Valproate associated acute pancreatitis

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ABSTRACT

There is a definitive association between valproate therapy and acute pancreatitis. More than 50 cases have been reported. Most of the reported cases were mild yet there were a few more cases with higher morbidity and mortality. The risk is higher in patients under 20 years of age, during the first year of therapy, on the patient having encephalopathy or chronic renal failure and on patients with anti-epileptic drug polytherapy. The treatment of pancreatitis is supportive, laparotomy should be avoided. Re-challenge is hazardous and should be avoided.

Keywords: Valproate, epilepsy, acute pancreatitis, drug toxicity.

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Acute pancreatitis is a serious disease which have numerous causes. Gall stones and alcoholism account for 80% of cases, while 10% remain idiopathic. Other miscellaneous causes are numerous and include abdominal trauma (accidental or iatrogenic), metabolic (hypercalceamia and hypertriglyceridemia), infections (mumps, hepatitis, rubella, mycoplasma, parasitis), ischaemia, vasculitis, inherited diseases, toxins and drugs.[1] Drugs account for approximately 2% of acute pancreatitis cases in the general population.[2] This percentage is much higher in children (15-30%) and in HIV patients.[3] The first reported drug causing pancreatitis was published in 1955.[4] Since then more than 85 drugs have been accused of causing pancreatitis. Most of these were isolated case reports. Definite association defined as symptoms subsiding on drug withdrawal and reappearing on re-challenge or consistent case reports supported by animal experiments.[5,6] Definite association exist for didanosine[7], aminosalicylate[8], calcium[9,10], estrogen[11], sodim stibogluconate[12], and sodium valproate. Valproate associated pancreatitis (VAP) was first reported in 1979. Since then more han 18 papers describing approximately 50 patients have been published.[13-29] Although detailed description of these patients were not always present, still they clearly showed definite association between valproate and acute pancreatitis.

Review of these cases showed that males nd females are equally affected. The age of onset ranged from 1-65 years with a mean age of 15.2 years. The highest incidence was in the second decade (40%) followed by the first decade (36%). Only two cases described below 2 years and one above 60 years. This could be secondary to the fact that valproate is more frequently used in the young age group. It is estimated that 50% of the population using valproate in USA were under 20.[30]

Presentation. The majority of patients presented with progressive abdominal pain, nausea and vomiting which might present for variable time, days or weeks, and occasionally it could be intermittent. Delay in diagnosis can occur as these symptoms are common with patients taking valproate without pancreatitis. Two patients presented wtih pancreatic pseudocyst without clear history of pancreatitis.[31] Most of these patients had mild pancreatitis which subsided by valproate withdrawal, elimination of oral intake, IV hydration and analgesics. Fourteen percent had severe hemorrhagic pancreatitis leading

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to severe complication such as shock, respiratory failure and disseminated intravascular coagulation. Five patients died, three of them post-operatively.[16-18] Pancreatitis can occur simultaneously in patients dying from hepatic failure and seven such cases have been reported.[32]

Intraoperative or necropsy findings in these patients showed serosanguinos peritoeal fluid and inflamed, oedematous, usually haemorrhagic necrotic pancreas was scattered areas of multiple mesentric fat necrosis. Pseudocyst was rarely found. Abdominal ultrasound may show enlarged pancreas and peritoneal fluid and it is very sensitive for associated cholilithiasis. Abdominal contrast - enhanced computed tomography is the imaging method of choice, yet it may miss 15-30% of cases with mild pancreatitis.[33] It will show enlarged pancreas, haemorrhagic infarction, pseudocyst and ascitis.

Investigation. Most patients with pancreatitis had serum amylase level 2-3 times above the upper limit of normal. Seven patients had normal level since amylase levels tends to be normalized 4-7 days after the onset of pain. Raised serum lipase level was found in all patients. Asymptomatic rise in serum amylase level in patients taking valproate has been frequently reported, figures ranged from 0%[16] to 24%[34] were found in the literature. It is probably found in 10% of patients. These patients remain asymptomatic and values tend to normalize on follow-up. Withdrawal of valproate on these patients is unnecessary and only close follow-up is needed. Screening serum amylase in asymptomatic patients on valproate is not recommended currently.[35]

Risk Factors. Pancreatitis can occur in any patients taking valproate and has no relation to the type of epilepsy. It was observed in patients with generalised or partial seizures. Chronic diffuse encephalopathy was found in 16 patients (32%). These patients suffered from moderate to severe developmental delay, mental retardation and cerebral palsy. Chronic renal failure (CRF) was found in 7 patients (14%).[36] Great care should be taken in diagnosing VAP in patients with chronic renal failure because serum amylase level is usually elevated in those patients and a rise of 4-6 times normal is needed for the diagnosis and CRF by itself is a risk factor of acute pancreatitis.[37] The association with other anti-epileptic drugs (AEDs) were looked for, 62% of patients were on a variety of other AEDs such as phenytoin, carbamazepine, phenobarbitone and primidone. Only carbamazepine has been reported to cause pancreatitis.[38,39] Polytherapy may increase the risk of VAP. [25]

Dose, duration and re-challenge of valproate therapy. The dose of valproate ranged from 10mg/kg to 56mg/kg and most VAP patients were within this range (84%), even in those who took higher doses serum level was within therapeutic ranges. The length of exposure to valproate vary from one week up to 8 years. Thirty two percent of cases occurred within the first three months after taking valproate and 56% within the first year. With the recently introduced intravenous route a duration of 24 hours have been reported.[27] The following data about precipitating factors is available on 6 patients: cluster of seizures (3), febrile illness (2), elective surgery (1) and steroid therapy (1). Re-challenge done in 10 patients, 8 had relapse, weeks to 14 months later, the other two had no relapse after follow-up for 12-14 months. One patient had dose dependent relapse.

Pathogenesis. Since VAP was not a dose related complication and was developed as early as 1 week and as late as 8 years after initiation of therapy, it is considered an idiosyncratic reaction.

The exact mechanism by which valproate induce acute pancreatitis is not known. The most attractive theory is capillary injury mediated by oxygen-derived free radicals.[40] These highly charged molecules which contain unpaired electron in their outer shells are produced endogenously in small amounts as a by-product of oxidative metabolism. Free radicals are detoxified by endogenous free radical scavengers such as intracellular superoxide dismaltase catalase and glutathion peroxidase and substances such as ascorbic acid and tocopherol. Free elements such as selenium, zinc and copper are essential for the functioning of these scavenging enzymes. In a variety of pathological conditions, excessive production may exceed this scavenging capability and tissue injury occur. These injuries are often manifested by endothelial cell damage and increase capillary permeability as a result. Valproate has been reported to enhance the clearance of zinc, selenium and copper, in a 5 year old girl who presented with VPA associated pancreatitis. This caused low level of free radicals scavenger activity and high serum lipid peroxidase concentration.[41]

Valproate associated pancreatitis is a serious complication and awareness and high index of suspicion is needed for its early detection. The risk is higher in patients below 20 years, in the first year of therapy, in patients with encephalopathy, in the presence of chronic renal failure and patients taking AEDs polytherapy. Early management included appropriate investigation and drug withdrawal. The medicine should be avoided in patients who had VAP because the relapse rate is high.

References

1. Steinberg W. Acute pancreatitis. N Engl J Med 1994; 330: 1198-1210.
2. Wilmink T, Frick WK. Drug induced pancreatitis. Drug safety 1996; 14: 406-423.
3. Cappell MS, Mark M. Acute pancreatitis in HIV seropositive patients: a case control study in 44 patients. Am J Med 1995; 98: 243-8.

4. Karch FE, Lasagna L. Adverse drug reactions: a critical review. JAMA 1975; 234: 1236-41.
5. Thomson S, Hendry W, McFarlane F, Davidson A. Epidemiology and outcome of acute pancreatitis. Br J Surg 1987; 74: 398-401.
6. Bircher J. Criteria for diagnosis of adverse drug reactions. Ballieres Clin Gastroenterol 1988; 2: 259-61.
7. Maxson C, Greenfield S, Turner J. Acute pancreatitis as a common complication of 2', 3' -dideoxyinosine therapy in the acquired immunodeficiency syndrome. Am J Gastroenterol 1992; 87: 708-13.
8. Rubin R. Sulfasalazine-induced fulimant hepatic failure and necrotizing pancreatitis. Am J Gastroenterol 1994; 89: 789-91.
9. Izsak E, Shike M, Roulet M, Khursheed N, Jeejeebhoy. Pancreatitis in association with hypercalcemia in patients receiving total parental nutrition. Gastroenterology 1980; 79: 555-8.
10. DeWaele B, Smith J, Willems G. Recurrent pancreatitis secondary to hypercalemia following vitamin D poisoning. Pancreas 1989; 4: 378-80.
11. Davidoff F, Tishler S, Rosoff C. Marked hyperlipidmia and pancreatitis associated with oral contraceptive therapy. N Engl J Med 1973; 289: 552-5.
12. McCarthy A, Keystone J, Kain K. Pancreatitis occurring during therapy with stibogluconate: Two case reports. Clin Infect Dis 1993; 17: 952-3.
13. Camfield P, Bagnell P, Camfield C, Tibbles J. Pancreatitis due to valproic acid (Letter). Lancet 1979; 1: 1198.
14. Batalden P, Van Dyne B, Cloyd J. Pancreatitis associated with valproic acid therapy. Pediatrics 1979; 64: 520-2.
15. Sasaki M, Tonoda S, Aoki Y, Katsumi M. Pancreatitis due to valproic acid (Letter). Lancet 1980; 1: 1196.
16. Coulter D, Allen R. Pancreatitis associated with valproic acid therapy for epilepsy. Ann Neurol 1980; 7: 92.
17. Parker P, Helinek G, Ghishan F, Greene H. Recurrent pancreatitis induced by valproic acid. Gastroenterology 1981; 80: 826-8.
18. Murphy M, Lyon L, Taylor J. Valproic acid associated pancreatitis in an adult. Lancet 1981; 1: 42.
19. Ng J, Disney A, Jones T, Purdie G. Acute pancreatitis and sodium valproate. Med J Aust 1982; 21: 362.
20 Wylie E, Wylie R, Cruse R, Erenberg G, Rothner D. Pancreatitis associated with valproic acid therapy. Am J Dis Child 1984; 138: 912-4.
21. Williams L, Emery J. Pancreatitis during sodium valproate treatment. Arch Dis Child 1983; 58: 543-4.
22. Rosenberg H, Ortega W. Hemorrhagic pancreatitis in a young child following valproic acid therapy. Clin pediatr 1987; 26: 98-101.
23. Lott J, Bond L, Bobo R, McClung H, Murray R. Valproic acid-associated pancreatitis: Report of three cases and a brief review. Clin Chem 1990; 36: 395-7.
24. Binek J, Hany A, Heer M. Valproic acid induced pancreatitis. Case report and review of the literature. J Clin Gastroenterol 1991; 13: 690-3.
25. Asconape J, Penry J, Dreifuss F, Reila A, Mirza W. Valproate-associated pancreatitis. Epilepsia 1993; 34: 177-83.
26. Buckley DS, Prasad AN, Penney S. Valproic acid induced pancreatitis revised. Epilepsia 1999; 40 (Suppl 2): 181.
27. Grosse P, Rusch L, Schnitz B. Pancreatitis complicating treatment of status epilepticus with intravenous valproate: Three case reports. Epilepsia 1999; 40 (Suppl 1): 267.
28. Plaza MM, Goyanes GR, Cuina L, Alonso R. On the toxicity of valproic acid. Nephrology 1999; 51: 187-189.
29. Hamad A, Aymen H, Bessisso M, Sokrab TO, Mesraua B, Momeni S. Valproate associated acute pancreatitis. Neurosciences 1999; 4 (Suppl 5): 379-85.
30. Dreifuss FE, Santilli N, Lnager DH, Sweeny K, Moline B, Menander K. Valproic acid hepatic fatalities: a retrospective review: Neurology 1987; 37: 379-85.
31. Baskie AM. Case report: pancreatic pseudocyst associated with valproic acid therapy. J Med Soc NJ 1984; 81: 399-400.
32. Scheffner D, Konig ST, Rauterber-Rulan I, Kochen W, Hofmann WJ, Unkelback ST. Fatal liver failure in 16 children with valproate therapy. Epilepsia 1988; 29: 530-42.
33. Balthazar EJ. CT. Diagnosis and staging of acute pancreatitis. Radiol Clin North Am 1989; 27: 19-37.
34. Jimenez-Rodriguezvila M, Caro-Paton A, Conde M, et al. Side effects of sodium valproate, mainly related to its hepatic and pancreatic toxicity. Int J Clin Pharmacol Res 1986; 6: 217-24.
35. Isom JB. On the toxicity of valproic acid. Am J Dis of Children 1984; 138: 901-903.
36. Ford MD, Portman RJ, Lum GM. Pancreatitis in children on chronic dialysis treated with valproic acid. Pediatric Nephrol 1990; 4: 259-261.
37. Padilla B, Pollak VE, Pesce A, Kant K, Gilinsky N, Deddens J. Pancreatitis in patients with end-stage renal disease. Medicine 1994; 73: 8-20.
38. Soman M, Swenson C. A possible cause of carbamazepine - induced pancreatitis. Drug Intell Clin Pharm 1985; 19: 925-6.
39. Tsao C, Wright F. Acute chemical pancreatitis associated with carbamazepine intoxication. Epilepsia 1993; 34: 174-6.
40. Sanfey H, Bulkley GB, Cameron JL. The role of oxygen derived free radicals in the pathogenesis of acute pancreatitis. Ann Surg 1984; 200: 405-13.
41. Pippenger CE, Xianzhong Meng, Van Lente F, Rothner A. Valproate therapy depresses free radical scavenging enzyme activity: a probable mechanism for induction of acute pancreatitis or hepatotoxicity. Neurology 1989; 39 (Suppl 1): 214.