Severe Acute Necrotising Pancreatitis Caused by Sodium Valproate: A Case Report

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ABSTRACT

Drug induced acute pancreatitis is an uncommon cause for acute pancreatitis. To make this diagnosis confidently, certain criteria should be fulfilled. The patient should be receiving the drug when acute pancreatitis develops and the pancreatitis should resolve with cessation of the drug. Also, other causes need to be excluded, and while the patient should ideally have recurrence of the pancreatitis if the drug is recommenced, as a confirmatory test this is not usually performed.

A case is reported of severe acute necrotising pancreatitis associated with the use of sodium valproate. Sixteen years previously a similar but milder episode of possible acute pancreatitis occurred in this patient, resulting in cessation of sodium valproate. On the present occasion the patient required aggressive resuscitation, inotropic and ventilatory support, antibiotics and enteral feeding for a prolonged period before making a complete recovery. (**Critical Care and Resuscitation 1999; 1: 366-367**)

Key words: Pancreatitis, acute necrotising pancreatitis, sodium valproate

A number of drugs have been implicated in acute pancreatitis. Definite proof of the drug causing acute pancreatitis usually depends on a) pancreatitis developing while patient is on the drug, b) other likely causes being excluded, c) pancreatitis resolving with cessation of the drug and d) the pancreatitis recurring with administration of the drug.[1] A case of severe necrotising pancreatitis induced by sodium valproate and meeting the above criteria is reported. A brief outline of the mechanism and disease process is also presented.

CASE REPORT

A 34 year old male was admitted to hospital with a 24 hour history of epigastric pain. The pain was constant with intermittent severe acute episodes and was associated with nausea and vomiting. A clinical diagnosis of acute pancreatitis was made, and he was treated with analgesia, intravenous fluids and nasogastric suction. Over the following 24 hours the patient's condition deteriorated as he became pale, sweaty and dyspnoeic with increasing epigastric pain. His vital signs included a temperature of 38 °C, pulse rate of 150 beats per min, mean arterial pressure of 50 mmHg, and respiratory rate of 32 breaths per min. Blood biochemical analysis revealed a serum sodium of 126 mmol/L, glucose 9.9 mmol/L, amylase 3592 U/L, and a white cell count of 17.3 $x10^9$/L. The chest x-ray showed that he had developed bilateral pleural effusions. An abdominal CT scan was performed which confirmed the diagnosis of acute necrotising pancreatitis. He was admitted to the intensive care unit (ICU) and on the third day required ventilatory and inotropic support for hypoxia, hypotension and poor peripheral perfusion.

At the age of 8 years, the patient was diagnosed with a grade 4 malignant glioma, later reclassified as an oliogdendroglioma-astrocytoma, and underwent a subtotal excision and radiotherapy. Subsequently he developed epilepsy, which proved difficult to treat, requiring various combinations of medications. In August 1981 he was commenced on sodium valproate and the dose was increased in February 1982. At this time he developed nausea, episodic vomiting and epigastric discomfort which continued until April 1982 when his sodium valproate was ceased. On this occasion the γ-glutamyltranspeptidase (GGT) was recorded as being 'elevated', the serum amylase however, was not measured.

In May 1998, sodium valproate was recommenced

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by another medical practitioner and in June 1998 he had a short episode of severe epigastric pain and vomiting. His dosage was increased again in July 1998 and this was one month prior to his admission with acute pancreatitis.

The patient was treated with general supportive measures (including intravenous fluids and inotropic agents), imipenem, gentamicin, famotidine, parenteral nutrition and clonazepam for the preexisting epilepsy. Over the next 32 days his ICU stay was complicated by ventilator-associated pneumonia, anaemia, haemorrhagic erosive gastritis, severe hypoalbumin-aemia, methicillin resistant *Staphylococcus aureus* colonisation and pseudocyst formation. On day 35, his tracheostomy was removed and soon after he was discharged to the ward where he made a complete recovery.

DISCUSSION

Acute pancreatitis has many causes including, alcohol ingestion (acute and chronic), biliary tract disease, infections (mumps, hepatitis, other viruses), hypertriglyceridaemia, post ERCP and drugs.[1] Drug induced acute pancreatitis is not common, but a number of drugs have been implicated which have been separated into two groups (i.e. definite and possible) by McArthur (Table 1).[2]

Table 1. Drug related pancreatitis

Definite	*Possible*
Azathioprine	Paracetamol
Sulphonamides	Nitrofurantoin
Diuretics	α-methyl DOPA
Sodium valproate	Erythromycin
Tetracycline	Salicylates
Pentamidine	NSAIDs
Contraceptive pill	ACE inhibitors
	Metronidazole

The first case of pancreatitis associated with sodium valproate was reported in 1979.[3] Since that time there have been over 55 cases recorded in the medical literature but none reported in Australia. In a study of 507 physicians with an interest in epilepsy in the United States of America, 14.5% stated they had seen a case of acute pancreatitis associated with sodium valproate.[4] Of these patients, 85% were classified as having mild to moderate disease and 15% as severe disease with haemorrhagic pancreatitis and disseminated intravascular coagulation, 3 of whom (i.e. 50%) had fatal outcomes.

The common presenting features of acute pancreatitis (e.g. nausea, vomiting and epigastric pain) are also common side effects of sodium valproate owing to gastric irritation or a possible central effect on the brainstem emetic centre. The reason why sodium valproate may cause pancreatitis is not known. Drugs may effect the process of zymogen granule formation within the pancreas, leading to release of enzymes and autodigestion; genetic predisposition of some patients may be a risk factor; trace element deficiency associated with diet, drugs or genetics may allow an increase in free radical formation or activity and an increase risk of pancreatitis. One study reported an asymptomatic elevated serum amylase in up to 25% of patients taking sodium valproate.[4]

In this patient, in 1982 there was a history of nausea, vomiting and epigastric pain associated with an increase in sodium valproate dose, and these symptoms disappeared on cessation of the medication. It is also noted that on this occasion there was a marked rise in the γ-glutamyltranspeptidase (GGT). GGT is a nonspecific marker of obstructive biliary disease and is often elevated in acute pancreatitis but may also be elevated in many other unrelated conditions. It would seem reasonable to conclude that this episode of nausea, vomiting and epigastric pain lasting off and on for 2 months in 1982 was caused by mild acute pancreatitis. On receiving the sodium valproate again some 16 years later, the patient initially developed identical symptoms to those experienced in 1982, and subsequently progressed to acute pancreatitis.

In summary, a 38 year old male is presented who developed severe necrotising pancreatitis associated with sodium valproate. He required aggressive resuscitation, inotropic and ventilatory support, antibiotics and enteral feeding for a prolonged period before making a complete recovery.

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REFERENCES

1. Steinberg W, Tenner S. Acute pancreatitis. N Engl J Med 1994;330:1198-1210.
2. McArthur KE. Drug induced pancreatitis. Aliment Pharmacol Ther 1996;10:23-38.
3. Batalden PB, van Dyne BJ, Cloyd J. Pancreatitis associated with sodium valproate. Pediatrics 1979;64:520-522.
4. Asconape JJ, Penry JK, Dreifuss FE, Riela A, Mirza W. Valproate associated pancreatitis. Epilepsia 1993;34:177-183.