

# How to Manage Thrombolysis Interruptions in Acute Stroke?

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**Objectives:** Tissue plasminogen activator (t-PA) is the only approved thrombolytic therapy for the treatment of stroke patients. Its effectiveness is highly time dependent because of the sensitivity of brain tissue to ischemia. Because of the short half-life of t-PA, it should be administered as a bolus followed by an immediate infusion. However, in clinical practice, there are sometimes delays between the application of the bolus and the start of the infusion; in addition, interruptions of the infusion may occur. There are no recommendations regarding how to handle such situations.

**Methods:** We simulate the effects on serum t-PA concentrations of different delays in administering t-PA using its known pharmacokinetic parameters in a 2-compartment model.

**Results:** Our results demonstrate that even short delays of only 1 minute between bolus and infusion severely affect serum t-PA concentrations. In addition, interruptions to the infusion that are over 1 minute in duration affect serum t-PA concentrations.

**Conclusions:** These results strongly suggest avoiding bolus-infusion delays by giving the bolus only when the infusion is ready. In case of a delayed start of the infusion, the possibilities are restricted to do nothing or to give a second bolus. We have estimated the dosing of the second bolus depending on the duration of the delay/interruption to allow for the achievement of appropriate serum t-PA concentrations. However, clinical safety data are needed to recommend the application of a second bolus.

**Key Words:** stroke management, thrombolysis, pharmacokinetics

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It has been established that the rapid initiation of a thrombolytic treatment is strongly beneficial to stroke patients.<sup>1,2</sup> The sensitivity of brain tissue to ischemia causes this time dependence of the effectiveness of tissue plasminogen activator (t-PA). Accordingly, the number needed to treat (NNT) for 1 patient to recover (modified Rankin scale 0–1) increases with increasing time (<1.5 hours NNT = 5; 1.5–3 hours NNT = 9; 3–4.5 hours NNT = 15).<sup>3–5</sup> Therefore, it is crucial to minimize the time between the onset of symptoms and the initiation of an effective thrombolytic treatment. In this context, an effective thrombolytic treatment refers to the attainment of target serum t-PA concentrations in the patient. This is normally achieved by administering 0.9 mg/kg t-PA (maximum of 90 mg), with 10% given as an initial bolus and the remainder infused over a period of 1 hour.<sup>6</sup> Because of the short half-life of t-PA (~4.5 minutes), the interval between the bolus and infusion must be kept to a minimum. In clinical situations, delays between the bolus and the start of infusion in addition to interruptions to the infusion may occur. For example, the preparation of the bolus may be accomplished much more rapidly than that of the infusion. If the bolus is immediately administered once it is prepared, a delay in the start of infusion may occur. A

recent retrospective single-center study has found a mean bolus-infusion delay of 9 ( $\pm 7$ ) minutes.<sup>7</sup> This study has further found a lower functional independence and higher mortality in bolus-infusion delays of more than 8 minutes compared with less than 8 minutes. However, this result does not reach statistical significance.<sup>7</sup> In our department, a retrospective analysis of stroke management has shown cases of time delays between bolus and infusion administration of up to 10 minutes. In these cases, the boluses were provided to the patients as rapidly as possible while they were within computed tomography (CT) scanners. Because the infusion had not been prepared at this time, the delay was used to perform CT angiography and CT perfusion scans, causing t-PA infusion to be further delayed. Because of the short half-life of t-PA, serum concentrations were already decreasing by the time of the delayed infusion start. In fact, it has been demonstrated that the delayed initiation of infusion results in a slow gradual increase in serum t-PA levels that remain below target concentrations for significant periods.<sup>8</sup> Similarly, interruptions in the infusion of t-PA affect serum concentrations (because of a nonfunctioning venous access or missing the end of the first infusion, after which a second t-PA infusion should have been started). A possible time delay between a bolus and infusion start is almost always recognized, but this may not be the case for an interrupted infusion. However, even if the delay between bolus and infusion start or the duration of an interrupted infusion is known, no recommendations exist regarding how to handle such situations.

Using pharmacokinetic and mathematical modeling based on known pharmacokinetic parameters,<sup>9</sup> we simulated the influence of bolus-infusion delays and infusion interruptions on serum t-PA concentrations. The pharmacokinetic model was then used to determine the optimal medication strategy for reaching target t-PA concentrations as fast as possible without overshooting target serum concentrations.

## METHODS

Simulations were performed using the Simbiology toolbox of MATLAB (Mathworks, Natick, Mass). In each simulation, t-PA activity was assumed to follow a 2-compartment model according to antigen activity. Such a 2-compartment model was shown to best fit experimental data<sup>10</sup> with t-PA infusion into plasma compartment, first-order elimination by the liver, and first-order transfer of t-PA to and from separate second compartments. The pharmacokinetic parameters that were used in the simulation were obtained from published literature<sup>9</sup> and were used in previous studies.<sup>8</sup> Pharmacokinetic parameters used in the simulation were volume of distribution of the central compartment (0.057 l/kg) and volume of distribution at steady state (0.11 l/kg). Drugs injected intravenously are removed from the plasma through 2 primary mechanisms: (1) the distribution to body tissues (elimination rate constant of the  $\alpha$ -phase = 9.45/h) and metabolism of t-PA (elimination rate constant of the  $\beta$ -phase = 1.039/h). The resulting decrease in the drug's plasma concentration follows a biphasic pattern. The micro elimination rate constant  $k_{21}$  was calculated as 1.34/h.<sup>8</sup>

A dose of 70 mg (0.9 mg/kg for a 78-kg person) of t-PA was applied by administering 10% of the dose as a bolus followed by the administration of 90% of the remaining dose over the course of 1 hour. The body weight was chosen arbitrarily, but it represents a

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common value. Simulations were performed to estimate the effects of different bolus-infusion delays and different durations of infusion interruptions. These simulations were then used to estimate the optimal dose of a second bolus that minimized the duration of decreased serum t-PA concentrations without overshooting the target serum concentrations of an undisturbed administration. This was done by starting the simulation with a second bolus dose of 0 mg and increasing the bolus dose by 0.01 mg until the target t-PA concentration of an undisturbed administration was exceeded. The last bolus dose that does not exceed the target t-PA concentration was selected as optimal dose of a second bolus. The second bolus is part of the cumulative dose of 0.9 mg/kg body weight.

## RESULTS

Using the known pharmacokinetic parameters of t-PA, we simulated serum t-PA concentrations for different durations of delays between bolus and infusion initiation in addition to the influence of a second bolus that was provided at the start of infusion (Fig. 1, Table 1). The left half of Table 1 shows the optimal doses of the second bolus that should be provided to allow for the target t-PA levels to be reached as fast as possible. The absolute dose of this second bolus is dependent on the duration of the delay and also on the body weight of the patient. A delay of more than 80 minutes after the initial bolus would require the reapplication of the full t-PA bolus.

An interruption in t-PA infusion was also observed to decrease serum concentrations severely. Therefore, a second bolus should be administered, followed by the immediate reinitiation of the infusion (Fig. 2, Table 1). The right half of Table 1 shows the optimal doses of the second bolus that should be provided in the case of an interruption in t-PA infusion. Because of the time-dependent saturation of the second compartment and the biphasic decrease in t-PA serum concentration, the time after which a full

dose of t-PA bolus should be given is dependent from the period over which the infusion continued.

## DISCUSSION

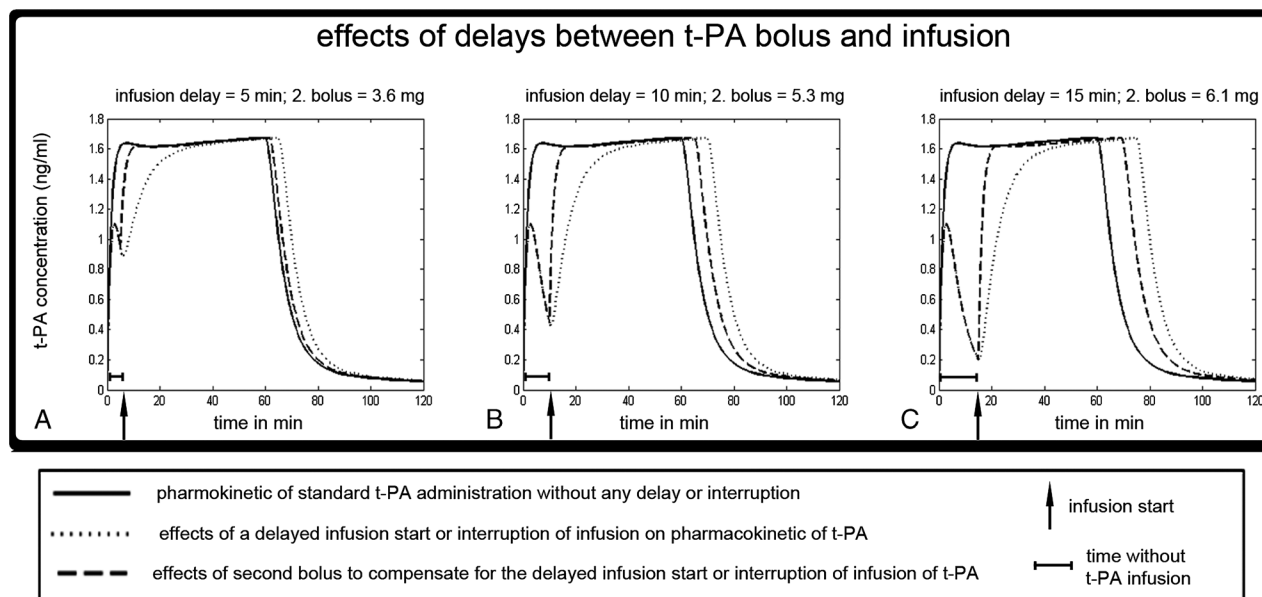
According to the pharmacokinetics of t-PA<sup>9</sup> and simulations that were performed with similar t-PA infusion delays,<sup>8</sup> we showed that bolus-infusion delays may significantly impact serum t-PA levels and may reduce the efficacy of thrombolysis. In accordance with previous reports,<sup>8</sup> we demonstrated that even short delays between bolus and infusion severely affected serum t-PA concentrations. We further demonstrated that such short delays or interruptions could potentially be handled with an additional bolus of t-PA to avoid long-lasting decreases in serum t-PA levels.

The reason for such a second bolus in addition to the standard application of the initial bolus is purely pharmacokinetic to ensure the rapid attainment of effective serum t-PA concentrations. One important prerequisite of any simulation was that the estimated second bolus, as shown in Table 1, does not increase serum t-PA concentrations above target levels.

We showed that the administration of the second bolus, as shown in Table 1, does not increase serum t-PA concentrations above target levels.

Any delay of the t-PA infusion prolonged the total time between t-PA bolus and the end of the infusion. The effects of such a prolonged time frame are not known and have not been investigated to date in any drug evaluation or clinical trials. The additional bolus could shorten this prolonged time frame because the infusion rate remained unchanged. This might prevent possible adverse effects by a prolonged time to the end of the infusion.

More importantly, a bolus-infusion delay causes a long-lasting reduction in the serum t-PA concentration compared with the undelayed start (Fig. 1). Up to now, it is not entirely clear whether the t-PA bolus should be injected as rapidly as possible in the case of a foreseeable delayed infusion start or whether the



**FIGURE 1.** The figure shows the effects of bolus-to-infusion delays on serum t-PA concentrations (delay: A, 5 minutes; B, 10 minutes; C, 15 minutes). The solid line in each plot shows the normal pharmacokinetics of t-PA if administered as recommended (bolus and immediate infusion start). The dotted line shows the effects of delays/interruptions without any additional bolus. The dashed line shows the effectiveness of an additional bolus in compensating for a delayed infusion start/interruption of infusion of t-PA. By giving the second bolus, the target t-PA concentration is reached (A, 5.8 minutes; B, 6.1 minutes; C, 6.0 minutes) after the application of the second bolus. Without an additional bolus (dotted line), t-PA concentration takes an asymptotic approach without reaching the target serum concentration of an undisturbed administration of t-PA.

**TABLE 1.** Recommendation for a Second Bolus in the Case of a Delay Between Bolus and t-PA Infusion Initiation (Left Half of Table) or an Interruption in t-PA Infusion (Right Half of Table)

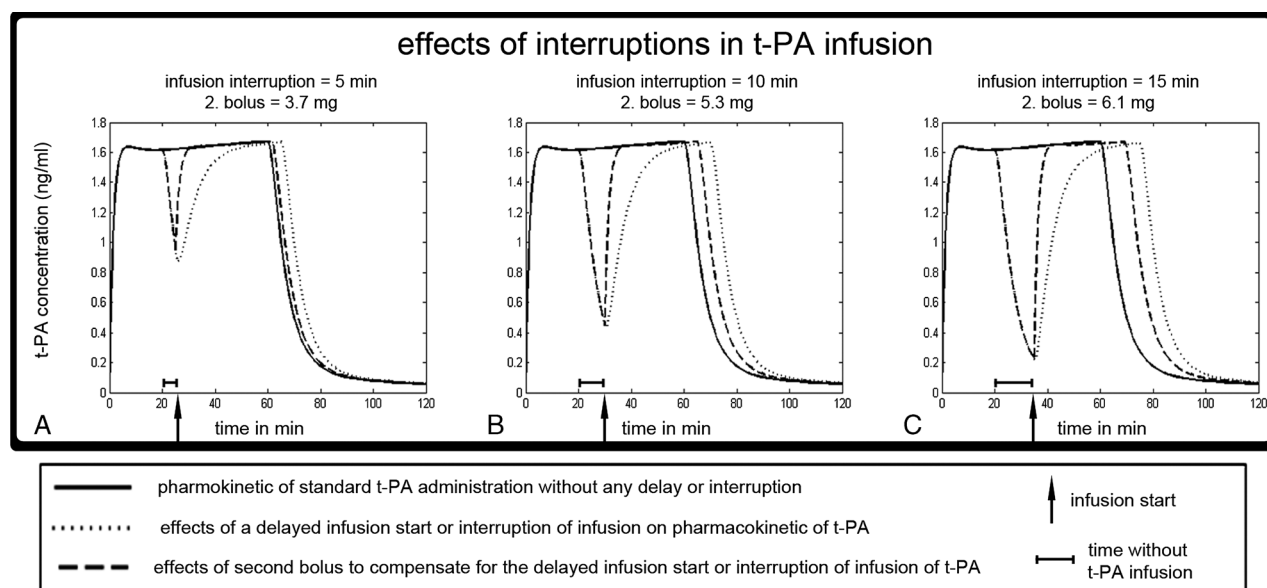
Time Delay/Interruption, min	Delayed Initiation of t-PA Infusion	Interruption in t-PA Infusion		
	Second Bolus, mg (78 kg)	Second Bolus, mg/kg	Second Bolus, mg (78 kg)	Second Bolus, mg/kg
1	0.9	0.0115	0.9	0.0115
2	1.8	0.0230	1.8	0.0231
3	2.5	0.0320	2.5	0.0320
4	3.1	0.0397	3.1	0.0397
5	3.6	0.0461	3.7	0.0474
6	4.1	0.0525	4.1	0.0526
7	4.5	0.0576	4.5	0.0577
8	4.8	0.0615	4.8	0.0615
9	5.1	0.0653	5.1	0.0654
10	5.3	0.0679	5.3	0.0680
11	5.5	0.0705	5.5	0.0705
12	5.7	0.0730	5.7	0.0731
13	5.9	0.0756	5.9	0.0756
14	6.0	0.0769	6.0	0.0769
15	6.1	0.0782	6.1	0.0782
16	6.2	0.0795	6.2	0.0795
17	6.3	0.0808	6.3	0.081
18	6.3	0.0808	6.4	0.0821
19	6.4	0.0820	6.5	0.0833
20	6.5	0.0833	6.5	0.0833

Body weights were capped at 100 kg for bolus estimations, and this value was used for subjects who exceeded this weight.

t-PA bolus should be injected later on but directly before the t-PA infusion. There is 1 case report demonstrating an at least partly successful thrombolysis because of a sole t-PA bolus.<sup>1</sup> However, the effects of a long-lasting reduced serum t-PA concentration

are not known but might severely affect the effectiveness of t-PA thrombolysis.

These results strongly suggest avoiding bolus-infusion delays. One possibility to circumvent any bolus-infusion delays is



**FIGURE 2.** The figure shows the effects of interruptions in the infusion of t-PA on serum t-PA concentrations (interruption: A, 5 minutes; B, 10 minutes; C, 15 minutes). The solid line in each plot shows the normal pharmacokinetics of t-PA if administered as recommended (bolus and immediate infusion start). The dotted line shows the effects of delays/interruptions without any additional bolus. The dashed line shows the effectiveness of an additional bolus in compensating for a delayed infusion start/interruption of infusion of t-PA.

the premixing of t-PA,<sup>11</sup> which additionally shortens the door-to-needle time. However, because of the high cost of t-PA, premixing should be reserved for cases where clinical symptoms strongly indicate an ischemic and not a hemorrhagic origin. In case of a delayed start of the infusion, there are only 2 possibilities left—do nothing or to give a second bolus. From the pharmacokinetic perspective, there seems to be no argument against the application of a second bolus because it reduces the time of a decreased serum t-PA concentration, while it simultaneously does not exceed the serum t-PA concentration over the target value of an undelayed infusion. We have estimated the dosing of the second bolus depending on the duration of the delay/interruption to allow for the achievement of appropriate serum t-PA concentrations (Table 1). The dosing of the second bolus is very similar for the interruption in t-PA infusion versus the delayed start of the infusion. This is caused by the fact that the bolus should counterbalance the distribution between the 2 compartments. An ideal dosed bolus should therefore lead to the same values for both situations (delayed start/interrupted infusion). Because of the interindividual variance in the volume of different tissue compartments at the same body weight, these small differences seem to be negligible in the clinical situation. Although clinical safety data are needed to recommend the application of a second bolus, the alternative of “do nothing” and accept a long-lasting decrease in t-PA concentration seems also not advisable. Therefore, we strongly suggest avoiding bolus-infusion delays by giving the bolus only when the infusion is ready.

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