

Review: Some new bolus tPA-derived fibrinolytics are comparable to tPA in acute MI, but others increase bleeding

Llevadot J, Giugliano RP, Antman EM. Bolus fibrinolytic therapy in acute myocardial infarction. JAMA. 2001 Jul 25;286:442-9.

QUESTION

In patients with acute myocardial infarction (MI), are the new bolus fibrinolytic derivatives of recombinant tissue-plasminogen activator (tPA) (reteplase [rPA], lanoteplase [nPA], and tenecteplase [TNK-tPA]) as effective and safe as accelerated infusion tPA?

DATA SOURCES

Studies were identified by searching MEDLINE, EMBASE/Excerpta Medica from 1983 to 2001, and *Current Contents*; contacting experts and pharmaceutical companies; and reviewing reference lists and annual meeting abstracts of 3 associations.

STUDY SELECTION

Trials presented at an official cardiology society meeting or published in peer-reviewed literature were selected if the pharmacokinetics or pharmacodynamics of rPA, nPA, or TNK-tPA were evaluated or if immediate and long-term outcomes were reported.

DATA EXTRACTION

Data were extracted on pharmacokinetics and pharmacodynamics, angiographic findings, death, stroke, intracranial hemorrhage (ICH), and bleeding.

MAIN RESULTS

138 studies were evaluated; 38 were included. 3 trials (only the most relevant were reviewed) reported on angiographic data and found that rates of Thrombolysis in Myocardial Infarction (TIMI) grade-3 flow at 90 minutes differed between double-bolus rPA and tPA (59.9% vs 45.2%, $P = 0.01$) but not between nPA (120 kU/kg of body weight) and tPA (57.1% vs 46.4%, $P = 0.14$) or TNK-tPA (40 mg) and tPA (62.8% vs 62.7%, $P > 0.99$).

One large phase-2 safety study evaluating 3 doses of TNK-tPA (30, 40, and 50 mg; the 50-mg dose was replaced with 40 mg because of increased bleeding associated with the 50-mg dose) found that death at 30 days was low in both groups (6.9% [30 mg] vs 6.0% [40 mg]) and that ICH occurred in 0.77% of patients overall. Prespecified analyses showed that efficacy and safety could be improved with weight-based dosing (0.53 mg/kg).

Two large phase-3 mortality trials evaluating double-bolus rPA and accelerated infusion recombinant tPA or streptokinase found comparable efficacy and safety of the treatments. One phase-3 mortality trial evaluated 120 kU/kg single-bolus nPA and tPA and found 30-day mortality between the 2 to be

equivalent (6.75% vs 6.61%, $P = 0.04$ for equivalence). Reinfarction, severe cardiac failure, and emergency revascularization occurred less often with nPA. However, ICH occurred more often with nPA (1.12% vs 0.64%, $P = 0.004$); this finding may have been related to the supratherapeutic activated partial thromboplastin time (aPTT) seen with nPA and standard heparin bolus plus infusion. One phase-3 mortality trial evaluated single-bolus TNK-tPA (30 or 50 mg, weight-adjusted dose) and tPA and found equivalent 30-day mortality (6.18% vs 6.15%, $P = 0.006$ for equivalence); it also found similar incidences of ICH and total stroke.

CONCLUSIONS

In patients with acute myocardial infarction, tenecteplase and reteplase are comparable to accelerated infusion recombinant tissue-type plasminogen activator for efficacy and safety. Lanoteplase and heparin bolus plus infusion are as effective as tPA for mortality, but the rate of intracranial hemorrhage is higher.

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COMMENTARY

The interest in bolus thrombolytic treatments is driven by 2 potential advantages: ease of use resulting in shorter door-to-needle times and a reduced chance of dosage errors and the facilitation of prehospital use.

Of the thrombolytic treatments reviewed by Llevadot and colleagues, TNK-tPA will probably have the greatest utility. The Assessment of the Safety and Efficacy of a New Thrombolytic Regime-II (ASSENT-II) trial (1) established the equivalency of 30-day mortality between bolus TNK-tPA and accelerated infusion tPA; the rates of ICH were similar. Of the 2 major rPA trials, only the International Joint Efficacy Comparison of Thrombolytics trial (2) was designed to show equivalency; the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries-III trial (3) was actually a failed superiority trial. As such, one could conclude that rPA is equivalent to streptokinase in efficacy and safety but not better than tPA. Whether rPA is equivalent to tPA, and hence an appropriate substitute, is debatable. nPA was associated with an increase in the rate of ICH and is thus not attractive. However, nPA is less fibrin specific, increases the aPTT, and may not require a heparin bolus.

The role of bolus fibrinolytic therapy as an alternative to primary percutaneous transluminal coronary angioplasty (PTCA) or as an adjunct to facilitated PTCA needs further study. Currently, if primary PTCA is

available in an experienced, higher-volume center, the evidence suggests that it is the most effective reperfusion strategy. However, cost and availability limit its widespread use.

Future studies may shed light on possibilities, including various combinations of bolus thrombolytic treatments, low-molecular-weight heparins, inhibitors of glycoprotein IIb/IIIa, and PTCA. Indeed, the ASSENT-III trial (4) with 6000 patients suggests that TNK-tPA plus enoxaparin, because of its effectiveness and ease of administration, is an attractive alternative reperfusion regimen.

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Reference

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3. Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. *N Engl J Med*. 1997;337:1118-23.
4. ASSENT-3 Investigators. *Lancet*. 2001;358:605-13.