ΕΝΔΟΦΛΕΒΙΑ ΘΡΟΜΒΟΛΥΣΗ ΣΕ ΟΞΥ ΙΣΧΑΙΜΙΚΟ ΕΓΚΕΦΑΛΙΚΟ ΕΠΕΙΣΟΔΙΟ ΕΠΕΙΤΑ ΑΠΟ ΑΝΑΣΤΡΟΦΗ ΤΟΥ DABIGATRAN ΜΕ IDARUCIZUMAB

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Περίληψη

Εισαγωγή: Η ενδοφλέβια θρομβόλυση (IVT) με ενεργοποιητή ανασυνδυασμένου ιστικού πλασμινογόνου (rt-PA) για τη θεραπεία του οξέος ισχαιμικού εγκεφαλικού επεισοδίου αντενδείκνυται σε ασθενείς που λαμβάνουν αναστολείς παράγοντα Χα είτε άμεσους αναστολείς θρομβίνης. Το Idarucizumab αναστρέφει πλήρως τη βιολογική επίδραση του dabigatran μέσα σε λίγα λεπτά.

Αναφορά περίπτωσης: Με το παρόν, παρουσιάζουμε την περίπτωση ενός άνδρα 65 ετών σε θεραπεία με dabigatran με σοβαρό οξύ ισχαιμικό εγκεφαλικό επεισόδιο και κατά τα άλλα κατάλληλο για θεραπεία με rt-PA. Χορηγήθηκε idarucizumab και ο ασθενής στη συνέχεια υποβλήθηκε σε θεραπεία με IV rt-PA. Παρά την IVT, η κλινική κατάσταση του ασθενούς επιδεινώθηκε και εμφάνισε έμφρακτο στην περιοχή της αριστερής μέσης εγκεφαλικής αρτηρίας με αιμορραγική μετατροπή.

Συμπέρασμα: Πρόσφατα η ενδοφλέβια rt-PA προτείνεται ως θεραπεία σε ασθενείς με οξύ ισχαιμικό εγκεφαλικό επεισόδιο υπό αντιπηκτική αγωγή με dabigatran μετά την αναστροφή με idarucizumab. Υπάρχουν ελάχιστα αναφερόμενα δεδομένα και δεν υπάρχουν μελέτες μεγάλης κλίμακας για την αποτελεσματικότητα και την ασφάλεια της IVT μετά την αναστροφή του dabigatran. Απαιτούνται περαιτέρω μελέτες και δεδομένα σχετικά με τα αντίδοτα και τη χρήση του rt-PA.

Λέξεις ευρετηρίου: ενδοφλέβια θρομβόλυση, αναστροφή dabigatran, idarucizumab

INTRAVENOUS THROMBOLYSIS IN ACUTE ISCHEMIC STROKE AFTER DABIGATRAN ETEXILATE REVERSAL WITH IDARUCIZUMAB

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Abstract

Background: Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA) for acute ischemic stroke treatment is contraindicated in patients who are actively taking either Factor Xa inhibitors or direct thrombin inhibitors. Idarucizumab completely reverses the biologic effect of dabigatran within minutes.

Case Presentation: Hereby, we present the case of a 65 old male on active dabigatran treatment with a severe acute ischemic stroke and otherwise eligible for rt-PA treatment. Idarucizumab was administered and the patient was subsequently treated with IV rt-PA. Despite the IVT, the patient's clinical condition deteriorated and he developed a left middle cerebral artery territory infarct with hemorrhagic transformation.

Conclusion: Recently intravenous rt-PA has been suggested as a treatment in acute ischemic stroke patients anticoagulated with dabigatran after the reversal with idarucizumab. There are little reported data

and no large scale studies of the efficacy and safety of IVT after dabigatran reversal. Further studies and register data are needed to provide additional information regarding the antidotes and the use of rt-PA.

Key words: intravenous thrombolysis; reversal dabigatran; idarucizumab

Background

Patients with atrial fibrillation are routinely treated with newer oral anticoagulants (NOAC). Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) for the treatment of acute ischemic stroke is contraindicated in patients actively treated with NOAC (either Factor Xa inhibitors or direct thrombin inhibitors) [1]. Idarucizumab (PraxbindTM is a fragment of a monoclonal antibody developed as a specific antidote for dabigatran. It binds dabigatran with high affinity, reversing its anticoagulant effects in a few minutes [2]. We present here the case of a patient who suffered an acute ischemic stroke during active dabigatran treatment and was otherwise eligible for treatment with IV rt-PA.

Case presentation

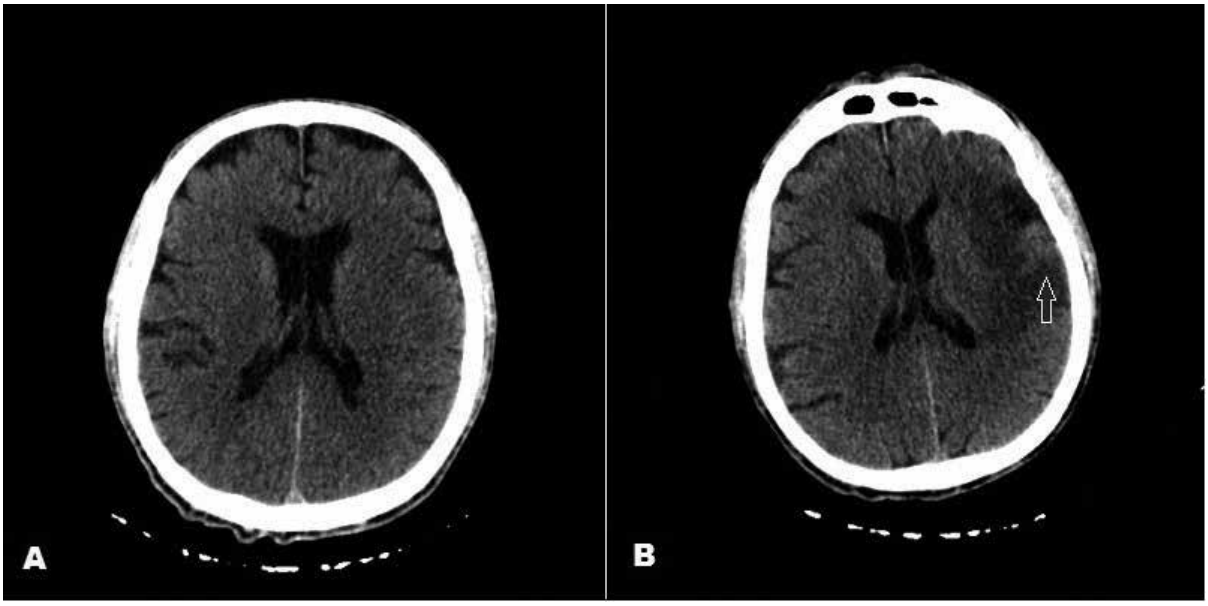
A 65-year-old male patient with a history of gastrointestinal malignancy and paroxysmal atrial fibrillation (PAF) was hospitalized in our clinic due to a transient ischemic attack (TIA) in the left middle cerebral artery territory (right hemiparesis and dysphasia). Blood testing, color-coded duplex ultrasound for large vessel atherosclerosis, and transcranial Doppler were unrevealing. The patient was treated with rivaroxaban (20 mg) at that point. Presumably, PAF was the cause of the TIA, and since dabigatran has a different mode of action than rivaroxaban, treatment was resumed with dabigatran 150mg bid.

Three days later the patient was admitted to our hospital with sudden-onset (45 minutes before admission) aphasia and severe right hemiparesis. Neurological examination revealed somnolence, severe right-sided paresis of the face, arm, leg, and severe aphasia. The NIHSS total score was 16. The patient had taken his last dabigatran capsule 7 hours before the onset of the stroke.

Acute computed tomography (CT) of the brain excluded intracranial hemorrhage, early features of ischemia, or other intracranial pathologies such as a tumor. CT angiography showed no relevant occlusion of the brain-supplying vessels. On admission, the prothrombin time was 16 seconds (normal range: 11-15 sec), and the activated partial thromboplastin time (aPTT) was 37.2 seconds (normal range: 20-36 sec). Other routine laboratory values, including creatinine, were normal.

Idarucizumab 5 g was given to the patient intravenously over 5 minutes to neutralize the anticoagu-

Figure 1. A) Non-contrast axial CT brain scan at the admission with normal findings, B) Non contrast axial CT brain 24h after IVT showing left MCA infarct with hemorrhagic transformation (red arrow)



lant effect of dabigatran. Immediately thereafter, intravenous thrombolysis was initiated with 50 mg rt-PA, equivalent to 0.9 mg alteplase/kg body weight (door to needle 120 min, onset to treatment 165 min). The aPTT measured after initiation of IVT was 32.3 seconds.

Brain CT scan 3 hours after the alteplase infusion was normal. Brain CT at 24 hours demonstrated a left middle cerebral artery (LMCA) area infarct with hemorrhagic transformation. Unfortunately, the patient's clinical condition deteriorated with global aphasia and hemiplegia (NIHSS: 23). On day 7, the NIHSS was still 23, and the new brain CT scan still demonstrated the hemorrhagic transformation of the infarct.

Conclusions

As the prescription of NOAC increases, the management of stroke on NOAC therapy is an issue. These patients exhibit an increased risk for ischemic stroke, despite the NOAC treatment. Current guidelines recommend that thrombolytic therapy should not be given within 48 hours of the last administration of NOAC [1]. Idarucizumab is a specific reversal agent for dabigatran and binds thrombin with a 350-fold higher binding affinity than dabigatran. Idarucizumab inverts the biological effect of dabigatran and achieves almost immediate reversal of anticoagulation [2].

IVT therapy with rt-PA was suggested after using idarucizumab in acute ischemic stroke patients anticoagulated with dabigatran [3]. The recommendation was based on limited data of a few case studies and systematic reviews [4-6]. A study investigating intravenous thrombolysis for stroke after reversal of dabigatran treatment with idarucizumab reported clinical improvement in 45 (81.9%) of 55 patients, whereas unfavorable outcomes were observed in 6 patients including 3 patients with hemorrhagic transformation and clinical deterioration or death [4]. Another retrospective study showed favorable outcome (median NIHSS improvement of 5 points) in 15 of 19 patients and no hemorrhagic transformation was reported [5]. Real-world data seem to suggest that this treatment is safe and effective, although the possibility of adverse events such as thrombosis, hemorrhage and clinical deterioration or death, as described in some reports [4-7], must be considered.

Our patient had an extensive infarction of the left MCA territory as a result of PAF. It is true that cardioembolic and large infarcts tend to undergo hemorrhagic transformation [8]. Thus, we cannot determine whether our patient's infarct hemorrhaged due to the size and type of infarct or due to the lack of idaricizumab's efficacy. Finally, the patient was hospitalized in our clinic for 20 days and discharged to a rehabilitation center. CT Scans showed gradual regression of hemorrhagic transformation and the patient restarted apixaban 5mg bid on day 20. The modified Rankin score was 4, 3 months after stroke.

We believe this case report provides useful information on patients with acute ischemic stroke treated with dabigatran and adds to the current literature. Large-scale trials regarding IVT therapy after reversal with idarucizumab in acute ischemic stroke should be conducted considering unfavorable outcomes such as thrombotic events, hemorrhagic transformation, and mortality to investigate potential concerns about the safety and efficacy of this treatment.

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