Acute Pancreatitis Associated with Valproate Treatment

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To the Editor: Drug-induced pancreatitis (DIP) is a rare cause. According to a German retrospective study, the incidence of pancreatitis caused by drugs was 1.4%.[1] A nationwide survey conducted by Japan showed that 1.2% of all cases of acute pancreatitis were caused by drugs.[2] The DIP is caused due to the drug itself or its metabolites, or organism-specific reactions caused by the introduction of hypersensitivity during pancreatic injury. Despite appropriate treatment, it demonstrated severe complications and high mortality.[3] Valproate (sodium valproate and divalproex sodium forms) is a commonly used medication that is approved by the U.S. Food and Drug Administration for the treatment of epilepsy, migraine, and bipolar disorders. Adverse effects associated with valproate are typically benign, but there are more serious effects that are less frequently observed. These effects include hepatotoxicity, teratogenicity, possible polycystic ovaries with a potential sterile effect, and acute pancreatitis.[4] Even though acute pancreatitis is an adverse effect of very low frequency, it is very important to be noted due to a high mortality rate of patients with acute pancreatitis as a consequence of the use of valproate.

A 26-year-old Chinese man was diagnosed with mania and received outpatient care at another mental hospital, and his positive symptoms included hallucinations and delusions. His condition has been well controlled by quetiapine. In June 2016, he met with a car accident, leading to multiple bone fractures in his foot, and he was given azithromycin for treating foot infection. After few days of medication, the patient had severe abdominal pain and diarrhea and so the antibiotics and quetiapine were suspended. Three days after the withdrawal, the mania condition relapsed, and then he was admitted in our hospital. The patient had a medical history of being never smoked, no alcohol intake, and no intake of any illegal drugs. After admission, the blood and urine routine examinations, hepatic and renal functions tests were performed and showed normal results. Electroencephalograms, electrocardiograms, and abdominal B ultrasonography showed normal results. Then, he had been taking quetiapine fumarate tablets (Hunan Dongting Pharmaceutical Co., Ltd.,) 400 mg/d and magnesium valproate sustained-release tablets (Hunan Xiangzhong Pharmaceutical Co., Ltd.,) 1000 mg/d. Six days after treatment, he developed abdominal tenderness, abdominal swelling, and vomitings. The beginning of the vomit included the stomach content, which was gradually turned into a dark green liquid. Blood tests indicated acute inflammation with a leukocytosis (white blood cell count 13.99; normal range 4–11 × 10^9/L) and neutrophilia (neutrophil count 12.72 and normal range 2.5–7.5 × 10^9/L). Amylase showed elevated levels at 368, which was about 3.0 times the normal value (normal range <122 U/L). Creatine kinase was within the normal range. Blood pressure was stable and within the normal range. Elevated serum amylase levels combined with severe abdominal pain often triggered the initial diagnosis of acute pancreatitis. Although results of the abdominal ultrasonography were negative, the results of digital radiography were positive for acute pancreatitis. A "sentinel loop" as a sign of intestinal obstruction and colonic truncation sign appeared in the plain abdominal X-ray film [Figure 1]. He was managed conservatively with intravenous fluid 2500 ml/d and moxifloxacin 400 mg/d, but the general condition of the patient was not improved. A chief psychiatrist has been consulted for this case. Factors such as alcohol use, obstruction, and trauma were excluded from the study. The possibility of drug-induced acute

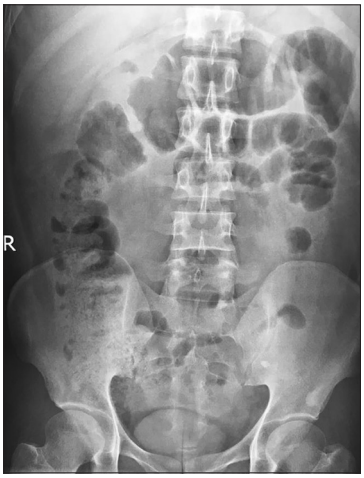

Figure 1: Results of digital radiography were positive for pancreatitis. A "sentinel loop" as the sign of intestinal obstruction (isolated intestinal loop in left upper quadrant) and colonic truncation sign (descending colon without air) appeared in the plain abdominal X-ray film.

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pancreatitis was considered. Through literature review, it was found that valproate was highly correlated with pancreatitis, and hence was withdrawn from his drug regimen. The patient continued treatment with fluid 2500 ml/d and moxifloxacin 400 mg/d, and he showed a substantial recovery within 1 week. Although rare, acute pancreatitis has been reported with the long-term use of valproate. The clinical features of acute pancreatitis are obvious but subtle clinical features made the diagnosis difficult in our patient. One may argue that the incrimination of valproate as an etiological cause of pancreatitis is not justifiable without reintroducing the drug to see the recurrence of pancreatitis. This was not done as we considered it to be unethical.

A substantial number of drugs commonly prescribed for gastrointestinal disorders are known to cause acute pancreatitis. In general, the etiopathological mechanisms involved in DIP remain unclear. It is difficult to establish or rule out definitely such unwanted event, especially in patients taking numerous medications prescribed for multiple comorbidities. Pharmacological agents are among etiologic factors that should be considered in all patients presenting with signs and symptoms consistent with acute pancreatitis. The diagnosis of DIP is often difficult to establish.[2] There are reports of life-threatening pancreatitis in children and adults after taking valproate. Some cases show rapid progression in bleeding from the initial symptoms till death, some are observed after the initial medication, and some appear after few years of medication.[5] Previous studies considered that valproate is a fatty acid. Valproate in the effective concentration range is highly bound to plasma protein. When the protein binding was saturated over a blood concentration of 86 μg/ml, then the free valproate (fatty acids) was increased, and had toxic effects on pancreatitis.[6] In this case, the patient took a normal dose range of magnesium valproate sustained-release tablets, there was a serious adverse drug reaction, it is possible that he belongs to poor metabolizing (CYP2C9-status) patients, leading to increased plasma concentrations.[7] Patient and guardian must pay attention to the symptoms of abdominal pain, nausea, vomiting, and loss of appetite even under normal usage and dosage. Such individuals were diagnosed as having pancreatitis, and usually should discontinue valproate. The treatment plan should be changed according to the clinical needs.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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