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How does pentoxifylline affect survival of patients with alcoholic hepatitis?

Evidence-based answer

Pentoxifylline improves short-term survival in patients admitted to the hospital with severe alcoholic hepatitis (strength of recommendation [SOR]: **B**, a single published randomized controlled

trial [RCT]). Pentoxifylline does not improve survival when it is substituted for steroids in hospitalized patients who aren't responding to steroids (SOR: **C**, case series).

Evidence summary

Patients with severe acute alcoholic hepatitis have elevated levels of serum tumor necrosis factor (TNF), suggesting that TNF release may play a role in liver inflammation.¹ Because pentoxifylline inhibits TNF synthesis, it has been evaluated as a potential therapy for alcoholic hepatitis.

Decreases in mortality and hepatorenal syndrome

In a hospital-based clinical trial, 101 patients admitted with severe alcoholic hepatitis (mean age 42 years, 74% men) were randomized to oral pentoxifylline 400 mg twice a day or placebo (vitamin B₁₂ tablets) for 4 weeks.¹ The main outcome measures were short-term survival and progression to hepatorenal syndrome. Severe alcoholic hepatitis was defined as a Maddrey discriminant factor (DF) >32, jaundice, and at least one of the following: tender hepatomegaly, fever, leukocytosis, hepatic encephalopathy, or hepatic systolic bruit. The DF is calculated as follows: $4.6 \times$ [prothrombin

time in seconds – control time] + bilirubin (mg/dL). Medical management was “individualized according to each patient’s condition.”

Pentoxifylline therapy was associated with decreased mortality during the index hospitalization (relative risk [RR]=0.59; 95% confidence interval [CI], 0.35-0.97; number needed to treat [NNT]=5). Hepatorenal syndrome also decreased (RR=0.29; 95% CI, 0.13-0.65; NNT=4). Patients in the pentoxifylline group tended to have more headaches and gastrointestinal side effects, but no other serious health hazards were observed.

In a recently published abstract, 50 patients with severe alcoholic hepatitis (defined as DF >32) were enrolled in a randomized, double-blind, placebo-controlled trial of oral pentoxifylline, 400 mg twice a day or placebo for 4 weeks.² Short-term survival and changes in laboratory values (TNF, creatinine, and DF) were the primary outcome measures.

Survival was 76% in the pentoxifylline group compared with 60% in the

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Treatment with pentoxifylline improves short-term survival in patients with severe alcoholic hepatitis



placebo group (P not given). In the subgroup of patients who died, however, hepatorenal syndrome was the cause of death in 83% of the pentoxifylline group and 60% of the placebo group (P not given).

In a 1991 pilot study, also published only in abstract form, 22 patients admitted to the hospital with severe alcoholic hepatitis were randomized to receive oral pentoxifylline (1200 mg daily) or placebo for 10 days. Serum creatinine dropped 0.3 mg/dL in the treatment group and rose 2.1 mg/dL in the control group ($P < .05$). At 30 days, 3 patients in the control group had died compared with 1 in the treatment group ($P =$ not significant).³

It's not effective for patients who don't respond to steroids

A cohort study evaluated the effect of switching to pentoxifylline in hospitalized patients with severe alcoholic hepatitis who didn't respond to initial therapy with steroids. Researchers identified 121 patients who were treated initially with 40 mg oral prednisolone daily. The 36 patients who failed to show a drop in bilirubin levels within 7 days were switched to oral pentoxifylline, 400 mg twice a day.

In the pentoxifylline group, 69% of patients died within 2 months, 27.6% of whom had some form of renal insufficiency. This outcome wasn't statistically different from that of 58 matched historical controls with severe alcoholic hepatitis who were maintained on oral

prednisolone despite failure to respond within the first week of therapy (65% mortality, 20% with renal insufficiency).⁴

Recommendations

The American College of Gastroenterology doesn't recommend giving pentoxifylline to patients with severe alcoholic hepatitis, citing lack of evidence for improvement of patient-oriented outcomes.⁵ However, a group of French hepatologists consider pentoxifylline a reasonable alternative to corticosteroids for severe acute alcoholic hepatitis based on the studies cited here.⁶ ■

References

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