Intravenous Ancrod for Treatment of Acute Ischemic Stroke

Sherman DG, Atkinson RP, Chippendale T, Levin KA, Ng K, Futrell N, et al. Intravenous ancrod for treatment of acute ischemic stroke. The STAT study: a randomized controlled trial. JAMA 2000;283:2395–403.

Study Overview

Objective. To determine the efficacy of ancrod, a pit viper venom derivative that induces rapid defibrinogenation but not thrombolysis, in the treatment of acute ischemic stroke.

Design. Multicenter, double-blind, block-randomized, placebo-controlled trial.

Setting and participants. 500 patients from 45 U.S. and 3 Canadian centers (primarily community hospitals) with acute or progressing nonhemorrhagic ischemic stroke were enrolled between August 1993 and January 1998. Patients were included if they were 18 years or older, had moderate or severe symptoms, and had controlled blood pressure. Those with prior strokes that would not interfere with functional status assessment were also included. Older adults primarily comprised the study cohort (mean age, 72.8 years).

Intervention. Participants were randomly assigned to receive a 3-day infusion of ancrod followed by 1-hour infusions at 96 and 120 hours ($n = 248$) or placebo ($n = 252$). Baseline characteristics between groups were statistically equivalent. The ancrod therapy was titrated to decrease fibrinogen to a goal level of 1.18 to 2.03 μmol/L. Importantly, treatment was to begin within 3 hours of stroke onset. The treatment window was extended to 3.5 hours for 70 patients and to greater than 3.5 hours for an additional 12 patients. Upper time limit was not specified.

Main outcome measures. Functional status was assessed by the Barthel Index (BI), which evaluates activities of daily living (0 = worst, 100 = best), and the Scandinavian Stroke Scale (SSS), which evaluates motor and speech (0 = worst, 46 = best). The gait component was excluded from the SSS score. These measures were taken every day for the first week and at 3 months. Favorable functional status (FFS) was defined as a BI score of 95 to 100 or a return to prestroke status.

Computed tomography (CT) scan of the head was performed at presentation and at 7 days to assess for intracranial hemorrhage (ICH). Laboratory data intervals were not specified. Causes of death were determined, although data sources (registries, ICD-9 coding, chart review, or investigator report) were not specified. Intention-to-treat analysis was predominantly used. Severity adjustment influenced raw outcomes by only a few percentage points.

Main results. At 3 months, severity-adjusted FFS was reached by 42.2% of ancrod-treated patients and 34.4% of placebo-treated patients ($P = 0.04$). Thus, the absolute risk reduction was 7.8% and the number needed to treat (NNT) to have 1 person reach FFS was 12.8. Regardless of time to treatment, more patients with ancrod achieved FFS. The worst post-treatment functional status (BI = 0 to 40) was seen in 11.8% of the ancrod group and 19.8% of the placebo group. However, those with the worst initial strokes also had the greatest mean improvement in BI. Speech and motor improvement was small (mean SSS change, 2.2) and not significant ($P = 0.07$).

At 3 months, mortality was similar between the ancrod and placebo groups (25.4% versus 23%). Symptomatic ICHs occurred in 5.2% of ancrod and 2.0% of placebo patients (odds ratio, 2.58; confidence interval, 0.95 to 8.21). As this closely approached statistical significance, the absolute risk increase was 3.2% and the number needed to harm (NNH) to cause 1 symptomatic ICH was 31.2. Increased time to treatment (2 to 3 hours, 3 to 3.5 hours, and 3.5 to 6 hours) was not associated with more symptomatic ICHs. Ancrod patients with therapeutic fibrinogen levels (< 3.82 μmol/L) showed a trend toward achieving favorable functional status (45.8% versus 34.6%, $P = 0.08$). Patients who were supratherapeutic (fibrinogen < 1.18 μmol/L) may have had more ICHs (4/30 versus 9/204), but the numbers were too small to compare. The 49 adverse events that resulted in trial discontinuation were not described. Similarly, adverse events other than ICH that occurred in participants who had completed the trial were not specified.

Conclusion

Treatment with ancrod results in improved functional status as measured by the BI but may result in more symptomatic ICH. No differences in mortality were seen at 3 months between ancrod and placebo patients. Increased time to treatment in this study was not associated with increased symptomatic ICH.

Commentary

Acute ischemic stroke results in high morbidity and mortality. Currently, tissue plasminogen activator (t-PA) is recommended for acute ischemic stroke within 3 hours of symptom onset, based on the National Institute of Neurological Disorders and Stroke (NINDS) study [1]. The NNT to achieve a BI of 95 to 100 in the NINDS study was 8.3 for t-PA, compared with 12.3 for ancrod as determined by Sherman et al. However, the NNH versus placebo was worse for t-PA at 19, compared with ancrod at 31. Additionally, the Second European-Australian Acute Stroke Study (ECASS II) showed that t-PA at 3 hours provided only a modest benefit that was not statistically significant on several scales [2], while the overall NNH (0 to 6 hours) was 19.6. In previous trials, t-PA administered past 3 hours resulted in no efficacy [3], while streptokinase was shown to cause increased ICH and death [4,5]. Intra-arterial urokinase has proven beneficial up to 6 hours after stroke onset in patients with middle cerebral artery occlusion by modified Rankin Index (the NNT for BI > 90 was 11 [$P = 0.24$]) but has an NNH for symptomatic ICH of 12 and requires a quickly activated interventional radiology laboratory [6].

Sherman et al's study indicates that ancrod may have a role in the future treatment of acute ischemic stroke. The fact that ancrod decreases fibrinogen levels but is not a thrombolytic may suggest that ancrod has a longer treatment window than t-PA. This might be especially significant given recent studies showing that protocol violations increase adverse events in patients treated with t-PA [7]. It is important to note, however, that although ancrod appears to be beneficial for greater than 3 hours without increase in ICH, only 12 study patients were treated with ancrod after 3.5 hours.

Applications for Clinical Practice

The use of ancrod should await the results of ongoing efficacy and safety trials in Europe. Currently, ancrod is only available in Canada and Europe. The utility of this agent may be limited by the long infusion times used in this study (3 days), which could require longer inpatient admissions. Still, ancrod promises to be an important agent in the treatment of acute ischemic stroke.

References

1. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 1995;333:1581–7.

2. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australian Acute Stroke Study Investigators. Lancet 1998;352:1245–51.

3. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study. JAMA 1995;274:1017–25.

4. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. Multicentre Acute Stroke Trial—Italy (MAST-I) Group. Lancet 1995;346:1509–14.

5. Thrombolytic therapy with streptokinase in acute ischemic stroke. The Multicenter Acute Stroke Trial—Europe Study Group. N Engl J Med 1996;335:145–50.

6. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. JAMA 1999; 282:2003–11.

7. Katzan IL, Furlan AJ, Lloyd LE, Frank JI, Harper DL, Hinchey JA, et al. Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. JAMA 2000;283:1151–8.