Therapeutic misadventure with paracetamol

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A 33-year-old woman presented with jaundice, tiredness, nausea, and vomiting of three days' duration after taking two glasses of gin and tonic together with 13 tablets of 500 mg paracetamol. Blood investigation results inferred a toxic hepatitis due to paracetamol overdose. She made an uneventful recovery. The case illustrates that if paracetamol is taken together with alcohol, even a relatively small dose of paracetamol can cause liver damage. Current studies of paracetamol poisoning are also discussed.

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Introduction

Paracetamol is a common over-the-counter preparation and patients tend to take paracetamol for common ailments. It is considered safe if the total dose in any single day for an adult is less than 4 g. Paracetamol poisoning occurs in cases of attempted suicide, accidental overdose in children, and therapeutic misadventure in adults. The last scenario is described in this case report.

Case report

The patient was a 33-year-old female executive without any previous history of psychiatric or liver disease. She was a social drinker and consumed about two to three glasses of wine each week. She drank two glasses of gin and tonic on the evening of the 19th August 1995. She experienced palpitations that night and took three tablets of 500 mg paracetamol at 1 am on the 20th August. She again took four tablets at 4 am and six tablets at 12 noon, totalling 6.5 g in 12 hours. She developed epigastric pain, nausea, and vomiting over the next three days. Supportive treatment for vomiting failed. She was admitted for management approximately 96 hours after taking her last dose of paracetamol.

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On admission, she looked tired, jaundiced, and dehydrated; but her vital signs were stable. No bleeding tendency was observed and there was tenderness in the epigastrium. The liver, spleen, and kidneys were not palpable. Urinalysis was positive for bilirubin and ketones. Her blood investigation profile is shown in the Table. Serology tests for acute viral hepatitis (HB_sAg, HB_cAb IgM, HAV IgM, HEV IgM) were all negative. Her paracetamol level on admission was < 1.00 μg/mL.

The patient was given oral N-acetylcysteine (because the intravenous form was not available), 6 g as a loading dose, followed by 3 g at four-hourly intervals for a further 12 doses. Intravenous fluid replacement was administered as well as oral Essentiale and silymarin. She was also given neomycin and lactulose for prophylaxis against hepatic encephalopathy. Over the next few days, she gradually improved and was discharged on the 27th August 1995.

Discussion

It was most likely that the patient suffered from toxic hepatitis due to paracetamol overdose. Serological tests for acute hepatitis A, B, and E were negative. The rapid onset of symptoms without a prodromal phase together with a rapid recovery discount a viral etiology. A very high ALT level (up to 10 000 U) is well-described for paracetamol poisoning, and is rarely seen in cases of viral hepatitis.

Paracetamol is an over-the-counter preparation. The general public is aware of the common side effects of aspirin but not of paracetamol. It is usual for patients

to take one to two tablets of paracetamol for minor ailments. Although the acute hepatotoxic dose is normally considered to be about 8 g, patients vary in their susceptibility. It has been reported that patients who take paracetamol often may tolerate a dose of up to 30 tablets.[1] Some may develop toxic hepatitis at a dose lower than 8 g as was illustrated by this patient (6.5 g). The dosage was nevertheless above 4 g, the limit often regarded as completely safe.

With paracetamol overdose, the conjugating pathway by the reduced glutathione in the liver is exhausted. A large amount of paracetamol is metabolised via the oxidative pathway to form a toxic intermediate metabolite known a N-acetyl-p-benzoquinone-imine (NAPQI). This NAPQI then binds to thiol groups on cysteine residues of intracellular proteins in the liver cell causing cellular necrosis. Alcohol induces hepatic microsomal oxidase and results in an increased production of NAPQI causing more cell damage. Clinicians should be aware of paracetamol overdosage in those patients who have pre-existing liver disease or are taking alcohol at the same time. There may also be an element of genetic susceptibility. For example, in Gilbert's syndrome, there is decreased glucuronidation and increased bioactivation of paracetamol.[2] In children, acute poisoning causing hepatotoxicity is less common, probably because of a relatively increased capacity for sulphation and an increased level of glutathione. Consequently, the total dose of paracetamol taken and its blood levels are not the only predictors of liver damage.

Because the production of the clotting factors II, V, VII, IX, and X are affected, the patient is vulnerable to developing a bleeding tendency. The INR should be monitored as well as the platelet count, which may fall as a result of fibrinolysis and intravascular coagulation. Hypoglycaemia can develop, a result of defective gluconeogenesis in the failing liver, as well as inadequate hepatic uptake of insulin. Acute liver failure, infections, encephalopathy, and cerebral oedema are well-recognised. The renal function should also be monitored since the renal tubules may suffer from damage similar to the liver cells. Fatal variceal haemorrhage has been reported 13 days after paracetamol overdose in a patient without previous liver disease.[3] Patients can also suffer from myocardial damage as a result of direct toxicity and severe metabolic disturbance.[4]

Early detoxification of paracetamol poisoning with N-acetylcysteine is life-saving. Late detoxification after 10 to 36 hours of ingestion can still give a better outcome in paracetamol-induced fulminant hepatic failure.[5] Although the patient was admitted very late (96 hours) after overdose, we decided not to withhold this potentially life-saving and benign therapy. Also, it is suggested that in alcoholics with paracetamol overdose, N-acetylcysteine should be given regardless of the serum paracetamol level after the overdose. The

Table. Serial blood investigation results following paracetamol poisoning and one week after admission

	Date			
	23/8/95	**24/8/95**	**26/8/95**	**1/9/95**
Total bilirubin μmol/L	55.2	48.6	40.0	24.2
Direct bilirubin μmol/L	27.9	20.7	16.7	–
Indirect bilirubin μmol/L	27.3	27.9	23.3	–
Alkaline phosphatase U/L	78	82	84	100
Aspartate aminotransferase U/L	7900	3280	380	44
Alanine aminotransferase U/L	9550	7090	2900	226
Total protein g/L	58	48	49	66
Albumin g/L	39	36	35	46
Globulin g/L	19	12	14	20
γ-Glutamyl transferase U/L	64	79	134	92
Glucose mmol/L	5.8	9.5	–	–
Platelet count x10^9/L	97	102	149	265
INR	2.72	1.80	1.2	1.0

exact role of N-acetylcysteine is unknown—it may serve as a precursor for glutathione synthesis, or it may form complexes with the toxic metabolites of paracetamol. It reverses tissue hypoxia by enhancing tissue oxygen delivery and consumption and may account for the lower incidence of multiorgan failure in fulminant liver failure.[6] The standard oral treatment is to give a loading dose of 140 mg/kg followed by 70 mg/kg four-hourly for a further 17 doses. As oral acetylcysteine was well tolerated by our patient, the intravenous form was not given. Besides its easy availability, the oral form may also be safer. Bronchospasm and respiratory arrest have been reported in patients with pre-existing asthma after the use of intravenous N-acetylcysteine.[7]

Oral methionine, 2.5 g given four-hourly up to a total of 10 g can be used as a second-line drug. Although Essentiale and silymarin are indicated in toxic metabolic liver diseases, their role in protecting the liver cells is not proven and they are not specific antidotes for paracetamol poisoning. Essentiale is alleged to provide essential phospholipids for the normal structure and function of the liver cells. Silymarin acts on the liver cell membranes, prohibiting the inflow of cell toxins as well as the loss of cell constituents. Detailed discussion of their possible efficacy is beyond the scope of this report. In one report of paracetamol overdose, hypothermia might have protected the liver against damage possibly by reducing the formation of the toxic intermediates.[8] Further study of induced hypothermia as an adjunctive treatment with acetylcysteine may be worthwhile. Studies in mice and in humans show that prostacyclin could also reduce hepatotoxicity.[6,9] For patients with fulminant hepatic failure, liver transplantation has been successful, the success rate being comparable to transplantation for other causes of liver failure.[10]

To limit the possibility of paracetamol overdose toxicity, adding an antidote such as methionine to all paracetamol preparations has been suggested.[11] Specific warning about the toxicity of paracetamol and its interaction with alcohol should be included on the packaging. Limiting over-the-counter sales of paracetamol may also reduce the incidence of dangerous overdoses.

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