Pharmacokinetics of a Slower Clearing Tissue Plasminogen Activator Variant, TNK-tPA, in Patients with Acute Myocardial Infarction

Nishit B. Modi, Stephen Eppler, Judy Breed, Christopher P. Cannon, Eugene Braunwald, Ted W. Love

From the Departments of 1Pharmacokinetics and Metabolism, 2Medical Affairs, and 4Product Development, Genentech, Inc., One DNA Way, S. San Francisco, CA, USA, and 3Cardiovascular Division, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA

Summary

The rapid clearance of t-PA from plasma requires administration by intravenous (IV) infusion. A slower clearing, fibrin-specific rt-PA variant may allow single intravenous bolus administration, thereby simplifying dosing. This study was designed to characterize the pharmacokinetics of the slower clearing, fibrin-specific tissue-plasminogen activator variant, TNK-tPA, in patients with acute myocardial infarction (AMI) following a single IV bolus injection. Single IV bolus doses of 5 to 50 mg of TNK-tPA were studied in an open-label, multicenter, dose escalation study. A total of 113 AMI patients were enrolled. Blood sampling for pharmacokinetics was conducted in eighty-two patients (72 men, 10 women), with 5 to 27 patients per dose. TNK-tPA was administered as an IV bolus over 5–10 s. Following IV bolus administration, there was a biphasic elimination of TNK-tPA from plasma. The initial phase had a mean half-life that ranged from 11 ± 5 to 20 ± 6 min and was followed by a terminal phase with a mean half-life that ranged from 41 ± 16 to 138 ± 84 min. Mean TNK-tPA plasma clearance was 125 ± 25 - 216 ± 98 ml/min, and the initial volume of distribution was 4.3 ± 2 - 8.4 ± 6 l. A decrease in TNK-tPA plasma clearance with increasing TNK-tPA dose was noted. In addition, women and patients with lower body weight or older age had a slower plasma clearance. In conclusion, TNK-tPA has a slower plasma clearance in patients with AMI than that reported for rt-PA, allowing administration as a single IV bolus.

Introduction

Thrombolytic therapy represents a major advance in the treatment of acute myocardial infarction that significantly reduces morbidity and mortality (1). Early administration of thrombolytic therapy in acute myocardial infarction achieves patency in the infarct-related artery and can improve survival (2). However, current thrombolytic regimens are limited by less than optimal initial recanalization and reocclusion in a significant number of patients. Even aggressive treatment with front-loaded thrombolytic regimens of recombinant tissue-type plasminogen activator (rt-PA) demonstrate failure of early recanalization in 15-20% of patients (3-6) with TIMI-3 flow at 90 min being achieved in only 54-60% of patients (5, 6). In addition, the short half-life and the rapid clearance of rt-PA from the circulation by the liver requires administration of rt-PA via intravenous infusion (7). Numerous attempts are currently underway to design rt-PA variants that maintain fibrin specificity and have a longer residence time in the circulation. Attempts to produce these variants have included domain deletions (8-11), and site-specific amino acid substitutions (12-14). The slower clearance of such t-PA variants could allow administration by intravenous bolus injection and may potentially result in further improvements in early infarct-related artery patency.

A novel rt-PA variant, TNK-tPA, has been designed by substitution of threonine to asparagine at amino acid 103, resulting in the addition of a novel glycosylation site; replacement of the asparagine at position 117 with glutamine, removing the high mannose carbohydrate normally at this site; and a tetra-alanine substitution at amino acids 296-299 (15). The thrombolytic effects of TNK-tPA have been demonstrated in a rabbit model of coronary artery thrombosis (16), and an embolic stroke model (17). In these models the thrombolytic potency of TNK-tPA was 5- to 10-fold greater than rt-PA, resulted in a longer duration of patency and was generally associated with a lower incidence of bleeding (16). In addition, TNK-tPA demonstrated a higher thrombolytic efficacy on a mg per kg body weight dose basis compared to rt-PA in a combined arterial and venous thrombosis canine model (18). The higher thrombolytic efficacy of TNK-tPA compared to rt-PA in this animal model was attributed to the slower plasma clearance (~ 4-fold) of TNK-tPA. Although TNK-tPA has 80% of the plasma clot lysis activity of t-PA (15), the slower TNK-tPA plasma clearance results in a larger exposure of the clot to the thrombolytic agent which more than offsets the slightly lower activity and produces a greater thrombolytic efficacy for TNK-tPA compared to rt-PA.

The objective of the current study, Thrombolysis in Myocardial Infarction trial (TIMI 10A), was to characterize the safety and pharmacokinetics of several doses of TNK-tPA in patients with acute myocardial infarction (AMI). This report provides the complete pharmacokinetic results from this trial. The preliminary efficacy and safety results from this trial have been reported separately (19).

Patients, Materials and Methods

Study Patients

Patients presenting within 12h of AMI symptom onset were eligible for enrollment in the study. In this Phase I study, patients who weighed less than 60 kg or who had other serious illnesses, or who had any major surgery within the previous 2 months were excluded. A total of 113 patients were enrolled in this open-label, multicenter study. Blood samples for pharmacokinetic analysis were obtained in 82 patients. The study protocol...
was approved by the Institution Review Boards of the hospitals, and patients provided informed consent.

**Medications, Dosage, and Study Design**

TNK-tPA was manufactured using recombinant DNA technology by Genentech, Inc. (S. San Francisco, USA) and was comprised of >70% of the single chain form as a lyophilized formulation in 20 mg vials. Vials were reconstituted by adding 4 ml of sterile water for injection. TNK-tPA doses were administered as a single intravenous bolus injection over 5–10 s via a peripheral vein. All patients who had not taken aspirin within the preceding 24 h received 325 mg non-enteric chewable aspirin immediately upon study entry. Intravenous heparin was administered as a bolus of 5000 IU, followed by an infusion of 1000 IU/h for 48–72 h. Heparin was started as soon as possible after entry study and the infusion rate was adjusted to maintain an aPTT of 55–85 s. The TNK-tPA dose was administered as soon as practical after the heparin was started. Patients had coronary angiography at 90 min after treatment for assessment of infarct-related coronary artery TIMI flow grade (20). Additional angiograms were obtained at 60 and 75 min if possible. All angiograms were reviewed by a blinded core angiographic laboratory.

**Blood Sampling and Assays for TNK-tPA**

Blood samples were collected through an indwelling catheter from a peripheral vein contralateral to the TNK-tPA injection site or from the sheath used for cardiac catheterization. The patency of the sampling catheter was maintained by an injection of heparin (10 IU/ml) or physiologic saline solution. A two-string blood sampling technique was used to ensure removal of any heparin prior to the actual blood sampling. For determination of the TNK-tPA immunoreactive concentrations, 5 ml blood samples were collected into SCAT-1 tubes containing 4.5 mmol/l EDTA as anticoagulant, 50 µmol/l of the synthetic pro tease inhibitor D-Phe-Pro-Arg-CH₂ (PPACK), and 150 KIU/ml aprotinin. PPACK blocks the active site of TNK-tPA (and t-PA) preventing in vitro artifacts (21-23). Blood samples were collected at baseline, 2, 5, 10, 20, 30, 60, 75, 90 min and at 2, 3, 6, 12, 24, and 48 h following the TNK-tPA bolus injection. Samples were transferred immediately on ice until they were cold centrifuged (10˚ C) at 8,000–10,000 RPM for 3-5 min. Samples were centrifuged within 1 h of collection. Following centrifugation, plasma was drawn, split into two aliquots and frozen at -20˚ C until assay. The immunoreactive concentration of TNK-tPA in the plasma samples was measured using a sensitive two site enzyme-linked immunosorbent assay (ELISA).

**TNK-tPA Assay**

The immunoreactive concentrations of TNK-tPA in the plasma samples were assayed using a double monoclonal ELISA. The assay has an inter- and intra-assay precision of < 9% CV over a wide range of the standard curve (0.5–7.8 ng/ml). Studies investigating the recovery of known TNK-tPA concentrations spiked into 2% human EDTA plasma have shown a > 96% recovery. Similar recovery studies in neat human serum and plasma have shown an accuracy of 89% and the absence of any matrix effect on the quantitation of TNK-tPA following a minimum 1:50 dilution. In this assay, the limit of detection of TNK-tPA in plasma was 8 ng/ml following a minimum 50-fold dilution. Plasma samples spiked with known concentrations of rt-PA and assayed in the TNK-tPA assay resulted in a 100% recovery suggesting that the assay does not discriminate between rt-PA and TNK-tPA.

**Pharmacokinetic Analysis**

The TNK-tPA plasma concentration versus time data were fit for each patient by use of the program PCNONLIN (SCI Software, Lexington KY). A one- or two-compartment model was used, incorporating elimination from the central plasma compartment. The following pharmacokinetic parameters were calculated using standard formulae (24): estimated initial TNK-tPA plasma concentration (c(0)), total plasma clearance (CL), plasma half-lives (t₁/₂) and corresponding partial AUC, mean residence time in the body (MRT), and initial and steady-state volumes of distribution (V₁ and V₂, respectively). Since the ELISA did not distinguish between endogenous t-PA concentrations and TNK-tPA, concentrations detected prior to the administration of TNK-tPA and concentrations less than approximately 30 ng/ml were not included in the pharmacokinetic analysis.

**Statistical Analyses**

To investigate whether TNK-tPA follows linear pharmacokinetics, a power model was fit to the AUC and c(0) :

\[ Y = a \times \text{Dose}^b \]

where Y represents the pharmacokinetic parameter (AUC or c(0)). The estimate of the exponent, b, along with its confidence interval may be used to quantify the degree of dose proportionality (25).

To identify potential patient characteristics that may be important in describing TNK-tPA pharmacokinetics, a stepwise linear regression was conducted. TNK-tPA plasma clearance and initial volume of distribution were examined as a function of TNK-tPA dose, total body weight, lean body weight (LBW), age, and gender. LBW was calculated as follows (26):

Male : \[ \text{LBW} = 1.1 \times \text{Weight} – 128 \]

Female : \[ \text{LBW} = 1.07 \times \text{Weight} – 149 \]

where weight is in kg and height is in cm. A similar regression analysis was done with the observed maximum TNK-tPA concentration, Cmax, to identify patient characteristics that are related to increased TNK-tPA plasma concentration. In addition, the effect of co-administered drugs (nitrates and beta blockers) was investigated as potential factors influencing TNK-tPA pharmacokinetics.

All statistical analyses were conducted for the group of 78 patients on whom complete pharmacokinetic and demographic data were available. A p-value of less than 0.05 was considered statistically significant. Statistical calculations were done using the programs StatView (Abacus Concepts, StatView, Berkeley, CA, 1992) or JMP (SAS Institute Inc., Cary, NC, 1994).

**Results**

Eighty-two patients (72 males and 10 females) were enrolled as pharmacokinetic/pharmacodynamic patients in this trial. Complete pharmacokinetic and demographic (weight, height, age, and gender) data were available for 78 patients (68 males and 10 females). The mean age of the patients for whom complete pharmacokinetic and demographic data were available was 55 years (range 29 to 72 years). The average patient weight was 85 kg (range 59 to 126 kg). All ethnic backgrounds were represented (70% of the patients were Caucasian, 12% were African American, and 14% were Hispanic).

**Pharmacokinetics**

Figure 1 shows the time course of the mean immunoreactive TNK-tPA plasma concentrations for the 5-50 mg dose groups. Also shown in Fig. 1 is the plasma concentration profile for 100 mg rt-PA following the 90-min dose regimen (27). Pharmacokinetic parameters for TNK-tPA are summarized in Table 1.

Estimated peak TNK-tPA plasma concentrations increased in a dose-dependent manner (881 to 10,700 ng/ml) from 5 to 50 mg. Following the bolus injection, TNK-tPA plasma concentrations decreased in a biphasic manner with an initial α-phase that had a mean (± SD) half-life that ranged from 11 ± 5 to 20 ± 6 min and was followed by
a slower β-phase with a mean half-life that ranged from 41 ± 16 to 138 ± 84 min. The α-phase was dominant, comprising 31 ± 22 to 69 ± 15 % of the total AUC. The estimated initial volume of distribution approximated plasma volume (4.3 ± 2 – 8.4 ± 6 l) and the steady-state volume of distribution was 6.3 ± 2 – 15 ± 7 l. The mean clearance of TNK-tPA from the plasma across all doses was 151 ml/min (CV = 37%), ranging from 216 ± 98 at a dose of 5 mg to 125 ± 25 ml/min at a dose of 50 mg. The mean residence time in the body was approximately 1 h.

As expected, the maximum TNK-tPA plasma concentration depended most on dose. A test for dose linearity using the power model suggested that there was a dose-proportional increase in the peak concentration, c(0). The estimated b for c(0) was 0.99 (95% confidence interval = 0.70–1.4). A similar analysis for AUC resulted in a b of 1.2 (95% CI = 0.95–1.4). While the 95% confidence interval encompasses unity, there was a trend suggesting that TNK-tPA exhibits non-linear pharmacokinetics in the dose range studied.

A linear regression analysis indicated that once dose was accounted for, women and patients with low LBW still tended to have higher peak concentrations when considered in a univariate manner. No statistically significant relationships were noted between initial volume of distribution and TNK-tPA dose, patient weight (or LBW), age or gender when considered in a univariate fashion (p >0.05).

TNK-tPA dose had modest predictive value in describing TNK-tPA plasma clearance, explaining 17% of the variability in clearance. The linear regression equation indicated that for a 10 mg increase in TNK-tPA dose there is a 17 ml/min decrease in plasma clearance (p = 0.0002). Figure 2 presents the relationship between TNK-tPA dose and plasma clearance showing the decrease in clearance with increasing TNK-tPA dose. Weight, LBW, age and gender were of lesser value in predicting plasma clearance. After dose was included in the regression model, patient weight (p = 0.009), lean body weight (p = 0.001), age (p = 0.023), or gender (p = 0.007) individually resulted in a statistically significant, but only modest (6 to 8%) further reduction in the residual variability in clearance (R² = 23–25%). A full model, i.e. one containing dose, weight, age, and gender, had a coefficient of determination of 30% indicating that addition of further covariates does not result in a substantial reduction in the CV.

Women generally had a slower plasma clearance (by 46 ml/min) than men after dose was accounted for (Fig. 3), although the number of women treated at each dose was small. While the study was not designed specifically to investigate the effect of nitrates and beta blockers on TNK-tPA pharmacokinetics, TNK-tPA plasma clearance did not differ in the group of patients that received nitrates or beta blockers compared to the group that did not (p = 0.09 and 0.36 for nitrates and beta blockers, respectively).

### Table 1

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<th>CL (ml/min)</th>
<th>V₁ (l)</th>
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**Fig. 1** Time course of the mean immunoreactive TNK-tPA plasma concentrations following intravenous bolus doses of 5 to 50 mg in patients with acute myocardial infarction. Each point represents the mean data for 5 to 26 patients. For comparison, the plasma concentration versus time curve for rt-PA administered using the 90-min administration scheme obtained as part of the TAPS trial (reference 27) is also shown (n = 7 patients). Standard deviations have been omitted in the figure for clarity

**Fig. 2** Relationship between TNK-tPA plasma clearance and dose. Each point represents the datum for a single patient. TNK-tPA plasma clearance decreased with increasing dose. The solid curve is a second order polynomial fit to the data

**Fig. 3** Relationship between TNK-tPA plasma clearance and gender. Women appeared to have a slightly lower TNK-tPA plasma clearance
Additional linear regression analyses were conducted to explore if a weight-adjusted TNK-tPA dose would provide further pharmacokinetic insight. Regression of TNK-tPA plasma clearance against weight-adjusted dose (Dose/W) resulted in a residual CV of 33% in clearance. Similarly, using lean body weight-adjusted dose (Dose/LBW) as the independent variable resulted in a residual CV of 32% in clearance compared to a residual CV of 34% with TNK-tPA dose alone.

**Discussion**

The GUSTO I trial demonstrated an improvement in the infarct-related artery patency with front-loaded rt-PA compared to previous thrombolytic regimens (5, 6). However, the rt-PA administration scheme requires an intravenous infusion and adjustments in the rate of infusion (3). Several small trials have shown that potentially modest improvements in patency rates are possible with single or double bolus administration of t-PA (28-31). However, these results were not reproduced in a large scale trial (32). A t-PA variant with a sufficiently long systemic residence time and optimal pharmacodynamic properties could potentially allow a single intravenous bolus regimen. Pharmacokinetic and efficacy data in animal models have suggested that the slower clearance and longer initial half-life of TNK-tPA compared to rt-PA may provide an adequate plasma concentration profile following single intravenous bolus injection. Data from the present study were obtained to investigate the pharmacokinetics of TNK-tPA in patients with acute myocardial infarction. A broad range of doses were studied to fully characterize the safety and pharmacokinetics of TNK-tPA. Since this was the first clinical study with TNK-tPA a conservative dose escalation strategy was used, starting at a low dose of 5 mg TNK-tPA (20-fold lower than the clinical dose of rt-PA) and escalating to 50 mg. The dose of 50 mg represented the highest bolus dose of a thrombolytic agent that had been safely administered to humans and was also half the clinical dose of t-PA. This broad range of doses was expected to provide an adequate characterization of TNK-tPA pharmacokinetics and safety to guide further dose selection for larger efficacy trials.

**Pharmacokinetics**

TNK-tPA concentrations were detected in pre-dose samples from several patients at levels that ranged from <8 ng/ml to 25.5 ng/ml. These concentrations represent endogenous human t-PA. Endogenous mean t-PA antigen concentrations in human plasma, measured using an enzyme-linked immunosorbent assay, range from 3.4 to 6.6 ng/ml (33, 34). Increased t-PA concentrations (7.6 ng/ml) have been reported after venous occlusion and acute coronary syndromes (35). In the pharmacokinetic analyses, concentrations less than 30 ng/ml were not included. Exclusion of these concentrations from the pharmacokinetic analysis results in a small overestimation of the plasma clearance.

The initial TNK-tPA plasma concentrations following the 50 mg dose (9.1 ± 1.7 μg/ml) were similar to those reported for a bolus dose of 50 mg rt-PA (9.8 ± 3.6 μg/ml) (29). As expected, the initial TNK-tPA plasma concentrations following the 50 mg dose were higher than those reported following the standard regimen with rt-PA (using a bolus of 10 mg) (36) or the accelerated regimen (using a bolus of 15 mg) (27).

TNK-tPA plasma clearance decreased with increasing TNK-tPA dose (Fig. 2). This decrease in clearance with increasing dose is similar to that reported for rt-PA and may be related to a saturation of hepatic receptors responsible for the clearance of TNK-tPA and rt-PA. Women, lighter patients, and older patients had a lower plasma clearance, although the difference was small compared to the variability in plasma clearance. Also, age, weight and gender are correlated, with women and older patients being lighter. The plasma clearance data for the 30 mg dose, where 27 pharmacokinetic patients were enrolled, indicated that patients who are older than 65 years had a mean plasma clearance of 97 ± 27 ml/min (n = 5 patients) compared to 143 ± 31 ml/min for patients younger than 45 years of age (n = 5 patients). Correspondingly, the younger patients had a lower observed maximum concentration (6,110 ± 2,400 ng/ml) compared to the older group (8,830 ± 4,900 ng/ml). These data are suggestive that older patients, who also tend to weigh less, may have a larger exposure (AUC) to thrombolytic agents compared to younger patients.

TNK-tPA had a 2- to 4-fold slower plasma clearance compared to that reported for rt-PA in patients with AMI (572 ± 132 ml/min) (27). The slower plasma clearance of TNK-tPA compared to rt-PA is a result of the longer initial half-life (> 3-fold compared to rt-PA) and may partly be related to the smaller percentage of material cleared during the initial phase (< 15% for TNK-tPA compared to 85 ± 15% for rt-PA). The initial and steady-state volumes of distribution for TNK-tPA are similar to that reported for rt-PA (27). The longer half-life and slower clearance of TNK-tPA from plasma result in a longer systemic residence time for TNK-tPA.

Pharmacokinetic data from this dose-ranging Phase I study suggest that nitrates and beta blockers do not affect TNK-tPA pharmacokinetics. Studies with t-PA have suggested that coadministration of nitrates with rt-PA decreases plasma t-PA concentrations and impairs the thrombolytic effect of t-PA (37). This difference in pharmacokinetic properties between t-PA and TNK-tPA may be due, at least in part, to the slower clearance of TNK-tPA, and hence the lower dependence on liver blood flow, compared with rt-PA. However, a direct comparison of the effect of nitrates on TNK-tPA and rt-PA clearance is difficult since the current study was not specifically designed to investigate this aspect and was conducted in a small number of patients with AMI.

Based on the relationship between TNK-tPA dose and AUC, it is estimated that a dose of 24 mg TNK-tPA administered as an intravenous bolus injection should result in a similar plasma AUC as that reported following administration of alteplase using the accelerated regimen in patients with AMI (175 μg × min/ml) (27). Thus, an intravenous bolus dose of 24 mg of TNK-tPA should provide a similar plasma exposure to the thrombolytic agent as 100 mg rt-PA, administered using the accelerated infusion regimen. Taking into account that TNK-tPA has approximately 80% relative activity in an in vitro clot lysis model compared to rt-PA (15), a dose of 30 mg TNK-tPA administered as a bolus should be pharmacodynamically similar to a 100 mg dose of rt-PA administered using the accelerated regimen. This prediction is based on the assumption that the thrombolytic effect of TNK-tPA depends only on plasma exposure and does not take into account several factors such as fibrin specificity and infarct location, both of which may be important in dose selection. However, the predicted dose of 30 mg serves as an estimate of the initial starting dose for further investigation in larger clinical trials that can better assess the efficacy and safety profile of TNK-tPA.

In the TAPS study investigating the accelerated rt-PA dosing regimen, Tanswell et al. (27) estimated that a Cmax (steady-state concentration at 30 minutes) of 3.2 μg/ml was associated with an increased velocity of coronary artery patency (3, 38, 39). This pharmacologic concentration is similar to the plasma concentration achieved at 30 min in the 30 mg TNK-tPA dose group. In addition, Tanswell et al. noted that the Cmin (steady-state concentration at 90 minutes) was 1.08 μg/ml, which is slightly higher than the 90-min TNK-tPA plasma concentra-
tion for the 30 mg dose group but is similar to that seen for the 50 mg dose group at 90 min.

Previous studies have presented the hypothesis that high initial concentrations of a thrombolytic agent are determinants of early coronary artery patency (27) and that prolonged later concentrations may prevent reocclusion (40). The hypothesis that sustained thrombolytic concentrations result in higher patency seems supported by the concentrations achieved with the 30-50 mg TNK-tPA doses in the present study. In the group of patients who had pharmacokinetic sampling, 58% of the patients in the 30 mg dose group and 71% of the patients of the 50 mg dose group had TIMI-3 flow at 90 minutes. While the number of pharmacokinetic patients in the 50 mg dose group is small (n = 7), these patency rates are similar to those reported for the main study (19).

An additional finding from this study was that weight- (Dose/W) or LBW-adjusted dose (Dose/LBW) did not result in an appreciable reduction in the residual variability in clearance compared to using dose alone. The residual CV for TNK-tPA clearance using Dose/W or Dose/LBW was 32-33% compared to 34% with dose alone. Thus, weight-adjusted TNK-tPA dosing does not reduce the inherent variability of TNK-tPA pharmacokinetics in patients with AMI. However, it is possible that a weight-adjusted dose for TNK-tPA may provide a better efficacy or safety profile. These pharmacokinetic results were obtained from a dose-ranging Phase I study with a relatively small number of patients per dose. Two larger Phase II studies with a narrower dose range (30-50 mg) have been conducted and should provide further information on the efficacy and safety profile of TNK-tPA and on the appropriate dosing regimen for TNK-tPA.

Conclusions

In summary, these pharmacokinetic data with TNK-tPA in patients with AMI indicate that TNK-tPA plasma clearance is 2- to 4-fold slower than that reported for rt-PA. A trend towards a decrease in plasma clearance with increasing TNK-tPA dose was noted. In addition, a slower plasma clearance was observed in women, lighter patients and older patients. The number of patients treated to date with TNK-tPA is relatively small and larger studies will be needed to fully characterize the safety and efficacy profile of this novel thrombolytic agent.

Acknowledgements

Study coordination with the clinical sites by Carolyn McCabe is gratefully appreciated. Comments on the manuscript and statistical analyses by Dr. James Reimann are gratefully acknowledged.

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Received March 1, 1997 Accepted after resubmission August 11, 1997