sec, partial thromboplastin time 73 sec and ammonia 170 mg/dl with no metabolic acidosis. His ultrasound showed moderate hepatomegaly. HIV ELISA, leptospira IgM, HBsAg, Hepatitis C antibody, Hepatitis A IgM ELISA were negative. His autoimmune markers for liver disease were negative and serum alpha fetoprotein was normal. He was treated with N-acetyl cysteine, fresh frozen plasma, lactulose and diazepam for seizures. He responded to above measures and recovered after 72 hours. Serum paracetamol levels could not be done in the child.

How should this child be treated?

Expert Opinion : Paracetamol is the most widely used medicine especially in young children, available over-the-counter to treat pain and fever. Acute deliberate self-poisoning, accidental pediatric exposure and inadvertent repeated supra-therapeutic ingestions are few of the causes of toxicity. In the United States and the United Kingdom it is the most common cause of acute liver failure. (1) Acetaminophen or paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. The concentration in plasma reaches a peak in 30 to 60 minutes and half-life in plasma is about 2 hours after therapeutic doses. (2) About 95% of paracetamol is conjugated in liver (glucuronic acid- 60%, sulfuric acid- 35%, cysteine - 3%).(3) A small proportion of acetaminophen undergoes cytochrome P-450 mediated N-hydroxylation to form N-acetyl-para-benzoquinonimine (NAPQI), which is a highly reactive and highly electrophilic intermediate. Under normal circumstances it is eliminated by conjugation with glutathione and then further metabolized to mercapturic acid and excreted into the urine. However, after ingestion of large doses of acetaminophen, the metabolite (NAPQI) is formed in amounts sufficient to deplete hepatic glutathione. This makes the hepatocytes very susceptible to oxidant injury and the reactive intermediate binds covalently to macromolecules leading to dysfunction of enzymatic systems. (4) Hepatotoxity occurs on ingestion of more than 150 mg/kg (5) as was seen in our patient. Symptoms that occur during first two days of acute poisoning may not reflect the potential seriousness of the intoxication. Nausea, vomiting, anorexia, diaphoresis and abdominal pain occur during initial 24 hours and may persist for a week or more. Clinical indications of hepatic damage manifest within 2-4 days.(4) Biopsy of liver reveals centrilobar necrosis with sparing of periportal vein.(6) In our patient, the dosage regimen of paracetamol caused toxicity and acute liver failure which is confirmed by increased levels of SGOT and SGPT in plasma, increase in ammonia levels (170 mg/dl) and increase in PTT (73 seconds) as well as exclusion of other causes of liver disease. We could not do paracetamol levels in our patient due to non-affordability.

The antidote of choice for acute paracetamol poisoning is administration of sulfahydryl compounds like N-acetyl cysteine which probably acts by replenishing the hepatic stores of glutathione as well as supportive management.(7) Our patient also responded to the same and recovered within 72 hours.

Conclusion: A particular dosage regimen should be followed due to toxicity risk of cumulative dose in children when prescribing paracetamol.

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