Stavudine-induced pancreatitis followed by lopinavir-ritonavir-induced pancreatitis

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Acute pancreatitis is a potentially life-threatening condition and is known to occur with antiretroviral drugs, particularly stavudine, didanosine, lamivudine and lopinavir-ritonavir fixed dose combination (FDC).[1] We report here a case of Stavudine-induced pancreatitis followed by lopinavir-ritonavir-induced pancreatitis.

Case Report

A 50-year-old south Indian male weighing 50 kg was admitted to the hospital with fever, loose stools, cough, breathlessness and upper abdomen tenderness over the preceding week. Three years back he was diagnosed to have human immunodeficiency virus (HIV) infection with pulmonary tuberculosis. Following the completion of tuberculosis treatment for six months, he was initiated on antiretroviral treatment with zidovudine 300 mg BD, lamivudine 150 mg BD and nevirapine 200 mg BD. At the time of initiating the antiretroviral treatment, his CD4 + count was 289 cells/mm^3. After 18 months, his antiretroviral therapy was changed to nevirapine 200 mg BD, lamivudine 150 mg BD and stavudine 30 mg BD as he had anemia suspected to be induced by zidovudine. He was also on prophylaxis for Prophylaxis, for *Pneumocystis carnii* pneumonia (PCP), with co-trimoxazole 80 mg OD for the past two years.

After six months of treatment with nevirapine, lamivudine and stavudine, he was hospitalized with complaints of nausea, vomiting, anorexia and pain in epigastric region. His serum amylase and lipase levels were 211 U/L (normal reference range - up to 100 U/L) and 1267 U/L (normal reference range - 114 to 286 U/L) respectively. He was diagnosed to have pancreatitis. Stavudine was suspected as the causative drug and was withdrawn. He was treated symptomatically and was discharged after seven days of hospitalization. At the time of discharge, serum amylase and lipase levels were 198 U/L and 1046 U/L respectively. After eight weeks of discharge from the hospital, amylase and lipase levels decreased to 142 U/L and 461 U/L respectively.

After 19 weeks of discharge from the hospital, considering his CD4 + count (23 cells/mm^3), antiretroviral treatment was initiated with emetricitabine 200 mg OD, tenofovir 300 mg OD and the recently approved[2] (in India) additional strength of the FDC of lopinavir-ritonavir (200 mg + 50 mg) BD. He was on this antiretroviral treatment for three weeks before the present hospital admission. During his present hospital admission, his serum amylase and lipase levels were 194 U/L and 951 U/L respectively. On the fourth day of admission, amylase and lipase levels increased to 214 U/L and 1018 U/L; lopinavir-ritonavir FDC was suspected as the causative drug for the recurrence of pancreatitis and was discontinued. During his present hospitalization he was treated with fluid resuscitation, azithromycin 500 mg OD, pantoprazole 40 mg OD, salbutamol and ipratropium bromide nebulization Q4H, co-trimoxazole 800mg in three divided doses, activated dimethicone + pancreatin (80 mg + 170 mg) TID, cefaperazone 1g BD and Cefaperazone + Sulbactum 2 g BD as per the blood culture sensitivity and for the management of PCP and pancreatitis. He died on the sixth day of hospitalization.

Discussion

The available data suggests pancreatitis due to 2 anti retroviral drugs. The demographics, personal history and medical history did not suggest any underlying pancreatic disease. The time sequence of the start of the drugs (stavudine and lopinavir-ritonavir) and onset of the disease is consistent with the diagnosis. Although no rechallenge was attempted, improvement of amylase and lipase levels suggests an association of the pancreatitis with the use of stavudine. Clear regression of the amylase and lipase levels after the discontinuation of stavudine despite persistent use of other drugs (nevirapine, lamivudine and co-trimoxazole) makes association with the other drugs unlikely.

We could not determine any decrease in serum amylase and lipase levels after the discontinuation of lopinavir-ritonavir. However, in this patient, the recurrence of pancreatitis signifies the involvement of lopinavir and ritonavir as pancreatitis is reported to recur with use of lopinavir-ritonavir in patients with previous history of pancreatitis.[1] There were no other causes and contributing factors (like alcohol ingestion, gall

stones, vasculitis, trauma, pancreas divisum, mumps infection, hereditary, renal failure, severe hypothermia and organ transplantation) for the pancreatitis other than the antiretroviral therapy. Hypertriglyceredemia has also been observed in patients with lopinavir-ritonavir-induced pancreatitis; in this case the serum triglyceride levels were not determined. A search of Medline found no pancreatitis being reported with lopinavir-ritonavir combination in the same patients who had a history of stavudine-induced pancreatitis.

Severe hypoxia and PCP pneumonia were the immediate cause of death with HIV as an antecedent cause. Factors that adversely affect the survival in acute pancreatitis such as hypoxemia (P_{o2} < 60 mmHg) and hypoalbuminemia (albumin levels < 3.2 g/dL) were present and hence antiretroviral therapy-induced pancreatitis was considered as the significant condition contributing to death. Causality and severity of the reactions are indicated in Table 1.

Approximately 2-5% cases of acute pancreatitis are drug-related. The number of drugs that have been associated with acute pancreatitis exceeds 260.[6] Drugs cause pancreatitis either by hypersensitivity reaction or by generation of toxic metabolite, in some cases it is not clear which of these mechanisms is operative. The mortality rate in acute pancreatitis is 10-15%. About 80% of all acute pancreatitis cases are usually mild and 20% are severe. The mortality rate in mild cases is about 5% while in severe cases it is about 98%. High incidence of infections (with cytomegalovirus, cryptosporidium and mycobacterium avium complex) and frequent use of medications (such as didanosine, pentamidine and co-trimoxazole) have increased the incidence of acute pancreatitis in patients with AIDS.[7,8]

Medical management of acute severe pancreatitis involves discontinuation of the offending drug and fluid resuscitation in excess of 5 to 6 L each day to maintain adequate intravascular volume. Respiratory care should be provided by obtaining oxygen saturation continuously by using pulse oximeter and oxygen should be provided if saturation falls below 90%. It is reasonable to use colloid in the form of albumin to maintain the patency of microcirculation of the pancreas. If hematocrit falls below 25%, packed red cells should be administered. If hypotension persists despite appropriate fluid resuscitation, dopamine may be of help in maintaining adequate systolic blood pressure. Severe hypotension and circulating enzymes may cause tubular necrosis which requires peritoneal dialysis or hemodialysis.[6,9]

Meperidine is the most commonly used analgesic. Narcotics such as morphine or hydromorphone are preferable to meperidine if large quantities of intravenous narcotics are required. Although morphine can cause spasm of sphincter of oddi and raise the serum amylase concentration, many patients with acute pancreatitis can be treated without untoward effects. Transient hyperglycemia has to be treated cautiously using insulin with widely spaced intervals. Hypocalcemia caused due to reduction in non-ionized calcium requires no specific therapy. If reduction in serum-ionized calcium is present and is coexisting with hypomagnesemia, replacement of magnesium should alone restore the calcium levels to normal. If hypomagnesemia is not coexisting, intravenous calcium gluconate should be administered. Patients may not be able to receive oral nourishment for three to six weeks and should receive nutritional support to preserve mucosal function and limit the stimulus to the inflammatory response. Enteral feeding seems to be safer than parenteral feeding, with fewer septic complications. The majority of studies have reported enteral feeding via a nasojejunal tube. The use of enteral feeding may be limited by the ileus. If this persists for more than five days, parenteral nutrition will be required.[9,10]

There is no proven therapy for the treatment of acute pancreatitis. Despite initial encouraging results, antiproteases such as gabexate, antisecretory agents such as octreotide and anti-inflammatory agents such as lexipafant have all proved disappointing in large randomized studies. The evidence to enable a recommendation about antibiotic prophylaxis against infection of pancreatic necrosis is conflicting and difficult to interpret. Some trials show benefit, while others do not. Imipenem, imipenem/cilastatin, cefuroxime, ofloxacin + metronidazole and ciprofloxacin + metronidazole have been tried with some degree of success. If antibiotic prophylaxis is used, it should be given for a maximum of 14 days. All patients with severe acute pancreatitis should be managed in a high dependency unit or intensive therapy unit with full monitoring and systems support. There is controversy regarding the roles of radiological drainage and surgical necrosectomy in the management of infected pancreatic and peripancreatic necrosis. Standard surgical practice is that all patients with infected necrosis should undergo necrosectomy. The choice of surgical technique for necrosectomy and subsequent postoperative management depends on individual features and locally available expertise.[10]

Conclusion

Our opinion is that pancreatitis can recur when fixed combination of lopinavir and ritonavir is used in patients with a history of stavudine-induced pancreatitis. Further research is required to determine if there exists a cross-sensitivity between

Table 1: Causality and severity of the adverse drug reactions

Reaction	Causality		Severity[5]
	WHO scale[3]	Naranjo's algorithm[4]	
Stavudine-induced pancreatitis	Probable	Probable	Level 4(B) (ADR was the reason for admission)
Lopinavir-Ritonavir-induced pancreatitis	Possible	Probable	Level 7 (ADR either directly or indirectly led to the death of the patient)

stavudine and lopinavir-ritonavir with respect to pancreatitis.

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