BRIEF REPORT

Pentoxifylline Treatment in Severe Acute Pancreatitis: A Pilot, Double-Blind, Placebo-Controlled, Randomized Trial

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In acute pancreatitis (AP) tumor necrosis factor-α mediates multi-organ failure; in animal models its blockade with pentoxifylline ameliorates AP. The efficacy of pentoxifylline in predicted severe AP (pSAP) was tested in a double-blinded, randomized, control trial. Twenty-eight patients with pSAP were randomized within 72 hours of symptom onset to pentoxifylline or placebo. Baseline characteristics were similar in both groups. The pentoxifylline group had fewer intensive care unit admissions and shorter intensive care unit and hospital stays of longer than 4 days (all $P < .05$). Patients receiving pentoxifylline had no adverse effects. Pentoxifylline within 72 hours of pSAP is safe; a larger study of pentoxifylline in AP is needed to confirm efficacy. ClinicalTrials.gov number: NCT01292005.

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Despite the high morbidity and mortality associated with severe acute pancreatitis (SAP), there is no specific drug to treat acute pancreatitis (AP). Tumor necrosis factor-α (TNF-α) plays a central role in the pathogenesis of SAP including[1] pancreatic and peripancreatic necrosis, systemic inflammatory response syndrome, and persistent organ failure. Pentoxifylline, a nonselective phosphodiesterase inhibitor, has well-established clinical efficacy and safety in other TNF-α–mediated diseases, notably acute alcoholic hepatitis.[2] In experimental models of AP, pentoxifylline reduced the severity of the disease.[3–8] However, human data regarding its efficacy in AP are limited.[9–11]

By using multiple institutional resources, we have developed mechanisms to identify AP patients within 24 hours of admission to the hospital. We conducted a double-blinded, allocation-concealed, placebo-controlled, pilot trial of oral pentoxifylline vs placebo in patients with predicted SAP (pSAP). The study was approved by the Mayo Clinic's Institutional Review Board. From 2009 to 2012 a total of 717 AP patients were identified and 226 showed at least one of the predictors of SAP (Supplementary Materials and Methods section and Supplementary Figure 1). A total of 102 of 132 patients approached to discuss the study declined to participate; 74 provided no reason, 20 were fearful of drug interactions or side effects, and 8 reported feeling better. Twenty-eight patients were allocated randomly to either the pentoxifylline or control group. Pentoxifylline 400 mg or placebo tablets were administered by mouth at enrollment and 3 times a day for 72 hours thereafter. None of the patients had any difficulty with oral intake of tablets. All other treatments for SAP (fluid resuscitation, antibiotics, pain control, and so forth) were implemented according to the standard of care. All authors had access to the study data and reviewed and approved the final manuscript.

On admission, the 2 groups were similar with regard to age, sex, body mass index, Acute Physiology and Chronic Health Evaluation, systemic inflammatory response syndrome score, and pancreatic necrosis or organ failure or baseline TNF-α, interleukin-6 (IL6), and C-reactive protein (CRP) levels (Supplementary Table 1). The median length of hospitalization was 3 days (range, 1–5 days) in the pentoxifylline group and 5 days (range, 1–30 days) in the control group ($P = .06$) (Table 1). Prolonged hospital stay (>4 days) was significantly less frequent in the pentoxifylline group ($P = .046$). No patient in the pentoxifylline group but 4 patients in the placebo group required intensive care unit (ICU) transfer: 3 patients owing to respiratory failure and 1 patient owing to severe hypophosphatemia and hypocalcaemia. The median length of ICU stay was 0 days, and the maximum stay was 13 days in the control group. Although no patient in the pentoxifylline group developed new necrosis or organ failure after receiving the drug, 2 patients in the placebo group developed pancreatic necrosis and 3 patients developed organ failure during hospitalization. Changes of serum levels of TNF-α, IL6, IL8, and CRP from days 0 to 1 and from days 0 to 3 of enrollment showed no difference between the 2 groups. There were no deaths in either of the groups. One patient was re-admitted twice within 1 year in placebo group and no patient was re-admitted in the pentoxifylline group.

We report a single-institution, randomized, placebo-controlled drug trial to determine the safety and efficacy of pentoxifylline in patients with pSAP. We found that pentoxifylline was well tolerated and patients receiving

Abbreviations used in this paper: AP, acute pancreatitis; CRP, C-reactive protein; ICU, intensive care unit; IL, interleukin; pSAP, predicted severe acute pancreatitis; SAP, severe acute pancreatitis; TNF-α, tumor necrosis factor α.

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Table 1. Clinical and Laboratory Outcomes of Patients in the Pentoxifylline and Placebo Groups

	Pentoxifylline (N = 14)	Placebo (N = 14)	*P* value
Length of hospitalization, days	3 (1–5)	5 (1–30)	.06
Length of hospitalization >4 days, n (%)	2 (14)	8 (57)	.046
Length of ICU stay, days	0 (0–0)	0 (0–13)	.03
Need for ICU, n (%)	0 (0)	4 (28)	.098
New-onset necrosis during hospitalization, n (%)[a]	0 (0)	2 (20)	.18
New-onset organ failure during hospitalization, n (%)	0 (0)	3 (21)	.22
Change in SIRS score from baseline to day 3	0 (-2 to 1)	0 (-2 to 2)	.96
Change in APACHE II baseline to day 3	-1 (-7 to 5)	0 (-1 to 5)	.08
Death	0	0	
Laboratory outcomes			
Inflammatory markers[b] (change day 0 to 1)			
TNF-α, *pg/mL*	0 (-1.2 to 0.5)	-0.1 (-0.9 to 49.2)	.74
IL6, *pg/mL4*	2 (-37 to 25)	0.9 (-62 to 152)	.58
IL8, *pg/mL*	-3 (-7.2 to 30.8)	-2.1 (38.2–49.2)	.90
CRP, *mg/L*	48.4 (-37.1 to 207.3)	60.6 (-71 to 283.2)	.62
Inflammatory markers[‡] (change day 0 to 3)			
TNF-α, *pg/mL*	0 (-1 to 0.5)	0 (-3.5 to 17.2)	.98
IL6, *pg/mL*	1.75 (-61 to 18)	0.95 (-340 to 65.8)	.45
IL8, *pg/mL*	-1.7 (-10.3 to 6.4)	-2 (-43.6 to 18.2)	.60
CRP, *mg/L*	30.7 (-157.4 to 255.3)	122.2 (-170 to 394.4)	.30

NOTE. Data are presented as median (range) unless otherwise indicated.
APACHE, Acute Physiology and Chronic Health Evaluation; SIRS, systemic inflammatory response syndrome.
[a]Patients with necrosis on admission were excluded for the analysis of necrosis after admission.
[b]Normal value range for TNF-α, 0–22 pg/mL; IL6, 0–5 pg/mL; IL8, 0–5 pg/mL; and CRP, 0–10 mg/L.

pentoxifylline showed improvements in outcomes of morbidity, as measured by the need for a hospital stay longer than 4 days and a reduced need for ICU transfer. However, there were no significant differences in the levels of inflammatory markers, including circulating TNF-α levels, between the 2 groups. Differences in levels of TNF-α, IL6, IL8, and CRP may be significant if the sample size is larger. Pentoxifylline has been proposed to reduce the systemic inflammation by reducing TNF-α, IL6, and CRP levels[12]; therefore, the exact mechanism of benefit of pentoxifylline in pSAP remains unclear. In an alcoholic hepatitis study, pentoxifylline did not decrease the TNF-α levels despite improvement in short-term survival and the investigators postulated the benefit was the result of improvement in microcirculation.[2] It also may blunt the deleterious vascular factors similar to angiopoietin-2,[13] and reduce the complications that correlate with severity.

Our study was limited by its small sample size. Also, drug administration earlier than 72 hours after diagnosis may be preferable because experimental models have suggested that giving the drug within a few hours of disease onset is effective. Pancreatic TNF-α production peaks at 24–36 hours and, hence, prophylactic administration of pentoxifylline has been shown to be useful in experimental animals but a randomized controlled trial to prevent post–endoscopic retrograde cholangiopancreatography pancreatitis failed to show benefit.[10] Another experimental study showed that delaying treatment until "AP is manifest" is more protective than prophylactic use.[14] Initiating drug therapy within a few hours is challenging although a 24-hour cut-off time may be feasible in appropriate settings. Despite these limitations, we showed that a single-institution drug trial for AP is feasible and that pentoxifylline is safe, cheap, and might have efficacy. This sets the stage for a larger trial of this drug in all patients with AP, to realize the goal of finding an effective drug that can be given within 24 hours of diagnosis in any setting.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.04.019.

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