SAJS
Gastro-intestinal

The early management of pancreatitis associated with hypertriglyceridaemia

F. ANDERSON, M.MED., F.C.S. (S.A.)
S. Z. MBATHA, M.B. CH.B
S. R. THOMSON, CH.M., F.R.C.S.
Department of Surgery, Addington Hospital and Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban

Abstract

Introduction. In triglyceridaemia-associated pancreatitis, decreasing the serum triglyceride level below 5.65 mmol/l alleviates abdominal pain and is purported to improve outcome. We analysed hypertriglyceride level normalisation and outcome in a patient cohort of acute pancreatitis.

Patients and methods. Patients presenting with pancreatitis and hypertriglyceridaemia were assessed. All patients with presenting triglycerides levels >10 mmol/l were assessed for resolution to a level below 5.65 mmol/l at days 3 and 5. Patients with triglyceride levels in excess of 10 mmol/l were treated with either standard supportive therapy or an insulin dextrose infusion.

Results. In the period June 2001 to April 2008, there were 503 admissions of 439 patients with a diagnosis of acute pancreatitis; 26 (6%) had hypertriglyceridaemia >10 mmol/l at admission. Standard therapy was used in all patients; in 6 patients, it was the sole therapy. A dextrose and insulin infusion was used in 20 cases. On day 3, 7 (32%) of the measured triglyceride levels had fallen below 5.65 mmol/l and, on day 5, all but 4 (83%) were <5.65 mmol/l. Three patients died.

Conclusion. Standard therapy was equivalent to the use of dextrose and insulin in the resolution of hypertriglyceridaemia. Our methods to reduce triglyceride levels produce morbidity and mortality rates similar to those attained when alternate lipid-lowering strategies are employed.

Initial restriction of oral intake, fluid resuscitation, analgesia and organ support are standard therapy in acute pancreatitis. When associated with hypertriglyceridaemia, the management of acute pancreatitis poses unique problems. Decreasing the serum triglyceride level below 5.65 mmol/l alleviates the abdominal pain.[1] Triglyceride levels fall quickly with supportive care and are usually below this level at 72 hrs.[1,2] Insulin, heparin and plasmapheresis have also been found to be effective in this regard.[3-5] Whether these additional measures are necessary, and which is more appropriate in not only reducing the triglyceride levels but also improving outcomes, is unclear. We describe our experience in this category of patients.

Patients and methods

Data were accrued prospectively on all admissions with a clinical diagnosis of acute pancreatitis admitted to a regional hospital. An amylase level more than twice the upper limit of normal range (25 - 125 U/l) was considered confirmatory.[5] In addition to routine aetiological assessment, triglycerides (TGs) levels were routinely assessed in all patients within 48 hours of admission. These were graded as mild (1.5 - 5 mmol/l), moderate(5 - 15 mmol/l) and severe(>15 mmol/l). All patients with TG levels >10 mmol/l at presentation were assessed for resolution to a level <5.65 mmol/l at days 3 and 5. Body mass index (BMI) was calculated. Disease severity was assessed by the Glasgow criteria.[6] Complications and mortality were noted.

Management of pancreatitis

Patients were managed initially by restricting oral intake and administering intravenous fluids and analgesia. Patients with predicted severe disease had a CT scan to assess for the presence of pancreatic necrosis. Six patients were managed with standard therapy of intravenous fluids, nil by mouth and supportive care alone. The mean glucose level was 8 mmol/l (5.8 - 9.4 mmol/l) in this group. In 20 patients with a mean glucose level of 16 mmol/l (9.8 - 27.9), 1:1 dextrose and insulin solution titrated to the glucose level was added to the treatment.

TABLE I. CHARACTERISTICS AND AETIOLOGY OF THE TOTAL COHORT

Age (range)	**39 (13 - 75) years**
Overall male:female ratio	**M:F 348 (69%):155 (31%)**
Aetiology	
Alcohol	**324 (64%)**
Gallstones	**57 (14%)**
Alcohol gallstones	**12 (3%)**
Primary dyslipidaemia	**29 (5%)**
HIV	**51 (10%)**
Other	**4 (1%)**
Idiopathic	**26 (5%)**
Mortality	**34 (7%)**
Early <1week	**22**
Late >1week	**12**

Results

In the period June 2001 - April 2008, there were 503 admissions of 439 patients with a diagnosis of acute pancreatitis (Table I). Lipids were assessed in 458 (91%) of the admissions within 48 hours. There were varying levels of hypertriglyceridaemia in 93 (18%). Twenty-six (6%) had TG levels >10 mmol/l at admission. Three patients had a BMI ≥30. Of the 26 patients with severe hypertriglyceridaemia, 11 were associated with excessive alcohol ingestion, and 13 had diabetes. In 2, the abnormality was a primary defect. Computed tomographic (CT) scan assessment was performed on 17 occasions, and 5 had evidence of pancreatic necrosis. The Glasgow score predicted severe disease in 8 cases.

Standard therapy was used in all patients with TG levels >10 mmol/l; in 6 patients it was the sole therapy. The decline in triglycerides at 3 and 5 days was similar with both standard and insulin therapy (Table II). Three patients with severe hypertriglyceridaemia (>10 mmol/l) died. Two patients with a fulminant course died within 24 hours, and 1 patient whose triglycerides failed to resolve below 5.65 mmol/l at day 5 died 13 days after admission (Table II). The majority of deaths were in patients with mild hypertriglyceridaemia at the time of admission (Table III).

Discussion

There are reports suggesting that patients with severe hypertriglyceridaemia have a more severe course of acute pancreatitis.[8,9] Linares *et al.* found that 20% of patients referred with severe hypertriglyceridaemia had acute pancreatitis that was severe in 71% of this group.[8] Contrary to this finding, mortalities in a cohort of pancreatitis associated with hypertriglyceridaemia were not dependent on the severity of the hypertriglyceridaemia, with most mortalities associated with mild hypertriglyceridaemia.[10]

The appropriate methods employed for reducing triglyceride levels and improving outcomes is controversial. Measures beyond standard therapy are considered unnecessary by some authors.[11,12] Dunne *et al.* reported on a rapid decline in

TABLE II. MANAGEMENT AND OUTCOME OF SEVERE HYPERTRIGLYCERIDAEMIA

Therapy	*N*	Average mmol/l (range)	Day 3 No. <5.65 (%)	Day 5 No. <5.65 (%)	Mortality
Standard	**6**	**31.6 (12.6 - 66.7)**	**2 (33%)**	**4(66%)**	**0**
Insulin	**20**	**46.6 (10.2 - 108.75)**	**5 (26%)**	**15 (79%)**	**3 (15%)**

TABLE III. OUTCOMES IN RELATIONSHIP TO DEGREE OF DYSLIPIDAEMIA

	Hypercholesterolaemia			Mixed	Hypertriglyceridaemia	
	Severe	Moderate	Mild	Hyperlipidaemia	Moderate	Severe
Number	**7**	**11**	**15**	**58**	**21**	**26**
Morbidity	**1**	**3**	**2**	**5**	**1**	**2**
Mortality	**0**	**0**	**0**	**10**	**3**	**3**

TABLE IV. REPORTED SERIES OF HYPERTRIGLYCERIDAEMIA-LOWERING THERAPY IN ACUTE PANCREATITIS

Author	*N*	Per cent severe	Therapy	Triglyceride range mmol/l			Mortality rate
				Day 1	**Day 3**	**Day4/5**	
Yeh J	**17**	**NS**	**PE**	**16.9 - 44.1**	**67% ↓**	**83% ↓**	**2 (12%)**
Berger	**5**	**80**	**HI**	**17.6 - 98.2**	**<5.65**	**NS**	**0**
Henzen	**5**	**80**	**HI**	**14.7 - 80.4**	**<10**	**NS**	**0**
Kyriakidis	**10**	**100**	**PH**	**11 - 26**	**NS**	**NS**	**1 (10%)**
This series	**26**	**31**	**Standard (6)**	**16.9 - 121**	**89% ↓**	**89% ↓**	**0**
			Insulin (20)	**19.7 - 120**	**76% ↓**	**81% ↓**	**3**

HI = heparin insulin; NS = not stated; PE = plasma exchange; PH = plasmapheresis.

triglycerides from a level of 138 mmol/l to near normal by 4 days with fluid administration only.[12] In a series of 40 patients with hypertriglyceridaemia at admission, the triglyceride values were found to resolve spontaneously to below 5.65 mmol/l over 4 - 7 days with standard therapy.[11] Occasionally, resolution was slower.[11] Ho and Yeo in a case report showed resolution in 1 day with fasting in a case of severe pancreatitis.[13] In this series, 2 out of 6 patients receiving nil by mouth and fluid resuscitation (standard therapy) had not resolved by day 5. None died.

Low-dose heparin infusion(10 000 IU/24 hours) and insulin infusion have also been shown to be effective in lowering triglyceride levels in case reports with favourable outcomes.[4,7,14-17] Beger *et al*. described 5 cases treated with heparin and insulin, with pancreatic necrosis demonstrated in 4 cases. No treatment-related complications were observed.[18] We are reluctant to use heparin in patients with pancreatic necrosis because of the theoretical risk of haemorrhage into the pancreas. In this series, 20 cases received insulin. Triglycerides did not resolve in 3 patients by day 5.

Mortality in this series was not associated with failure to resolve to below 5.65 mmol/l at 5 days(1 of 4 patients). Failure for resolution to below 5.65 mmol/l was not associated with a particular therapy.

A number of case reports have shown that plasmapheresis is effective in reducing triglyceride levels.[9,19,20] This entails replacing plasma with donor plasma lacking in triglycerides. Yeh *et al*. found plasmapheresis to be effective in reducing triglycerides in 17 patients. Complications developed in 2 (12%), and 2 patients died. Complications related to the plasmapheresis were observed in 5 (29%) of their patients;[20] these were hypotension, bleeding and anaphylaxis.

Chen *et al*. found that plasma exchange, although effective in reducing triglycerides over 2 hours, did not alter the rate of complications or the mortality when comparing historical controls or patients with predicted severe disease.[21] However, therapy was commenced 2 - 6 days after onset of symptoms. Kyriakidis described 10 patients with severe pancreatitis. Nine were treated with plasmapheresis, which was effective in lowering the lipids. The mortality was 10%.[15]

Plasmapheresis is not available in our institution, and whether it would be more effective in reducing triglyceride levels in fulminant pancreatitis is unclear. Our results depicting decline in triglycerides over 3 - 5 days compares favourably with the use of plasmapheresis by Yeh *et al*. (Table IV).

In this series, 3 (12.5%) developed complications – 2 pseudocysts and 1 pancreatic abscess. Three (12.5%) of the patients died within 2 weeks of presentation – 2 associated with alcohol consumption and 1 with primary hypertriglyceridaemia. These results compare with the overall 8% mortality rate of all cases of acute pancreatitis in the same period. The majority of mortalities were in patients with mild hypertriglyceridaemia.

Conclusion

The majority of the severe cases of hypertriglyceridaemia had reduced to <5.65 mmol/l at 5 days. Standard therapy was equivalent to the use of dextrose and insulin. Our morbidity and mortality were similar to the levels quoted when plasmapheresis or other TG-lowering strategies were used in other centres. A controlled randomised study will be required to assess differences between alternate therapies commenced on admission in terms of speed of resolution and its affect on outcome.

REFERENCES

1. Toskes PP. Hyperlipidaemic Pancreatitis. Gastroenterol Clin North Am 1990;19:783-791.
2. Yuan G, Al-SHali KZ, Hegele RA. Hypertriglyceridaemia: its etiology, effects and treatment. CMAJ 2007;176(8):1113-1120.
3. Kyriakidis AV, Raitsiou B, Sakagianni A, et al. Management of acute severe hyperlipidemic pancreatitis. Digestion 2006;73:259-264.
4. O'Donoghue DJ. Acute pancreatitis due to nadolol-induced hypertriglyceridaemia. Br J Clin Pract 1989;43(2):74-75.
5. Steinberg WM, Goldstein SS, Davis ND, et al. Diagnostic assays in acute pancreatitis. A study of sensitivity and specificity. Ann Intern Med 1985;102:576-580.
6. Blamey SL, Imrie CW, O'Neill J, Gilmour WH, Carter DC. Prognostic factors in acute pancreatitis. Gut 1984;25:1340-1346.
7. Yavasoglu I, Kadikoylu G, Bola man Z. Treating hypertriglyceridaemia. CMAJ 2007;177(6):603.
8. Linares CL, Pelletier AL, Czernichow S, et al. Acute pancreatitis in a cohort of 129 patients referred for severe hypertriglyceridemia. Pancreas 2008;37(1):13-22.
9. Li-Hui Deng, Ping Xue, Qing Xia, et al. Effect of admission hypertriglyceridaemia on the episodes of severe acute pancreatitis. World J Gastroenterol 2008;14(28):4558-4561.
10. Anderson F, Thomson SR, Clarke DL, et al. Dyslipidaemic pancreattitis clinical assessment and analysis of disease severity and outcomes. Pancreatology 2009;9(3):252-273.
11. Fortson MR, Sandra MD, Freedman N, Webster PD. Clinical assessment of hyperlipidaemic pancreatitis. Am J Gastroenterol 1995;90:2134-2139.
12. Dunne MJ, Shenkin A, Imrie CW. Misleading hyponatraemia in acute pancreatitis with hyperlipaemia. Lancet 1979;1:211.
13. Ho KM, Yeo J. Plasmapheresis in the management of pancreatitis related to hypertriglyceridaemia. Anaesth Intensive Care 1999;27(1):117.
14. Monga A, Arora A, Makkar RPS, Gupta AK. Hypertriglyceridaemia-induced acute pancreatitis- treatment with heparin and insulin. Indian J Gastroenterol 2003;22:102-103.
15. Alagozlu, Cindoruk M, Karakan T, Unal S. Heparin and insulin in the treatment of hypertriglyceridaemia-induced severe acute pancreatitis. Dig Dis Sci 2006;51:931-933.
16. Chee-Chuen Loo, Jackie YL Tan. Decreasing the plasma triglyceride level in hypertriglyceridemia-induced pancreatitis in pregnancy: A case report. Am J Obstet Gynecol 2002;187:241-242.
17. Jain P, Rai RR, Udawat H, et al. Insulin and heparin in treatment of hypertriglyceridemia-inducedpancreatitis. World J Gastroenterol 2007;13(18):2642-2643.
18. Berger Z, Quera R, Poniachik J, et al. Heparin and insulin treatment of acute pancreatitis caused by hypertriglyceridemai. Experience of 5 cases Rev Med Chil 2001;129(12):1373-1378.
19. Routy J, Smith GHR, Blank DW, Gilfix BM. Plasmapheresis in the treatment of an acute pancreatitis due to protease inhibitor-induced hypertriglyceridemia. J Clin Apheresis 2000;16:157-159.
20. Yeh J, Chen J, Chiu H. Plasmapheresis for hyperlipidemic pancreatitis. J Clin Apheresis 2003;18:181-185.
21. Jui-Hao Chen, Jiann-Horng Yeh, Hsiin-Wen Lai, Chao-Sheng Liao. Therapeutic plasma exchange in patients with hyperlipidaemic pamncreatitis. World J Gastroentrol 2004;10(15):2272-2274.
22. Ford P, Breheny F, Jenkins I. Plasmapheresis in the management of pancreatitis related to hypertriglyceridaemia. Anaesth Intensive Care 1998;26(5):598.