Arch Neurosci. 2018 October; 5(4):e67359. doi: 10.5812/ans.67359.

Published online 2018 July 28. **Brief Report**

Intravenous Thrombolysis for Stroke in Patients Receiving Oral Factor Xa Inhibitors

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Received 2018 February 11; **Revised** 2018 July 12; **Accepted** 2018 July 25.

Abstract

We present 3 patients who were taking oral direct factor Xa inhibitors (ODFXIs) within 24 hours prior to receiving intravenous recombinant tissue plasminogen activator (IV rtPA) for acute ischemic stroke (AIS). Two patients were on Rivaroxaban (20 mg once daily) and one on Apixaban (2.5 mg twice daily). All 3 received IV rtPA within 3 hours of symptom onset. Their aPPT, PT and INR levels were within normal ranges. They all received the last dose of the ODFXI within the last 24 hours prior to IV rtPA administration. One patient underwent mechanical thrombectomy of a large vessel clot after IV rtPA. None had intracranial hemorrhage (ICH) on 24 hour head CT post IV rtPA. They all had acute infarcts on their brain MRI, diffusion weighted image. Although we had a very low number of patients in our case series, our findings suggest that neither IV rtPA nor the combination of IV rtPA and intra-arterial thrombolysis increases the risk of ICH in AIS patients who are taking ODFXIs and their coagulation parameters are within normal range.

Keywords: Intravenous Thrombolysis, Stroke, Factor Xa Inhibitors

1. Background

Non-vitamin K antagonist oral anticoagulants (known as novel oral anticoagulants (NOACs)) are more frequently being used as high quality data show that they are as effective as warfarin in stroke prevention in patients with non-valvular atrial fibrillation with lower rates of hemorrhagic strokes and better patient adherence (1). The most recent American Stroke Association statement on management of patients with acute ischemic stroke does not recommend the use of IV rtPA in patients with acute ischemic stroke (AIS) who were taking NOACs within 48 hours prior to the time of IV rtPA administration unless sensitive laboratory tests such as aPTT, INR, ECT, TT, or appropriate direct factor Xa activity assays are normal, due to a possible increase in the risk of bleeding complications, particularly intracranial hemorrhage (ICH) (2-7).

Only a few AIS patients who received IV rtPA and had been taking NOACs prior to the treatment have been reported thus far. The majority of these reports are about oral direct thrombin inhibitor, Dabigatran, since it was approved and available in the market earlier than the oral direct factor Xa inhibitors (ODFXIs) (8). We present 3 patients who were taking ODFXIs prior to receiving IV rtPA.

2. Methods

The medical records of the patients who received IV rtPA (0.9 mg/kg) for AIS at our tertiary academic medical center from January 2006 till August 2017 were reviewed retrospectively. Demographics and home medication list were abstracted for each patient. A subset of patients who were taking ODFXIs within 48 hours prior to IV rtPA administration was identified. Follow up head CT scans within 24 to 36 hours of IV rtPA administration were reviewed to determine the number of patients with ICH in this subset. We found 2 patients on Rivaroxaban (20 mg once daily) and one on Apixaban (2.5 mg twice daily). All 3 of them were on ODFXIs for non-valvular atrial fibrillation. One patient underwent mechanical thrombectomy of right middle cerebral artery (M1) clot after IV tPA administration. None had ICH on 24 hour head CT post IV rtPA. Table 1 shows the characteristics of the patients.

Table 1. Characteristics of the Patients Who Were Taking Oral Factor Xa Inhibitor

Patient No.	1	2	3
Age, y	88	64	86
Gender	M	M	F
NIHSS on admission	15	6	16
h/o DM	Yes	Yes	No
h/o A. Fib	Yes	Yes	Yes
PT/INR/APTT on admission	13.7/1.09/32.0	13.30/1.07/36.0	13.0/1.0/27.0
Creatinine clearance (mL/min)	90.28	102.66	20.45
Anticoagulant	Rivaroxaban	Rivaroxaban	Apixaban
Dosage	20 mg daily	20 mg daily	2.5 mg every 12 hour
Last dose to IV tPA interval time (hour)	5	12	24
Symptom onset to IV tPA time (min)	40	180	148
Infarct on post IVT brain MRI	Multiple areas in bilateral hemisphere	L-MCA	R-MCA
ICH	No	No	No
Discharge (mRS)	5	2	3

Abbreviations: A. Fib, atrial fibrillation; APTT, activated partial thromboplastin time; DM, diabetes mellitus; F, female; h/0, history of; ICH, intracranial hemorrhage; INR, international normalized ratio; IVT, intravenous thrombolysis; L, left; M, male; MCA, middle cerebral artery; mRS, modified rankin scale; NIHSS, national institute of health stroke scale; No., number; PT, prothrombin time; R, right.

3. Discussion

A computerized search in Medline, PubMed and Google Scholar till July 2016, revealed 12 reported cases of IV rtPA given for AIS in patients who were taking ODFXIs, 10 being on Rivaroxaban and 2 being on Apixaban. None of them developed ICH post IV thrombolysis (9-20). Combining our 3 cases with the 12 cases previously reported in the literature, we have 15 AIS patients who were taking ODFXIs within last 48 hours prior to receiving IV rtPA with no ICH.

ODFXIs may prolong the PT and aPTT, but these responses are not reliable enough to reflect the effect of the drug and the drug concentration. To date, no bedside tests are available that reliably assess the anticoagulatory effect of ODFXIs. Steiner et al. (21) recommend checking anti-factor Xa activity for making decision for or against thrombolysis, but performing those test are time consuming and the threshold which would allow "safe IV rtPA administration" has not yet been established. In addition, those tests are not widely accessible. In our patients, routine coagulation panel including INR, prothrombin time (PT) and partial thromboplastin time (aPTT) were within normal range and anti-factor Xa assays is not available in our center. In addition, among the previously published cases, 10 out 12 had normal coagulation and none of them developed ICH post thrombolysis. We suggest that until reliable and accessible tests exist, the anticoagulation effect of ODFXIs should be estimated by the coagulation panel including PT and aPTT assays as qualitative indices only. The other key consideration is the pharmacokinetics of the ODFXIs including the time since last dose of the drug, renal function and concomitant use of other drugs such as P-glycoprotein inhibitors. Peak plasma levels of the ODFXIs are observed about 2 - 4 hours after intake. They have short half-lives (Apixaban ~ 12 hours, Rivaroxaban 5 - 13 hours) and predictable pharmacokinetics with very few drug-drug and drug-food interactions (6). Although among the 15 cases discussed above some received IV rtPA within 6 hours of the last dose of the drug with no ICH after thrombolysis, we expect less anticoagulant effect with more prolonged time from the last of dose of drug.

Considering the small size of the patients in our case series and variable characteristics of the previously published cases, no solid general conclusion can be drawn about the safety of IV rtPA in AIS patients who were taking ODFXIs, but the favorable outcome of the patients in our series and previously published cases indicates that IV rtPA might be considered on an individual basis considering coagulation profile (PT, PTT), timing of the last dose of the drug, renal function, severity of the stroke, potential for alternative treatment and also availability of anti-factor Xa assays. We encourage other centers to look into their data and provide further information on the safety profile of IV rtPA in such patients.

Acknowledgments

We would like to thank Ms. Deborah A. Steck, RN, MS, CNS, SCRN for her valuable and constructive guidance for our data collection.

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