# AN UNUSUAL ETIOLOGY OF ACUTE NECROTIC PANCREATITIS IN A COMATOSE PATIENT

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## Abstract

Introduction: The etiology of an acute necrotic pancreatitis is represented by gallstone disease, alcohol intake, abdominal trauma and drugs (in about 2% of cases). There are at least 100 drugs which can determine acute pancreatitis. Valproic acid-induced pancreatitis is reported as a complication of chronic therapy with this drug.

Case Report: We report here the firt case of acute necrotic pancreatitis in a 22-year-old mocatose woman with valproic acid acute overdose in attempted suicide, a patient naive to valproate therapy. The patient presented 24 hours after ingestion of a massive dose of extended release valproate with profound coma, and features of acute necrotic pancreatitis, confirmed by contrast enhanced abdominal CT scan. She had a favorable outcome with supportive and conservative treatment only.

Conclusion: Emergency physicians should be aware of this unusual presentation of valproate toxicity, even in patients at first exposure to this drug.

**Introduction**

Acute pancreatitis secondary to a drug overdose is rare in clinical practice, representing at most 2% of the total cases (1,2). The first case of drug-induced acute pancreatitis after chlorthalidone and cortisone was reported in 1955. The list of drugs responsible for this complication has increased to about 500 agents (3). Only statins, diuretics, antiretroviral agents, and anticonvulsants are responsible for acute necrotic pancreatitis (4,5).

The incidence of acute pancreatitis induced by chronic valproate therapy increased since 1979, when the first case was reported, because of its extensive use in the medical practice (4-8).

The usual toxic effects after an acute valproate overdose are: central nervous system depression, gastro-enteral effects, pancreatitis, metabolic acidosis with a high anionic gap, dyselectrolytemia and hyperammonemia (1,7,9).

All published literature on the subject reveals this complication only after chronic therapy with valproate for different conditions, or after valproic acid overdose in patients already using this drug.

Currently, there are no reports of patients with necrotic pancreatitis as a complication of valproic acid acute overdose, in patients naïve to valproate therapy. Our aim was to present diagnostic challenges faced by Emergency Department (ED) physicians in the management of a comatose patient with a rare form of acute pancreatitis.

**Case Report**

A 22 year-old female patient, without significant medical history, was brought unconscious to the ED. The empty boxes for approximately 60 pills of 300 mg valproate sodium extended release were found at her residence. The family reports no chronic medical therapy, no alcohol, tobacco or drug use in this patient. The last contact with the patient was more than 24 hours before presentation. Upon admission to ED, the patient had a Glasgow Coma Scale score of 3, respiratory depression, a blood pressure of 100/60 mmHg, and a regular heart rate of 108 beats/min. She was intubated and mechanically ventilated.

A cranio-cerebral CT scan was performed and revealed

no abnormalities. Blood tests showed increased glucose (127 mg/dL), ammonia (98 mmol/L), calcium (6.63 mg/dL), lactate (37 mg/dL), creatine kinase (1471 U/L), amylase (2989 U/L) and lipase (1328 U/L). Toxicological screen for drugs and alcohol was negative. The serum valproate level was 105 mg/L in our patient. The therapeutic reference range for valproate is 50-100 mg/L (9).

The increased values of amylase and lipase, in the absence of a medical history of gallbladder disease or ultrasound changes of the gallbladder, lead to a suspicion of pancreatitis, confirmed by a contrast-enhanced abdominal CT scan (Figure 1), revealing specific changes of acute necrotic pancreatitis, with a Balthazar score of 5.

We excluded another etiology for necrotic pancreatitis. We initiated only supportive treatment, parenteral hydration with crystalloid solutions 250 ml/h for the first 48 hours, and correction of electrolytes. Seventy-two hours from admission in our department, the patient regained consciousness and declared the ingestion of Depakine Chrono®, her father's medication for a psychiatric condition. She had no abdominal complaints during hospitalization.

The evolution was favorable, with pancreatic enzymes normalization 14 days from the moment of admission. An abdominal CT scan 15 days later showed the presence of pancreatic pseudocysts, treated conservatively.

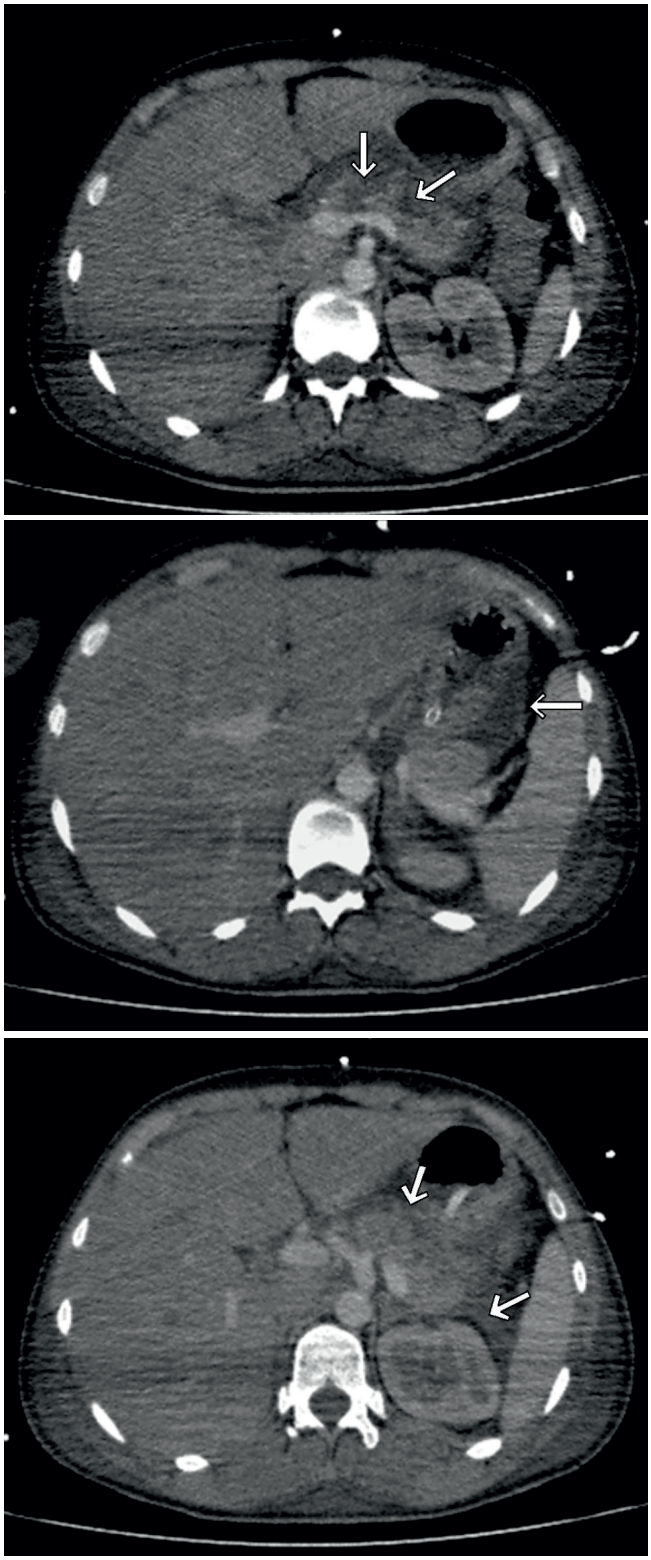

FIGURE 1. A. Non-homogeneous pancreatic structure, with necrotic areas (arrows). B. Liquid collection with a thin iodophile wall, near the large curb of the stomach (arrow). C. Infiltrates of the peripancreatic fat, and a liquid fuse expanded into anterior left pararenal area (arrows).

**Discussion**

Valproic acid is one of the new antiepileptic drugs used extensively in the last twenty years for epilepsy, bipolar affective disorders, schizophrenia, and for migraine attacks prophylaxis (9).

Literature has recorded numerous information on drug-induced pancreatitis (Table 1), and case reports of acute pancreatitis in patients with chronic valproic acid treatment, including acute necrotizing pancreatitis (4). All these case reports documented acute pancreatitis in patients already receiving valproate therapy since childhood, or after increasing the dose of a chronic valproate therapy (4, 10). However, there are no reports regarding necrotic pancreatitis after an acute overdose of valproic acid, in patients naïve to this treatment, or at first exposure to this drug.

**TABLE 1.** Agents involved in drug-induced acute pancreatitis

| | |
|---|---|
| Anticonvulsants | Carbamazepine, valproic acid, lamotrigine, topiramate |
| Antiretroviral drugs | Interferon, lamivudine, didanosine, ribavirin |
| Antineoplastic agents | 5-fluorouracil, vincristine, cyclosporine, L - asparginase, cytarabine, doxurubicine, cisplatin, azathioprine, cyclophosphamide |
| Analgesics and NSAID's | Codeine, paracetamol, aspirin, sulindac, mefenamic acid, indomethacin, COX2 inhibitors |
| Antidiabetics | Metformin, sitagliptin, exenatide |
| Antibiotics | Macrolides, metronidazole, rifampicin, co -trimoxazole, ampicillin, tetracyclines, fluoroquinolones, ceftriaxone, ertapenem |
| Anesthetics | Propofol |
| Antihypertensive drugs | ACE-inhibitors, diuretics, amlodipine, irbesartan, methyldopa, prazosin |
| Statins | Pravastatin |
| Antiarrhythmic agents | Amiodarone, procainamide |
| Gastric secretion inhibitor drugs | Omeprazole, cimetidine, ranitidine |
| Antidepressants | Venlafaxine, mirtazapine |
| Hormones | Corticosteroids, estrogens |

NSAID's, non-steroidal anti-inflammatory drugs; COX, cyclooxygenase; ACE, angiotensin converting enzyme.

Acute pancreatitis induced by valproic acid is not dose-dependent and is the result of an idiosyncratic reaction (4,7,9). The mechanism of acute pancreatitis induced by valproic acid overdose is not yet elucidated (4,7). The direct toxic effect of oxygen free species on pancreatic tissue, and the depletion of superoxide dismutase, catalase and glutathione peroxidase can be involved (5).

There is no correlation between the serum level of valproic acid and the severity of the acute poisoning (7). The plasmatic peak of valproic acid occurs 18 hours from ingestion, and the half-life is up to a maximum of 48 hours, in the setting of an acute overdose (7).

Our patient, although presenting necrotic pancreatitis in the setting of an acute severe valproate poisoning, had a serum level of valproate corresponding to a therapeutic level. However, the assay was performed 48 hours from ingestion.

The evolution was favorable, and the coma was resolved after 72 hours with supportive treatment. Although the profound coma was prolonged, cerebral CT scan showed no brain edema, which occurs 12 hours after valproic acid overdose and lasts for four days (9,11).

Pancreatitis' evolution was favorable with medical treatment. The patient was discharged 16 days later without complaints, with normal laboratory tests.

Necrotic pancreatitis induced by a valproate overdose can be asymptomatic. The diagnosis in our patient was based on elevated pancreatic enzymes and imagistic tests, as literature suggests (12).

To our knowledge, this is the first reported case with necrotic pancreatitis induced by an acute overdose of valproic acid in a patient naïve to this treatment. A PubMed search using keywords:" valproate, poisoning, pancreatitis" showed only 21 papers, all revealing this complication after chronic therapy with valproate for different conditions, or after valproic acid overdose in patients already using this drug.

The ED practitioners must be aware of this etiology of necrotic pancreatitis, especially in the assistance of unconscious patients having elevated levels of pancreatic enzymes, even if the patients are naïve to valproate therapy.

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