Safety of Intravenous Thrombolysis among Stroke Patients Taking New Oral Anticoagulants—Case Series and Systematic Review of Reported Cases

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Background: Current guidelines do not recommend the administration of intravenous tissue plasminogen activator (IV-tPA) to patients with acute ischemic stroke (AIS) who take new oral anticoagulants (NOACs). We present a multicenter case series of IV-tPA use while the patients are on NOACs, as well as a systematic review of the literature. *Methods:* We reviewed the medical records of consecutive patients on NOACs who received IV-tPA for symptoms of AIS at four participating stroke centers in the United States and Europe. Safety endpoints were post-thrombolysis symptomatic intracranial hemorrhage (sICH) or other serious systemic bleeding. *Results:* Between October 2010 and October 2014, 6 patients received IV-tPA for possible AIS while taking dabigatran. None of the patients had sICH or any other hemorrhagic complication. Literature review resulted in a total of 26 patients receiving IV-tPA while on NOACs (dabigatran: 15, rivaroxaban: 10, apixaban: 1). Among them, two patients experienced sICH and died. None of the patients experienced major extracranial hemorrhage; however, minor and asymptomatic hemorrhagic complications were described in 7 patients. Pooled analysis indicates an sICH rate of 6.45% (95% CI by the adjusted Wald method: .8-21.7%). The mean interval between the last dose of NOAC and IV thrombolysis was 12 ± 7.8 [4-28.3] hours. *Conclusions:* Although the safety of IV-tPA cannot be definitively confirmed in a small series, consideration of stroke severity and management of hemorrhage risk with general precautions with post-tPA management protocols

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can justify treatment in the absence of coagulopathy. **Key Words:** Acute ischemic stroke—anticoagulants—new oral anticoagulants—acute stroke therapy—thrombolysis—tPA—intracerebral hemorrhage.

Introduction

New oral anticoagulants (NOACs), also known as novel oral anticoagulants and nonvitamin K antagonist oral anticoagulants, are thought to lead to better therapeutic compliance because of lack of required monitoring. In addition, because of lower rates of systemic embolism, hemorrhagic stroke, and mortality associated with NOACs, use of these agents has continued to increase in routine practice.[1-5]

Intravenous tissue plasminogen activator (IV-tPA) is an approved treatment in acute ischemic stroke (AIS). Several comprehensive studies have been conducted on the safety of IV-tPA; however, most of the studies excluded patients on oral anticoagulants.[6,7] According to the American Heart Association (AHA)/American Stroke Association (ASA) guidelines, IV-tPA is indicated among patients taking warfarin with international normalized ratio (INR) less than 1.7.[8-10] However, much of the literature conducted regarding the safety of IV-tPA was performed prior to the approval of NOACs.

With the increasing use of NOACs, administration of IV-tPA to patients prescribed these agents who present with AIS symptoms can be a dilemma because of the increased risk of hemorrhagic transformation. The most recent AHA/ASA AIS guidelines do not recommend IV-tPA among patients taking direct thrombin inhibitors (e.g., dabigatran) or direct factor Xa inhibitors (e.g., rivaroxaban or apixaban) unless sensitive laboratory tests such as activated partial thromboplastin time (aPTT), INR, platelet count, thrombin time (TT), ecarin clotting time (ECT), or appropriate direct factor Xa activity assays are normal.[11] Despite AHA/ASA AIS guidelines, further studies debate the validity and availability of mentioned laboratory tests in screening for IV-tPA candidates.[12,13] Other factors, such as time elapsed since the last dose of NOAC, might affect the ultimate outcome of IV-tPA therapy.[14,15]

Since the first NOAC was made available in the United States in 2010, several case reports have been published examining the safety of IV-tPA among patients taking these agents. In the present study, we present a case series of patients who received IV-tPA while taking NOACs. We also performed a systematic review of similar published case reports and discussed the safety and factors affecting the risk of symptomatic intracranial hemorrhage (sICH) following IV-tPA in patients receiving NOACs.

Methods

Case Series

We reviewed the medical records of consecutive patients on NOACs who received IV-tPA for acute symptoms of ischemic stroke at four participating tertiary care stroke centers (University of Alabama Hospital, Birmingham, Alabama; Methodist University Hospital, Memphis, Tennessee; Methodist Germantown Hospital, Germantown, Tennessee; and Attikon University Hospital, Athens, Greece). Although the current use of NOACs is one of the exclusion criteria in our centers, these patients inadvertently received IV-tPA because there was no knowledge of their NOAC intake before the tPA administration. Every patient had a magnetic resonance imaging (MRI) of the brain in addition to a pre- and post-(24-hour) IV-tPA computed tomography (CT) scan of the head. The inclusion and exclusion criteria are listed in Table 1. The primary outcome of this case series was to evaluate the safety of IV-tPA administration in those receiving NOACs. Safety endpoints were post-thrombolysis sICH or serious systemic bleeding. The section *Outcome and Complication*

Table 1. *Inclusion and exclusion criteria for our case series*

Inclusion criteria:
Patients who
a presented to the hospital with acute focal neurological deficit.
b was under treatment with NOACs.
c was otherwise candidate for IV thrombolysis and received IV-tPA.
Exclusion criteria:
Patients in whom
a the post-tPA MRI was negative for an acute stroke or the final diagnosis was a stroke mimic.

Abbreviations: IV-tPA, intravenous tissue plasminogen activator; MRI, magnetic resonance imaging; NOAC, new oral anticoagulant.