14th Residential Course on Clinical Pharmacology of Antiretrovirals

Beyond Liverpool site: how to evaluate the impact of a DDI in the clinical setting

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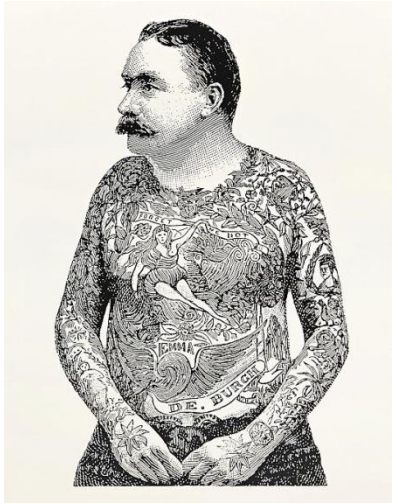
CLINICAL CASE

G.M.



- 59 yo Caucasian male
- History of previous IVDA
- Heavy smoker
- Borderline personality disorder
- HIV/HCV+ since 1996, diagnosis of esophageal candidiasis in another tertiary care Hospital
- Followed in our centre since 2011 → HIV-RNA: undetectable , CD4+: 341 cell/µl ,39%, ratio 1.2
- Cirrhosis HCV-related, genotype 4
- Cervical and lumbar degenerative disease with severe pain symptomatology (pregabalin, oxycodone)

2011 **HAART: FPV 1400 mg BID + TDF/FTC** (reported previous VF with ABC/3TC/AZT)

May 2013 : increasing creatinine value (no sign of tubulopathy) STOP **TDF/FTC → ABC/3TC**

creatinine 1.4 ---> 0.98 mg/dl

HIV-RNA: undetectable, CD4+: 558 cell/µl, 42%, ratio 1.2

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CLINICAL CASE

High CV risk

10.9% Current 10-Year ASCVD Risk

Heavy smoker:30 pack years

2013: hypertension treated with telmisartan

2014: Peripheral arterial disease with a severe stenosis of common femoral artery → **clopidogrel** 75 mg

FPV 1[illegible]0 mg BID + ABC/3TC

RAL 400 BID + ABC/3TC

Clopidogrel is a prodrug and is converted to its active metabolite via CYP 3A4,2B6, 2C19 and 1A2. The effect of induction of CYP 2C19 and inhibition of CYP3A4 by ritonavir decreases exposure of the active metabolite leading to non-responsiveness to clopidogrel

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CLINICAL CASE

CIRRHOSIS
HCV-related

SVR !

HCV-RNA: 894126 UI/ml gen 4a/c/d, treatment naïve

Tx: propranolole ½ x 3, pantoprazole 20 mg

Transient elastography: Stiffness: 24.5 KPa CAP 280 dB/m

2015: start OBV/PTV/**r** + riba 24 w

BUT…

Do Not Coadminister
OBV/PTV/r
Clopidogrel

In HIV-positive subjects, the presence of a pharmacoenhancer (ritonavir n=8; cobicistat n=1) **decreased** the AUC and Cmax of clopidogrel's active metabolite both by **69%** when compared to values obtained in HIV-negative subjects (n=12).

SWITCH to **TICLOPIDINE** during DAAs regimen

Potential Interaction
OBV/PTV/r
Ticlopidine

Induction of CYP2C19 and CYP2B6 to active metabolite and inhibition of CYP3A4 by ritonavir but may decrease exposure of the active metabolite leading to non-responsiveness to ticlopidine.
Close monitoring is recommended.
An adjustment in ticlopidine dose may be needed.

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CLINICAL CASE

STOP 24w of OBV/PTV/r + riba → **clopidogrel** 75 mg

RAL 400 BID + ABC/3TC

But progressively worsening of claudication symptoms and stability of artery lesion at Doppler Ultrasound

The patient ensures perfect adherence to his therapy

QUESTION: IS CLOPIDOGREL FULLY EFFECTIVE ?

PLATELET AGGREGATION
& FUNCTION TEST

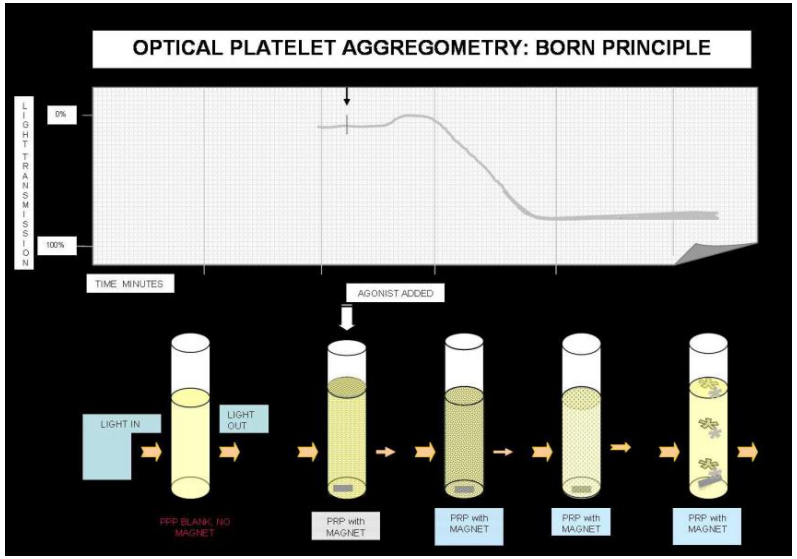
TECHNIQUES OF PLATELET AGGREGOMETRY

- Thromboxane A2 metabolites
- **Optical Aggregometry**

The historical "gold standard", turbidometric platelet aggregometry which measures platelet aggregation in PRP (platelet-rich plasma), it is based on the detection of difference in light transmission by a photometer after adding a platelet agonist to PRP

↓

Light Transmission[Born] Aggregometry (**LTA**)



Aggregating agents (agonists):
- Collagen
- **ADP**
- Epinephrine
- **Arachidonic acid**
- Ristocetin

Result expressed as **%**

- **Platelet Function Analyzer**

(**PFA-100** for monitoring aspirin and Innovance **PFA-200**→ **PFA P2Y** for thienopyridines) (result in sec)

simple, rapid, point-of-care whole blood method, low sample volumes and no sample preparation

- VerifyNow (point-of care, platelet aggregation by turbidimetric–based optical detection in anticoagulated whole blood, fast and simple, small sample volume, no pipetting)
- Impact-R
- Plateletworks (based on GP IIb/IIIa dependent platelet aggregation)
- Impedance aggregometry (MEA)
- Thromboelastrography
- Flow Cytometry Methods

Koltai K et al.c Platelet Aggregometry Testing: Molecular Mechanisms, Techniques and Clinical Implications. Int J Mol Sci. 2017 Aug; 18(8): 1803

OUR EXPERIENCE WITH AGGREGATION TEST…

HIV+ PATIENTS ON SECONDARY PREVENTION with Aceltylsalicylic Acid – ASA (n 7)

	LTA (% final aggregation) *		HAART
	Arachidonic acid 250 mcg/ml	Arachidonic acid 500 mcg/ml	
1	3%	0%	TAF/FTC + RAL
2	8%	70%	ABC/3TC/DTG
3	0%	4%	ABC/3TC + NVP
4	4%	0%	DTG + DRV 600/R BID
5	0%	0%	3TC + DRV/R
6	9%	0%	TDF/FTC + NVP
7	11%	8%	RAL+DRV 600/R BID + ETV

*** Normal value: > 60%** → platelets aggregate normally

HIV+ PATIENTS ON SECONDARY PREVENTION with THIENOPYRIDINES (n 15+1)

Dual Antiplatelet Tx (n 16)	LTA (% final aggregation) [NV > 60%]		PFA 200 – P2Y12 [NV <106 sec]	HAART
	ADP 5.0 µM	ADP 10 µM	Closure Time (CT) in sec.	
TICLOPIDINE (N 1)	82%	83%	74	DRV 600/R BID + 3TC 2 x 2 + ddI + ENF
PRASUGREL (N 3)	3%	0%	140	ABC/3TC/DTG
	4%	6%	>300	DRV 600/R BID + ETV 2x2 + MVC 300 + ENF
	0%	3%	>300	RPV + DTG
TICAGRELOR (N 2)	0%	0%	234	TAF/FTC/RPV
	0%	5%	>300	TAF/FTC + DTG
CLOPIDOGREL (9)	10%	21%	>300	TDF/FTC + RAL
	21%	37%	ND	TDF/FTC + RAL
	0%	10%	>300	TDF/FTC+ DRV/R
	0%	3%	ND	TAF/FTC + RAL
	5%	6%	>300	TAF/FTC/RPV
	21%	27%	ND	DTG+3TC
	29%	49%	ND	TAF/FTC + RAL
	33%	51%	ND	ABC/3TC+RAL
	31%	52%	80	DRV/R+ MVC 300

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QUESTION: IS CLOPIDOGREL FULLY EFFECTIVE ??

PLATELET AGGREGATION & FUNCTION TEST

May 2018

LTA (final aggregation)*		PFA 200 -P2Y12 **
ADP 5 µM	ADP 10 µM	Closure Time
65 %	74 %	80 sec

*normal value : > 60 %

**normal value <106 sec

Normal response to ADP, normal closure time despite ongoing antiplatelet therapy

WHY ?

CONCOMITANT MEDICATIONS	
RAL 400 bid + ABC/3TC	
pregabalin	haloperidol
oxycodone	biperiden
propranolol	lorazepam
Pantoprazole 20 mg	allopurinol

CLOPIDOGREL DOESN'T WORK !

Higher dosage of pantoprazole may reduce the effectiveness of clopidogrel

We decide to continue pantoprazole because of painful atrophic gastritis and…

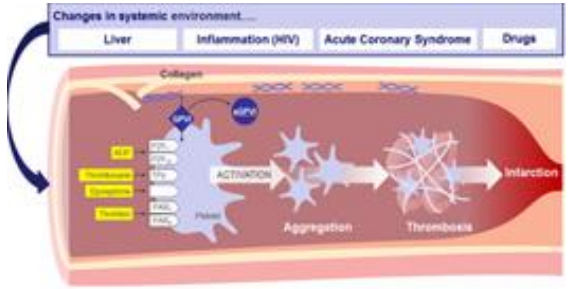
…we remind what presented at CROI 2018

2018 CROI Conference on Retroviruses and Opportunistic Infections
Boston, Massachusetts
March 4–7, 2018

3 presentations on the mechanism contributing to the increased risk of MI previously seen with ABC in large cohort studies:

- Platelet (PLT) dysfunction and activation[1-3]
  - ABC causes a reversible PLT defect that increases the risk of thrombus formation, evidenced by:[1-2]
    - Increased PLT reactivity
    - Decreased expression of PLT surface and soluble glycoprotein VI (sGPVI)
  - ABC enhances PLT aggregation by blocking nitrous oxide-mediated PLT inhibition[3]
- PLT-leukocyte-endothelial cell activation
  - ABC induces PLT-leukocyte-endothelial cell interactions, promotes leukocyte recruitment, and increases leukocyte adhesion resulting in thrombus formation in *in vitro* and *in vivo* models[4-6]
    - Mechanism involves purinergic signalling, especially activation of ATP-P2X7 receptors

These presentations all support the role of ABC interfering with endogenous purine pathways of endothelial inflammation and platelet activation



1. Mallon P, et al. CROI 2018. Boston, MA. Oral 80
2. Mallon P, et al. CROI 2018. Boston, MA. Poster 677LB
3. Taylor K, et al. CROI 2018. Boston, MA. Poster 673
4. Collado-Diaz V, et al. CROI 2018. Boston, MA. Poster 674
5. Andujar I, et al. CROI 2017. Seattle, WA. Poster 609
6. Collado-Diaz V, et al. EACS 2017. Milan, Italy. Poster 2-7

G.M.

CLINICAL CASE

Jun 2018: Considering his high cardiovascular risk we decide to switch away from ABC to **TAF/FTC**

The patient tolerates the therapy well, complains only a moderate weight gain

HIV-RNA: <20 cp/ml, CD4+: 487 cell/µl, 38%, ratio 1

PLATELET AGGREGATION & FUNCTION TEST

	HAART Back-bone	LTA (final aggregation)* ADP 5 µM	ADP 10 µM	PFA 200 -P2Y12** Closure Time
Sep 2018	TAF/FTC	21 %	23 %	>300 sec

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CLOPIDOGREL WORKS !

CONCLUSIONS

- Several PK and PD factors can influence antiplatelet treatment (APT) with different clinical outcome.
- Rapid and simple methods, like PFA, can be used to measure platelet function during APT and, even if not fully standardized, may guide the management in complex patients.
- Abacavir was related to high cardiovascular risk in HIV + patients, which mechanisms are not fully elucidated, however there is an increase number of reports of heightened platelet reactivity (HPR) as key factor.
- This is the first clinical case measuring a significant reduction of HPR following the switch to an ABC-free regimen in a patient with peripheral arterial disease (PAD).
- The assessment of residual platelet function in HIV patients in secondary prevention for CV events deserves more attention as a clinical option to prevent recurrences in such high CV risk population.

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