Severe thrombocytopenia after paracetamol overdose

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Abstract

Two patients with severe thrombocytopenia after paracetamol overdose are described. The platelet count was lowest two days after the overdose. Neither leucopenia nor anaemia occurred.

Case histories

PATIENT 1

A previously healthy 48 year old man took an overdose of 100, 500 mg paracetamol tablets. No other drugs or alcohol were taken. He presented to hospital 10 hours later, at which time his plasma paracetamol concentration was 250 mg/l. He was started on n-acetyl-cysteine treatment 11 hours after the overdose. The patient was transferred to this hospital two days later because of a considerable deterioration in the results of biochemical tests. His prothrombin time ratio was 10 times greater than normal and the alanine aminotransferase activity was 12 500 IU/l, but he did not have hepatic encephalopathy. On admission to this hospital a full blood count, which had not been done previously, showed: platelets $3 \times 10^9/l$ (checked manually), white cells $6.1 \times 10^9/l$, and haemoglobin concentration 14.6 g/dl. He was given a transfusion of four units of platelets and four units of fresh frozen plasma. The next day he developed severe epistaxis which required nasal packing. A further four unit platelet transfusion was given and repeated the following day. There were no further serious episodes of bleeding. Although he became temporarily more jaundiced, he remained free of hepatic encephalopathy. His haematological and biochemical results are shown in the Table. He was discharged 19 days after hospital admission and was well when reviewed in outpatients clinic three weeks later.

PATIENT 2

A 19 year old man was transferred to this hospital for consideration for a liver transplant. He had presented to another hospital nine days earlier complaining of right upper quadrant pain and

nausea. He denied recent heavy alcohol intake or an overdose of paracetamol. There was no notable past medical history. On examination he had no fever but had rebound tenderness, guarding, and a possible mass in the right upper quadrant. Investigations showed: platelets $10 \times 10^9/l$, white cells $4.9 \times 10^9/l$, haemoglobin 14.6 g/dl, prothrombin time ratio 1.6. He was thought to have a hepatic haematoma secondary to a blood dyscrasia. Ultrasound scan showed a normal liver, spleen, and kidneys. The gall bladder was oedematous but did not contain stones, and the biliary tree was not dilated. There was a considerable volume of free peritoneal fluid, with areas of 'clot-like tissue.' He was given a transfusion of six units of platelets and four units of fresh frozen plasma.

After two days and further transfusion of a total of 15 units of platelets, his abdominal pain had settled. He had developed purpura and subconjunctival haemorrhages, but there had been no further serious bleeding. A bone marrow examination was histologically normal, showing plentiful megakaryocytes. He had become drowsy, however, and was now noticed to have abnormal liver function tests (Table). A diagnosis of acute hepatic failure was made. He again denied taking paracetamol. Later that day he became aggressive and confused (grade III hepatic encephalopathy) and he was therefore sedated and ventilated. Results of investigations to determine the cause of his hepatic failure were: HBsAg negative and monospot test negative.

After nine days, his bilirubin concentration was continuing to rise and he was transferred to this hospital. By now he was no longer encephalopathic. We believed that his initial thrombocytopenia, other investigations, and clinical course indicated that he had taken a paracetamol overdose. At first he denied having done so, but when the importance of the correct diagnosis was explained to him, he admitted to having taken 70-80, 500 mg paracetamol tablets two days before admission to hospital, but continued to deny having drunk any alcohol with the overdose. A transplant was not performed and medical management continued. Hepatitis A

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Results of haematological and biochemical investigations after paracetamol overdose in two patients

	Patient 1 Days after overdose						Patient 2 Days after overdose					
	2	3	4	5	14	43	2	3	4	5	11	37
Platelets ($\times 10^9/l$)	3	9	94	111	226	292	10	16	25	68	98	286
White cells ($\times 10^9/l$)	6.1	8.0	7.7	9.3	10.3	12.4	4.9	8.2	9.4	10.1	19.4	13.9
Haemoglobin (g/dl)	14.6	11.8	9.8	9.9	10.5	12.1	14.6	13.8	10.8	11.3	12.3	11.1
Prothrombin time ratio	10	4.4	3.1	1.7	1.2	1.1	1.6	4.2	6.1	3.2	1.8	1.3
Fibrinogen (g/l)*	0.7	0.9	1.1	1.4	1.8	2.6	—	0.96	0.70	—	0.84	1.38
Fibrin degradation products (mg/l)*	60	60	20	<10	<10	<10	—	80	80	—	80	20
Alanine aminotransferase (IU/l)	12 500	7 826	4 820	3 422	29	21	—	—	10 780	4 920	1 127	180
Bilirubin ($\mu\text{mol/l}$)	87	116	189	233	256	21	—	—	117	220	546	390
Creatinine ($\mu\text{mol/l}$)	171	240	261	230	121	88	—	—	182	152	116	66

*Normal ranges: fibrinogen 1.5-4.0 g/l, fibrin degradation products <10 mg/l.

IgM was found to be negative. Serum copper, caeruloplasmin, and α_1 antitrypsin values were normal. He was well enough to be discharged 38 days after his overdose.

Discussion

These two patients indicate that severe thrombocytopenia may be a complication of paracetamol overdose. In neither case were other drugs or alcohol taken. Patient 1 was given n-acetylcysteine treatment, but there are no reports of this drug producing thrombocytopenia (Duncan, Flockhart and Co Ltd – personal communication) and it was not given to the second patient.

A moderate reduction in platelet count is common in acute liver failure. Severe thrombocytopenia after paracetamol overdose does not, however, seem to be described.¹⁻⁴ For example, Gimson and colleagues studied 76 patients with acute liver failure and grade III–IV hepatic encephalopathy, most of whom had taken a paracetamol overdose.¹ Just before starting charcoal haemoperfusion treatment, the patients' mean (SEM) platelet count was $200 (20) \times 10^9/l$. Furthermore, these patients' mean platelet count fell over the following four days. In contrast, our patients' thrombocytopenia was worse at presentation and improved during the next few days. Similarly, thrombocytopenia in association with acute liver failure caused by non-A non-B hepatitis is usually part of a peripheral blood pancytopenia and occurs some weeks after the onset of the illness,⁵ whereas neither of our patients had leucopenia or appreciable anaemia.

Thrombocytopenia in acute liver failure is usually attributed to disseminated intravascular coagulation, though this is a difficult diagnosis to substantiate as the plasma concentrations of both fibrinogen and fibrin degradation products may

be altered by the hepatic impairment. An alternative explanation in our patients may be a direct toxic effect of paracetamol or one of its metabolites on their platelets. In support of this possibility, there are a few single case reports of therapeutic doses of paracetamol causing thrombocytopenia.⁶⁻¹⁰ Both the patients we describe had taken 1 g of paracetamol before on many occasions without any overt bleeding. Therefore, in these patients, there would seem to be a dose-dependent as well as an idiosyncratic element to this adverse reaction to paracetamol.

Bleeding in patients with acute liver failure may easily be assumed to be caused by the impaired synthesis of liver derived clotting factors. In both our patients, thrombocytopenia was most severe two days after the overdose. Since it may be potentially life threatening but readily treatable by platelet transfusion, an immediate check of the platelet count in such patients seems desirable.

- 1 Gimson AES, Braude S, Mellon PJ, Canalese J, Williams R. Earlier charcoal haemoperfusion in fulminant hepatic failure. *Lancet* 1982; ii: 681–3.
- 2 Gimson AES, Williams R. Serial charcoal haemoperfusion in the treatment of fulminant hepatic failure. In: Williams R, ed. *Liver failure*. Edinburgh: Churchill Livingstone, 1986: 208–33.
- 3 Read AE. The liver and drugs. In: Wright R, Alberti KGMM, Karran S, Millward-Sadler GH, eds. *Liver and biliary disease*. London: WB Saunders, 1979: 822–47.
- 4 Meredith TJ, Vale JA, Proudfoot AT. Poisoning caused by analgesic drugs. Paracetamol (aceta-minophen). In: Weatherall DA, Ledingham JGG, Warrell DA, eds. *Oxford textbook of medicine*. 2nd ed. Oxford: Oxford University Press, 1987: 6.18–20.
- 5 Gordon-Smith EC. Aplastic anaemia and other causes of bone marrow failure. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford textbook of medicine*. 2nd ed. Oxford: Oxford University Press, 1987: 19.46–54.
- 6 Heading RC. Purpura and paracetamol. *Br Med J* 1968; iii: 743–4.
- 7 Eisner EU, Shahidi NT. Immune thrombocytopenia due to a drug metabolite. *N Engl J Med* 1972; 287: 376–81.
- 8 Kornberg A, Polliack A. Paracetamol-induced thrombocytopenia and haemolytic anaemia. *Lancet* 1978; ii: 1159.
- 9 Scheinberg IH. Thrombocytopenic reaction to aspirin and acetaminophen. *N Engl J Med* 1979; 300: 678.
- 10 Schoenfeld Y, Shaklai M, Livni E, Pinkhas J. Thrombocytopenia from acetaminophen. *N Engl J Med* 1980; 303: 47.