Use of Idarucizumab in Ischemic Stroke: A National Experience in a Middle Income Country and a Concise Review.

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Case Report

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USE OF IDARUCIZUMAB IN ISCHEMIC STROKE: A NATIONAL EXPERIENCE IN A MIDDLE INCOME COUNTRY AND A CONCISE REVIEW.

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Abstract

Background: Despite receiving anticoagulation for primary or secondary prevention for atrial fibrillation, new embolic events may occur. Current stroke guidelines contraindicate the use of thrombolysis if oral anticoagulants are used within 48 hours of symptom onset. Idarucizumab may be an alternative for patients receiving dabigatran with an acute stroke when alteplase is indicated. We present a series of four cases of patients who received idarucizumab in neurological emergencies in a middle-income country in Latin America.

Methods: Using the national pharmacologic surveillance data, we retrospectively collected the cases of idarucizumab used in acute stroke, including retinal thrombosis in Colombia between 2018 and 2020.

Results: Four male patients with atrial fibrillation received thrombolysis for acute stroke, and two of them received mechanical thrombectomy. No major complications during hospitalization were present. One of the patients that received combined therapy presented with hematuria; the other

patient that received thrombolysis presented with groin hematoma, but none required transfusion. All had favorable mRS at discharge and 90-day follow-up.

Conclusion: The use of thrombolysis after reversal with idarucizumab in patients with ischemic stroke is safe. Our patients presented favorable mRS at discharge and 90-day follow-up. The low number of cases is related to the poor availability of idarucizumab. Only 11 hospitals in 5 cities have storage of the medication. Stronger public policies are needed to guarantee optimal stroke treatment in patients with atrial fibrillation receiving anticoagulation, including access to reversal and reperfusion therapies to reduce further disability, especially in a middle-income country such as Colombia.

Keywords: stroke, atrial fibrillation, thrombolysis, thrombectomy, Latin America, anticoagulation

Background

Worldwide, atrial fibrillation (AF) accounts for 15% to 30% of ischemic strokes (1). Nonetheless, there is a dearth of data on the general use of anticoagulants, atrial fibrillation, and stroke in Latin America, where atrial fibrillation is estimated to account for 13% of the population over the age of 70. (2). In 2014, a cross-sectional study of administrative data revealed that 1.310 people received direct oral anticoagulant (DOACs) therapy in a database of 6.5 million people affiliated with the Colombian Health and Social Security System. Rivaroxaban was used in 53.1 percent of cases, dabigatran was used in 44.6 percent of cases, and apixaban was used in 2.3 percent of cases (3). Other local studies in a high-level hospital between 2008 and 2013 revealed use of warfarin (71.2%), enoxaparin (5%), rivaroxaban (14.8%), dabigatran (8.2%), and apixaban (0.8%) (4).

Historically, vitamin K antagonists (VKA) were the first line of anticoagulation treatment for patients with atrial fibrillation as a stroke prevention strategy due to their beneficial effect on mortality and disability (5). DOACs, on the other hand, have demonstrated non-inferior efficacy to VKA in patients with non-valvular atrial fibrillation (NVAF) (6). This is why the FDA approved rivaroxaban, apixaban, dabigatran, and edoxaban for the purpose of preventing stroke in patients with NVAF. Unlike VKA, DOACs have a broad therapeutic window, do not require frequent dose adjustment, and have few known interactions with food and other pharmacological groups. Nonetheless, DOACs lacked agents capable of rapidly, precisely, and safely reversing their effect. As a result, particular emphasis has been placed on developing specific agents capable of reversing DOAC's anticoagulant effect. As a result, andexanet alfa, idarucizumab, and ciraparantag have been evaluated for their potential use in reversing the effects of direct anticoagulants (7). Idarucizumab is a humanized monoclonal antibody fragment that has a high affinity and specificity for dabigatran and is capable of rapidly reversing anticoagulant activity (8). These drugs have been most frequently used in emergency situations for hemorrhage or urgent surgery. However, the pivotal trials excluded the possibility of using the drug in patients with ischemic stroke. It was quickly used in this clinical scenario prior to thrombolysis and

thrombectomy. Concerns about its efficacy and safety in these patients were raised, but individual case reports and small case series quickly reported a possible use in this subgroup of patients. Additionally, some cases of reperfusion combined therapy (intravenous thrombolysis plus thrombectomy) following idarucizumab reversal have been reported with favorable preliminary results (9). We describe the use of idarucizumab prior to reperfusion procedures in four cases of ischemic stroke in Colombia where access to this medication is still limited. See figure 1.

Cases presentation

Between 2018 and 2019, four male patients aged 64 to 79 years presented to the emergency department of three institutions in Colombia, two in Bogotá and one in Cali, due to neurological deficits. Each patient had a previous modified Rankin scale (mRS) score of 0, a history of AF, and was receiving dabigatran anticoagulation. Two patients presented with severe National Institute of Health Stroke Scale (NIHSS) 21 and 22, while the remaining two presented with mild to moderate stroke (2 and 9). All patients received thrombolysis following reversion to idarucizumab. In 3/4 of cases, a prolonged time from door to needle (> 60 minutes) was observed. Two patients required mechanical thrombectomy, which took 200 and 260 minutes from door to groin, respectively. In one patient, an asymptomatic hemorrhagic transformation was observed. Inpatient care lasted between six and fourteen days. Two patients developed mild complications as a result of hematuria and a groin hematoma that did not necessitate transfusion or intervention. All patients were discharged with an NIHSS score of 1 to 5 and an mRS score of 1 to 2. The patients did not experience any new neurological events or mRS deterioration during the 90-day follow-up period. Table 1 contains detailed characteristics of clinical cases.

Discussion

We describe the safe use of an anticoagulation reversal agent in neurological emergencies in Latin America. The disparity in access to health care in this part of the world creates significant barriers to stroke prevention, care in specialized centers, and access to safe reversal strategies when indicated. Anticoagulant therapy with VKA or DOACs reduces the risk of AF-related thromboembolic events. However, between 1% and 2% of patients with NVAF who are anticoagulated with DOAC have an ischemic stroke (10,11). Nonetheless, patients who have been chronically anticoagulated with any agent have been excluded from intravenous thrombolysis and mechanical reperfusion trials. Thrombolysis was considered, however, if the prothrombin time (PT) was less than 1.5 during VKA therapy or if the last dose of DOAC was administered within the previous 12-24 hours with a normal glomerular filtration rate (11). Other studies justified its use when the last dose was administered 12 hours prior to the event or when a Thrombin Time (TT) of 38 seconds and a PTTa of less than 37 seconds were obtained (12).

Because serum DOAC levels are not routinely determined in clinical practice, the need for specific DOAC reversers was generated. Idarucizumab is a monoclonal antibody fragment that rapidly reverses the effects of dabigatran and has been shown to be effective and safe in patients requiring emergency surgery or bleeding (12,13). Nevertheless, none of the REVERSE-AD cohort patients received thrombolysis or mechanical reperfusion therapy for stroke. Around 225 patients have been reported to have received thrombolysis prior to reversal with idarucizumab since 2016, but only 35% of them received mechanical thrombectomy. Even fewer patients receive combined therapy (see table 2). Thrombotic complications occurred up to 30 days after follow-up in the REVERSE-AD. Nonetheless, the presentation rate of these complications was low in the reported cases, and no thrombotic complications occurred during the three-month follow-up period following idarucizumab administration. However, these events, particularly in patients with cardioembolic strokes, may be related to the prothrombotic risk associated with AF per se (11).

The average NIHSS score at admission was ten points in the cases reported, with 90 percent of patients presenting with a moderate to severe stroke, two of them with non-severe hemorrhagic complications. One patient was admitted with an NIHSS score of 21, was discharged with an NIHSS score of 2, and was followed for three months. Hematuria was present in this patient, but there were no cystoscopic abnormalities. Another patient presented with an inguinal hematoma at the puncture site, which had no effect on functional outcome but resulted in an additional ten days in the hospital. Table 2 compares clinical and demographic data of the reported cases with the series published so far as we know.

Due to a paucity of published information on anticoagulation and reversal agents in our country, we conducted a survey of general practitioners, medical students, residents, and members of various medical specialties to ascertain their knowledge of DOACS and its use in an emergency. 34.4 percent of the 337 respondents were general practitioners, 35% were specialists, 21.1 percent were residents, and 9.5 percent were medical students. Internal medicine physicians comprised 17.3 percent of specialists and residents, followed by neurologists at 13.9 percent, emergency medicine practitioners at 5.8 percent, intensive care unit physicians at 3.4 percent, cardiologists at 2.4 percent, anesthesiologists at 3.1 percent, and other internal medicine subspecialties at 2.4 percent. 7.8% were from other medical specialties. 56.7 percent worked in a private academic hospital, 19.3 percent in a public academic hospital, 19 percent in a private non-academic hospital, and 5% in a public, non-academic hospital. In general, 99 percent of respondents were familiar with warfarin, 95.5 percent with rivaroxaban, 93.2 percent with apixaban, and 91.6 percent with dabigatran, but only 32.3 percent with edoxaban. Globally, 95.5 percent of people were aware of specific anticoagulant antagonists; 73.9 percent were aware that dabigatran has a specific antagonist, but only 72.6 percent were aware of the specific name. When asked about the antagonist name for dabigatran in a hemorrhagic situation, 75.2 percent correctly identified idarucizumab as the indicated treatment. Despite this, only 23.6 percent of hospitals have idarucizumab on hand, 27.8 percent have VII factor, 44.4 percent have prothrombin complex, 60.4 percent have cryoprecipitate, and 34.9 percent are unaware of these

drugs' availability. 24.3 percent of 337 patients had used Idarucizumab in an emergency situation, with the most common indications being digestive bleeding, hemorrhagic stroke, trauma, or previous surgical intervention. The medication's limited availability may explain why idarucizumab is rarely used in Colombia. According to national pharmacologic surveillance data for Idarucizumab in Colombia, only 11 private institutions have access to this medication in the form of limited units of ampoules (Figure 1). Additionally, it requires a customized electronic formulation for public and private healthcare users, adding to the burden of obtaining the medication.

Finally, a significant question that arises when a patient is discharged is how to manage secondary prevention to minimize the risk of new events. Numerous patients in the case series did not provide information about post-stroke management in the presence of dabigatran. Nonetheless, the switch to a direct factor Xa inhibitor is common, despite the lack of evidence from prospective studies. Thus, in the presence of NVAF and a history of intracranial hemorrhage and a contraindication to anticoagulation or recurrent stroke, percutaneous closure of the left atrium may be considered (12, 13).

Idarucizumab is still unavailable in a number of centers, illustrating the disparity in access to care services within a developing country's health system, such as Colombia. Nonetheless, it has become a viable option for anticoagulated patients with a thrombolysis indication when available. It has been performed safely and with a low complication rate in patients with moderate to severe NIHSS. Nonetheless, additional public policies are required to ensure the availability of idarucizumab in developing countries in order to reduce stroke-related disability.

List of abrevation

AF: Atrial fibrillation

DOAC: direct oral anticoagulant

CRA: Central retinal artery

ICU: Intensive Care unit

MCA: Middle cerebral artery

mRS: modified rankin scale

N.A: not available

NIHSS: National Institute of Health Stroke Scale

NVAF: non-valvular atrial fibrillation

PTP: partial time of thromboplastine

TICI thrombolysis in cerebral infarction

VKA: vitamin K antagonist

Declarations

Ethics approval and consent to participate:

All patients included in this study were registered with the institutional stroke registry at Fundación Valle del Lili, Fundación Santa Fé de Bogotá, and Clínica del Country. Protocols that have been evaluated and approved previously by the Institutional Review Board (IRB).

Consent for publication

All patients consented for publishing their information.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

No funds were used to perform this study.

Authors' contributions

JR: conceived and presented idea. Wrote first manuscript, made search strategy

AA: wrote first manuscript, developed and applied survey

HB: contributed clinical information on patients, reviewed manuscripts

EJ: contributed clinical information on patients, reviewed manuscripts

PA: conceived idea, followed up patients, revised final manuscript

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273 Tables and figures.

274 **Table 1. Patients with ischaemic stroke treated with idarucizumab: characteristics and clinical**
275 **outcomes**

	Patient 1	Patient 2	Patient 3	Patient 4
Year	2018	2019	2019	2018
Gender	Male	Male	Male	Male
Age	67	64	69	79
Comorbidities	Parkinson disease Heart failure	Previous stroke Dyslipidemia Smoker	Hypertension Bradi-tachy syndrome	Hypertension
Atrial fibrillation				
Type	Paroxysmal	Paroxysmal	Permanent	Paroxysmal
CHA2DS2-VASc	4	5	5	5
Dabigatran				
Dose (mg/day)	300	300	300	300

Last intake (h)	6	22	7	10
Stroke				
Previous mRS	0	0	0	0
Occluded artery	Left MCA	CRA	Right MCA	Left MCA
Last known well (min)	120	130	73	120
Arrival NIHSS	21	2	9	22
PTT (sec)	39	-	42	38
Reperfusion therapy				
IV thrombolysis	Yes	Yes	Yes	Yes
Mechanical thrombectomy	Yes	No	No	Yes
Door-to-needle (min)	59	130	75	220
Door-to-groin (min)	200	-	-	260
TICI scale	3	-	-	3
Hemorrhagic transformation	No	No	No	HI 1

Inpatient care				
Global stay	14	7	6	10
ICU stay	5	2	2	2
30-day systemic thrombosis	No	No	No	No
30-day systemic hemorrhage	Hematuria	No	Hematoma*	No
Discharge NIHSS	2	2	1	5
Discharge mRS	2	2	1	1
Follow up				
90-day NIHSS	2	2	0	N.A
90-day mRS	2	2	0	N.A
Secondary prevention	Apixaban	Dabigatran	N.A	Dabigatran

MCA= Middle Cerebral Artery, IV= intravenous, TICI= Thrombolysis in Cerebral Infarction, ICU: Intensive Care Unit, NIHSS: National Institute of Health Stoke Scale, mRS: Modified Rankin Scale, NA: not available, CRAO= central retinal artery occlusion, *Groin hematoma.

280 **Table 2. Summary of reported cases of idarucizumab prior to stoke reperfusion therapies**

Author	**Šaňák et al.**	**Barber et al.**	**Pretnar et al.**	**Kermer et al.**	**Synthesis of Isolated Reported Cases**
n	13	51	19	80	62
Country	Chech Republic	New Zeland	Slovenia	Germany	Multiple
Age (y), mean ± SD	70.0 ± 9.1	73.3 (12.2)	75 (11.2)	75.9 (10.7)	73 (9.7)
Males, n (%)	7 (53)	37 (72.5)	10 (53)	51 (67.3)	36 (58)
Arterial Hypertension, n (%)	12 (92.3)	-	14 (74)	-	41 (66)
Diabetes mellitus, n (%)	4 (30.1)	-	1 (5)	-	13(20)

Ischaemic Heart Disease, n (%)	6 (46.2)	-	-	-	7 (11)
Atrial Fibrillation, n (%)	11 (84.6)	-	-	-	57 (91)
Hyperlipidemia, n (%)	6 (46.2)	-	-	-	-
Previous Stroke, n (%)	-	-	2 (11)	-	14 (22)
CHA2DS2–VASc, mean ± SD	-	-	3 (4)	-	5 (1,2)
Admission NIHSS, median (range)	7 (3-23)	8 (5–17)	9 (18)	9.7 (5.1)	10 (7,5)
Dabigatran dosage					
Dabigatran 150 mg BID, n (%)	8 (61.5)	-	7 (37)	32 (25.6)	26 (41.9)
Dabigatran 110 mg BID, n (%)	5 (38.5)		12 (63)		29 (46.7)
Dabigatran 75 mg BID, n (%)	-		-		2 (3.2)

Dabigatran, dosage unknown, n (%)	-		-		5 (8.0)
Proximal Vessel Occlusion, n (%)	-	-	-	-	25 (40.4)
Admission aPTT (s), mean ± SD	38.1 ± 27.8	-		42.7 (15.1)	37.7 (20.8)
aPTT above normal, n (%)			15 (78)		
Admission TT (s), mean ± SD	-	-	-	104.5 (63.9)	112 (53)
The interval between the last intake of DB and stroke onset (min), mean ± SD	291 ± 235	-	-	-	300±343

rTPA full dose	-	-	-	-	50 (80)
rTPA diminished dose	-	-	-	-	8 (12.9)
Tenecteplase	-	-	-	-	1 (1.6)
Not specified	-	-	-	-	4 (6.4)
Door-to-needle time, min; n (%)	-	83 (54–110)*	-	-	73 (38.2)
Mechanical Thrombectomy, n (%)	1 (8)	8 (16.7)	12 (63)	6	8 (12.8)
Door-to-groin time (T1, T2, T3) min	-	-	-	-	103, 110, 374
90-d good clinical outcome (mRS score 0-2), n (%)	10 (76.9)	-	16 (84)	-	
Dabigatran restarted, n (%)	10 (70)	-	-	-	22 (35.4)
Apixaban started, n (%)	3 (30)	-	-	-	5 (8)

Discharge good clinical outcome (mRS score 0-2), n (%)	-	-	-	-	40 (64)
Recurrent Stroke, n (%)	2 (15.4)	-	-	-	2 (3.2)
Other Thrombotic events, n (%)	None	None	-	-	2 (3,2)
ICH on control CT or MRI, n (%)	2 (15.4)	-	4 (21)	-	5 (8)
SICH on control CT or MRI after 24 h, n (%)	1 (7.7)	2 (3.9)	1 (5)	-	2 (3.2)
Other bleeding complications	None	-	-	-	None
Mortality, n (%)	3 (23.1)	3 (5.9)	2 (10)	-	2 (3.2)

281

282

Figure 1. Distribution map of cities and centers with availability of Idarucizumab in Colombia according to the Idarucizumab surveillance program in Colombia. The number indicates the total center with availability of the drug.