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Lanoteplase

Prop INN; USAN

Tissue-Type Plasminogen Activator
Treatment of Acute Myocardial Infarction
Thrombolytic

nPA
SUN-9216
One Plus™
Oneplas™

N-[N^2-(*N*-Glycyl-L-alanyl)-L-arginyl]-117-L-glutamine-245-L-methionine-(1-5)-(87-527)-plasminogen activator (human tissue-type protein moiety)

CAS: 171870-23-8
CAS: 153484-31-2 (as reduced)

EN: 184765

Description and Production

Lanoteplase is a new bolus fibrinolytic drug derived from tissue-type plasminogen activator (t-PA, alteplase). The t-PA molecule consists of several regions with specific functions: the fibronectin finger region is responsible for the high-affinity binding to fibrin, the epidermal growth factor and the kringle-1 regions for the binding to receptors in the liver, and the kringle-2 region for the low-affinity binding to fibrin. The protease domain is responsible for the cleavage of plasminogen and also binds the plasminogen activator inhibitor type-1 (PAI-1), inhibiting the proteolytic function of t-PA. The asparagine in positions 117, 184 and 448 carry carbohydrate chains that affect the plasma clearance of the molecule via hepatic endothelial cells (Fig. 1).

Lanoteplase is derived from t-PA by deleting its fibronectin finger and epidermal growth factor domains and mutating asparagine 117 to glutamine 117 (designated Gln36 in lanoteplase). The deletion involves the removal of t-PA residues Cys6 through Ile86, and the mutation results in the elimination of an N-linked glycosylation site. Lanoteplase is produced by cell culture fermentation using a Chinese hamster ovary cell line. The purified protein is primarily a single-chain molecule with the plasmin cleavage site intact. The molecular weight of lanoteplase, which includes carbohydrate content is 53.6 kDa (1-3).

Introduction

The central reaction of the fibrinolytic system is conversion of the inactive proenzyme, plasminogen, to the proteolytic enzyme, plasmin, through cleavage of a single peptide bond by specialized plasminogen activator proteases. Plasmin digests fibrin to soluble degradation products. Conversion of plasminogen to plasmin is activated intravascularly through the intrinsic pathway by factor XIIa, the initiator of the coagulation cascade, and extravascularly through the extrinsic pathway by “tissue activators” (Fig. 2).

A pathological situation in which fibrinolytic therapies are indicated is the acute thrombus occlusion of coronary arteries leading to myocardial infarction (4). In its early stage, acute myocardial infarction with ST-segment elevation is frequently associated with thrombotic coronary artery occlusion. One treatment approach consists of pharmacological dissolution of the blood clot by intravenous infusion of plasminogen activators that activate the fibrinolytic system. Rapid coronary reperfusion limits infarct size, decreases ventricular dysfunction and improves survival.

Thrombolytic agents have been classified as first-, second- and third-generation drugs (5). Streptokinase and urokinase are first-generation fibrinolytic agents that have been shown to be effective in thrombolysis. These drugs exhibit low fibrin specificity and are able to convert circulating plasminogen to plasmin. In addition, streptokinase may induce immunogenic reactions. The second-generation agents, tissue plasminogen activator (t-PA)

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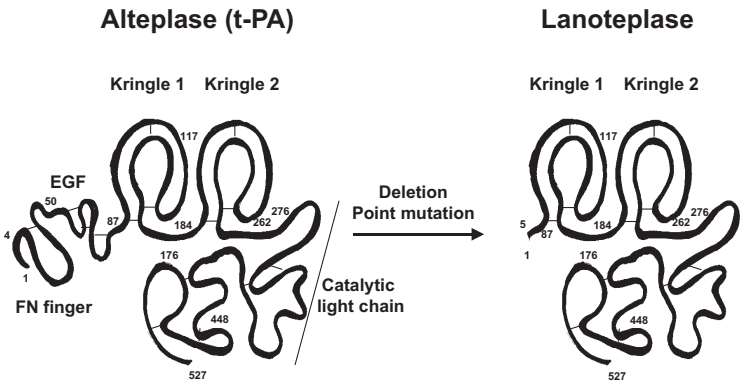

Fig. 1. Molecular structures of alteplase (t-PA) and lanoteplase. Lanoteplase is derived from t-PA by deleting the fibronectin (FN) finger-like and epidermal growth factor (EGF) domains and mutating Asn117 to Gln117.

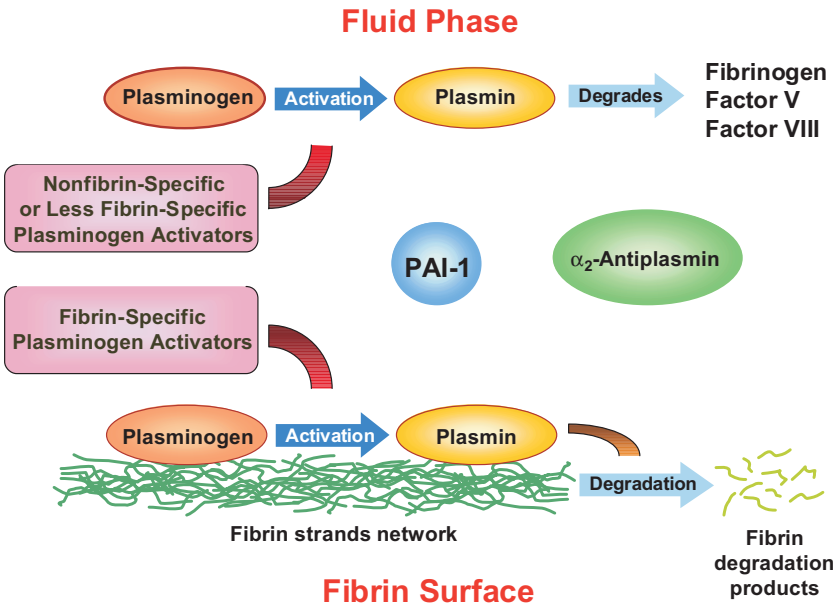

Fig. 2. Fibrinolytic system.

and single-chain urokinase type plasminogen activator (scu-PA, also called u-PA or urokinase), are also serine proteases capable of generating plasmin. Both activators bind avidly to fibrin, enabling them to cause efficient and localized digestion of the clot or thrombus. The high doses of these agents required produce a mild to moderate decrease in levels of fibrinogen and plasminogen. The risk of intracranial hemorrhage with t-PA is slightly greater than with streptokinase.

It is important that fibrinolytic agents exhibit fibrin specificity, since less fibrin-specific plasminogen activators induce more extensive systemic plasminogen activation, and after saturation of α_2-antiplasmin, excess plasmin may degrade several proteins including fibrinogen, factor V and factor VIII, causing greater systemic coagulopathy, with an increased risk of bleeding.

The need for a thrombolytic agent that is highly effective and safe, yet simple and rapid to administer, has led to the development of third-generation plasminogen activators. These new compounds have been designed in order to lengthen the half-life of the drug, increase resistance to plasma protease inhibitors and to improve the specificity for fibrin (6). Third-generation plasminogen activators are variants of the natural human enzyme t-PA. Lanoteplase is one representative of this new class of fibrinolytic agents.

Pharmacokinetics and Pharmacodynamics

Deletion of the fibronectin finger and the epidermal growth factor regions results not only in a reduction of the

Table I: Characteristics of lanoteplase and t-PA.

	t-PA	Lanoteplase
Molecular weight (kDA)	70	53.6
Plasma half-life (min)	3.5 ± 1.4	37 ± 11
Plasma clearance (ml/min)	572 ± 132	57 ± 19
Elimination	Hepatic	Hepatic
Mode of administration	Infusion over 90 min	Single bolus
Dose	≤ 100 mg	120 kU/kg
Weight-adjusted dosing	Yes	Yes
Plasminogen activation	Direct	Direct
Fibrin specificity	++	+
Inhibition by PAI-1	Yes	No
Immunogenicity	–	–

high-affinity binding to fibrin but also in a decrease in binding to receptors in the liver. In addition, with the amino acid substitution in position 117, clearance by the mannose receptor is reduced. Lanoteplase, therefore, is slightly less fibrin-specific than t-PA but more potent as a fibrinolytic agent. The changes mentioned above in the molecule reduced the plasma clearance and extended the in vivo half-life to 37 min as compared with 4-6 min for t-PA, without affecting efficacy at therapeutic concentrations (Table I).

The thrombolytic action of lanoteplase, as measured by patency rates, is increased by about 10-fold compared to wild-type t-PA in animals (2). The efficacy of lanoteplase was initially compared to that of t-PA in a rabbit model of jugular vein thrombosis. Half-maximal thrombolysis was obtained with 0.07 mg/kg lanoteplase and 0.6 mg/kg t-PA. At these doses no major differences in fibrinogen and α_2-antiplasmin depletion were observed at 2 h after initiating thrombolytic therapy (3). In a photochemically induced thrombus model in rat femoral artery, lanoteplase administered either as an i.v. infusion (1.0 mg/kg) or as a single bolus i.v. injection (1.0 mg/kg) showed higher activity than an i.v. infusion of t-PA (3.0 mg/kg) (7).

The pharmacokinetics and thrombolytic properties of lanoteplase were studied in dogs with copper coil-induced thrombosis of the left anterior descending coronary artery (8). Bolus injections were given during 2 min to groups of 3 dogs. Injection of 0.15 mg/kg resulted in peak plasma antigen levels of 1.58 ± 0.72 μg/ml (mean ± SEM) and caused reperfusion within 14 ± 6 min. With 0.075 mg/kg, corresponding values of 0.81 ± 0.20 μg/ml and 31 ± 15 min were obtained. A bolus of 0.038 mg/kg yielded peak plasma levels of 0.43 ± 0.20 μg/ml but did not cause coronary recanalization within 3 h. A bolus injection of natural t-PA at a dose of 0.1 mg/kg in 4 dogs resulted in peak plasma levels of 0.46 ± 0.09 μg/ml and caused partial coronary artery reperfusion within 3 h in 1 of 4 dogs (after 31 min). None of these injections caused a significant decrease in fibrinogen levels. Pharmacokinetic parameters for lanoteplase were 14-18 min, 72-125 min and 21-36 ml/min for $t_{1/2\alpha}$, $t_{1/2\beta}$ and plasma clearance, respectively. The corresponding values for t-PA were 3 min, 8 min and 520 ml/min. Lanoteplase had a markedly longer plasma $t_{1/2}$ than t-PA and, when administered as a bolus injection, greater thrombolytic efficacy.

Clinical Studies

Lanoteplase (15-120 kU/kg) was evaluated in the InTIME-I trial, which included 602 patients (Box 1). This study was a multicenter, randomized, double-blind, dose ranging angiographic trial with a primary endpoint of complete coronary perfusion, represented by TIMI grade 3 flow 60 min after initiation of thrombolytic therapy. Flow grade was defined by investigators in the Thrombolysis in Myocardial Infarction (TIMI) Trial (9) as follows: grade 0, a totally occluded artery (no flow); grade 1, flow into the thrombus but not beyond (blood flow occluded); grade 2, sluggish flow through the vessel (still not normal flow); and grade 3, normal brisk flow through the artery.

Favorable angiographic results were obtained with lanoteplase when compared to t-PA (10, 11). TIMI grade 3 flow increased with increasing doses of lanoteplase at both 60 and 90 min. At 90 min, TIMI grade 3 was achieved in 57.1% of patients who were given high-dose lanoteplase and in 46.4% of patients who had accelerated administration of t-PA. Major and moderate bleeding complications were similar in both groups.

In a substudy of the InTIME-I study, the impact of thrombolytic therapy on hemostatic variables was evaluated in 27 patients. Fibrinogen, plasminogen and α_2-antiplasmin levels were measured at 2 h after treatment with lanoteplase or t-PA and compared with baseline values. There was a decrease in levels with increasing concentrations of lanoteplase. Levels observed with t-PA were the same as those with 60-120 kU/kg of lanoteplase, indicating that at equieffective doses both drugs exhibited comparable fibrin specificity (12).

PAI-1 is the primary regulator of the fibrinolytic system. In order to evaluate the effect of lanoteplase on PAI-1 activity, a study was carried out in 21 patients with acute myocardial infarction, 8 of whom were treated with

Box 1: InTIME-I study: Intravenous lanoteplase for the Treatment of Infarcting Myocardium Early: A comparative, multicenter, double-blind, randomized study (12, 18)

Design	Patients with acute myocardial infarction ≤ 6 h (n = 602), hemostatic data available (n = 27)					
Treatments	Lanoteplase, 15 kU/kg iv bolus sd (n = 4) Lanoteplase, 30 kU/kg iv bolus sd (n = 2) Lanoteplase, 60 kU/kg iv bolus sd (n = 8) Lanoteplase, 120 kU/kg iv bolus (n = 6) t-PA, 100 mg accelerated infusion (n = 7)					
		L15	L30	L60	L120	t-PA
Results	TIMI grade 2-3 flow rate (%) at 90 min	54.1	62.4	72.5	83.0*	71.4
	Death/reinfarction/major bleeding/heart failure rate (%) at 30 d	12.3	6.5	12.3	9.0	21.8
	Fibrinogen levels, % change at 2 h	112	92	82	27	51
	Plasminogen levels, % change at 2 h	87	76	71	32	45
	α_2-Antiplasmin levels, % change at 2 h	82	63	53	25	30
	D-dimer (fold after drug) at 2 h	6.4	12	36	36	32
	Fibrinogen degradation products (fold after drug) at 2 h	2.1	1.9	3.6	53	51
	PAI-1 values (fold after drug) at peak				6h: 2.8 24h: 1.5	8h: 3.9 24h: 1.9
Conclusions	The extent of systemic plasmin generation for the highest lanoteplase dose (120 kU/kg) was similar to that of t-PA except for PAI-1 levels					

*$p < 0.001$

Box 2: InTIME-II study: Intravenous lanoteplase for the Treatment of Infarcting Myocardium Early: A comparative, multicenter, double-blind, randomized study (14, 17, 19-21)

Design	Patients with ST elevation acute myocardial infarction (n = 15,078)		
Treatments	Lanoteplase, 120 kU/kg iv bolus sd + heparin + aspirin t-PA, 100 mg iv infusion over 90 min		
		Lanoteplase	t-PA
Results	Death rate at 30 d	6.8	6.6
	Death rate at 30 d-6 mo	2.1	2.6
	Death rate at > 6 mo	8.7	8.9
	Stroke rate (%)	1.9	1.5
	Stroke rate due to intracraneal hemorrhage (%)	1.1	0.6*
	-if monitoring aPTT at 6 h after heparin administration (%)	1.2	0.7
	-if monitoring aPTT at 3 h after heparin administration (%)	1.0	0.5
	Clinical deficit (death or disabling stroke) (%)	7.2	7.0
	Severe cardiac heart failure (%)	2.3	2.6
	Recurrent myocardial infarction at 30 d (%)	5.0	5.5
	Emergency revascularization during admission (%)	5.4	6.2**
	Emergency revascularization -at 30 d (%)	7.0	6.3
	Any revascularization during admission (%)	23.0	24.4
	Any revascularization -at 30 d (%)	25.8	26.9
	Second-third degree AV block (%)	3.6	4.5**
	Major hemorrhage (%)	0.5	0.6
	Moderate hemorrhage (%)	2.4	2.4
	Minor hemorrhage (%)	14.8	19.7+
Conclusions	Lanoteplase was as effective as t-PA in reducing 30-day mortality, intracraneal hemorrhage and major cardiac events in combination with heparin, showing a lower mortality rate at 6 months		

*$p < 0.004$; **$p < 0.05$; +$p < 0.0001$

lanoteplase and 13 with recombinant t-PA (13). PAI-1 activity at 4 h after initiating thrombolysis was shown to be significantly lower in the lanoteplase group than in the t-PA group (8.7 ± 5.5 IU/l *vs.* 26.7 ± 3.4 IU/l, $p< 0.01$). There was a mild peak in plasma PAI-1 activity 24 h after beginning thrombolysis. The results suggest that thrombolytic therapy with lanoteplase gives faster recanalization and lower PAI-1 activity after successful thrombolysis as compared to recombinant t-PA.

The InTIME-II trial (Box 2) was a randomized, double-blind, multicenter trial designed to compare the effects of lanoteplase with accelerated recombinant t-PA in reduc-

ing mortality and major morbidity in patients with suspected acute myocardial infarction presenting within 6 h of symptom onset. A total of 15,078 patients from 855 hospitals worldwide were enrolled in the study. Patients were randomized in a 2:1 ratio to receive either lanoteplase (120 kU/kg single i.v. bolus) or t-PA (100 mg i.v. infusion for 90 min). Adjuvant therapy included 100-325 mg aspirin and heparin at a dose adjusted to maintain the activated partial thromboplastin times (aPTT) between 50 and 70 s (70 U/kg bolus [maximum 4000 U] and 15 U/h infusion [maximum 1000 U]).

Results from the study indicated that at 30 days lanoteplase was equivalent to t-PA with regard to mortality (14). Reinfarction, severe cardiac failure and emergency revascularization occurred less often with lanoteplase than with t-PA. Incidence of stroke was similar with both treatments. Rates of intracranial hemorrhage were significantly higher in lanoteplase-treated patients than those treated with t-PA (1.12% *vs.* 0.64%), possibly due to higher early aPTT and the use of bolus heparin or to an excessive dose of lanoteplase. Investigators recently pointed out that that there is a geographic variation in patient and hospital characteristics, management and clinical outcomes in ST-elevation myocardial infarction treated with fibrinolysis (15).

In the InTIME-IIb study, the effects of lanoteplase without heparin bolus were analyzed. Preliminary results revealed an absence of the early aPTT spike observed in the main InTIME-II trial, and a lower intracranial hemorrhage rate (16). In view of these results, earlier monitoring of the aPTT with a lower dose of concomitant heparin may reduce the risk of intracranial hemorrhage after fibrinolytic therapy (17).

Conclusions

Third-generation thrombolytic agents offer promise with increased fibrin specificity and longer half-lives, allowing bolus administration. The single-bolus regimen should shorten the time between onset of symptoms and treatment and be especially convenient for administering in an emergency or out-of-hospital setting. The preserved fibrinolytic activity and reduced plasma clearance of lanoteplase allows single-bolus administration. Lanoteplase is eliminated via the liver and its immunogenic profile is similar to that of t-PA. The results of two clinical trials comparing this new thrombolytic agent with t-PA have demonstrated that a single-bolus infusion of weight-adjusted lanoteplase is as effective as an accelerated infusion of t-PA in terms of its impact on survival, with a comparable risk-benefit profile.

Source

Originated at Genetics Institute Inc. (US); licensed to Suntory Ltd. (JP).

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