DOSE ADJUSTMENT WITH CLOPIDOGREL ORAL SOLUTION IN HYPER-RESPONDERS PATIENTS WITH INTRACRANIAL ANEURYSMS TREATED WITH STENT AND IDENTIFICATION OF CYP2C19 POLYMORPHISMS.

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BRACKGROUND AND AIMS:

The growing use of intracranial stents and flow diverting devices for intracranial aneurysm has come a growing need for the neurointerventional community to understand the pharmacology of medications used for modifying platelet function, as well as the testing methodologies available. In this context our goal is to describe the individualization of dose adjustments with clopidogrel oral solution in hyper-responders patients with intracranial aneurysm treated with stent.

EPIDEMIOLOGY	TOTAL N=15 (%)	UNRUPTURED N=12(%)	RUPTURED N=3(%)
Age (years)	53 (48-60)	52 (48-60)	55 (51-59)
Gender (M/F)	5 (33%) /10 (66%)	2 (16.7%)/10 (83.3%)	3 (100%)0
mRs [Median/IQR]	0 (0-0)	0 (0-0)	0 (0-0)
Diabetes	1 (6.7%)	1 (8.3%)	0
Hypertension	9 (60%)	7 (58.3%)	2 (66.7%)
Current smoker	4 (26.7%)	2 (16.7%)	2(66.7%)
Dyslipidemia	3 (20%)	4 (33.3%)	1 (33.3%)
Coronary artery disease	3 (20%)	2 (16.7%)	1 (33.3%)

METHOD:

Prospective study (from 2015 thru June 2017) in patients taking clopidogrel prior to endovascular treatment. Platelet reactivity after clopidogrel therapy was evaluated with the VerifyNow PRU Test. Initial values less than 60 PRU (P2Y12 reactivity units) were classified as a hyper-response. Patients were treated with clopidogrel for 7-10 days before stent treatment. Patients with SAH received a clopidogrel loading dose of 300 mg the night before. Adjustments to the dose with clopidogrel oral solution (1 ml = 5 mg) were made according as needed to reach the target PRU range. PRU determinations were made 123 times. The dose of clopidogrel oral solution was gradually reduced (30 mg, 20 mg, 10 mg, 5 mg) until 1 ml (5 mg) /day. Characterization of the most common allelic variants of CYP2C19 was carried out in patients.

RESULTS:

Fifteen patients with 16 aneurysm (treated with 15 stents: 11 flow diverter, 4 intracranial stent) were classified as having a hyper-response to clopidogrel. Mean age was 55.2 yo (range 42-64) and 71.4% were women. Mean baseline PRU value and the percentage of platelet inhibition were 8.57±11.5 PRU and 92.05±7.5% respectively. The mean time used to decrease the dose of clopidogrel oral solution to 5 mg/day was 13 days in SAH patients and 32±14.1 days in the other patients. Modified dosing strategies showed to increase the final PRU values and decreased the percentage of platelet inhibition (137.42±27.4 and 41.5±14.8%) and subsequently decreased their risk of bleeding. On angiographic follow-up, there was a 81.25%% rate of complete aneurysm occlusion observed at 6 months. No patients suffered thromboembolic events related to the dose adjustment of clopidogrel with 5 mg/day in the follow up. 10 patients were ultrarapid metabolizers (17:17, 1: 17), 3 extensive (1:1) and 2 patients intermediate-poor metabolizers (1:2 , 2: 2).

PATIENT Ruptured Unruptured	STENT (TYPE)	BLEEDING COMPLICATIONS	OCCLUSION RATE FOLLOW-UP (MONTH)	PATIENT Ruptured Unruptured	STENT (TYPE)	BLEEDING COMPLICATIONS	OCCLUSION RATE FOLLOW-UP (MONTH)	PATIENT Ruptured Unruptured	STENT (TYPE)	BLEEDING COMPLICATIONS	OCCLUSION RATE FOLLOW-UP (MONTH)
	ELVIS CLOSED-CELL	SAH EPISTAXIS URETRAL BLEEDING	COMPLETE (18)		PIPELINE FLOW DIVERTER	SAH POST-TREATMEN T	COMPLETE (6)		PIPELINE FLOW DIVERTER	NO	COMPLETE (6)
	SOLITAIRE CLOSED-CELL	NO	PENDING		PIPELINE FLOW DIVERTER	NO	COMPLETE (6)		NEUROFORM ATLAS OPEN-CELL	NO	COMPLETE (6)
	FRED FLOW DIVERTER	NO	PARTIAL (5)		NEUROFORM ATLAS OPEN-CELL	NO	COMPLETE (6)		FRED FLOW DIVERTER	METRRORRHAGIA	COMPLETE (6)
	FRED FLOW DIVERTER	NO	COMPLETE (12)		SOLITAIRE	NO	COMPLETE (6)		PIPELINE FLOW DIVERTER	NO	COMPLETE (6)
	FRED FLOW DIVERTER	NO	PARTIAL (6)		P64 FLOW DIVERTER	NO	COMPLETE (6)		SURPASS FLOW DIVERTER	NO	PARTIAL (3)

PRU DETERMINATIONS 5-7 DAYS

CONCLUSION:

The individualization of treatment with clopidogrel oral solution using platelet function testing to to achieve a target PRU value in hyper responder patients may be reasonable.