EX-VIVO PHARMACODINAMIC EFFECTS OF ESCALATING TICAGRELOR CONCENTRATIONS AND TICAGRELOR-MORPHINE INTERACTION IN PATIENTS WITH ACS

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INTRODUCTION

Optimal inhibition of platelet aggregation (PA) by oral $P2Y_{12}$ inhibitors such as ticagrelor is recommended in acute coronary syndrome (ACS) patients to mitigate the risk of ischemic events. The use of drugs for pain relief such as morphine blunts the onset of action of oral $P2Y_{12}$ inhibitors. This effect has been explained by delayed oral $P2Y_{12}$ inhibitor absorption. Whether morphine mitigates the effect of oral $P2Y_{12}$ inhibitors irrespective of delayed absorption is unknown. We investigated the pharmacodynamic (PD) effects of escalating ticagrelor concentrations and the ticagrelor-morphine interaction in consecutive ACS patients.

METHODS

This prospective, single-center study in 10 ACS patients included two phases: (1) in the first 5 patients ex-vivo PD effects of escalating ticagrelor doses (0, 1000, 2000, 4000, 10000 nmol/l) with and without morphine were investigated at baseline and at 30±5 minutes from loading dose; (2) in the remaining 5 patients, maximal ticagrelor dose followed by morphine or viceversa was added at baseline. PA was evaluated by light transmittance aggregometry (LTA with ADP 5 umol/l as agonist) and Multiplate.

RESULTS

Baseline and procedural characteristics of included patients are shown in **Table 1**. Escalating ticagrelor doses achieved greater platelet inhibition at baseline and 30 minutes (**Figure 1**). After highest ticagrelor dose spiking (baseline), morphine reduced platelet inhibition at both Multiplate (AUC: 12, interquartile range [IQR]: 5-16 vs 16 [IQR: 7-27], p=0.04) and LTA (28% [IQR: 26-41%] vs 42% [IQR: 43-48%], p=0.05) (**Figure 1**). Ex-vivo morphine administration led to greater PA at LTA when supplemented before (17% [IQR: 15-44%] than after ex-vivo ticagrelor spiking (11% [IQR: 10-22%; p=0.043] (**Figure 2**).

Table 1. Baseline and procedural characteristics. Values are mean ± standard deviation or n (%).

	N=10
Baseline characteristics	
Age, yrs	72 ± 11
Female sex	4 (40%)
Arterial hypertension	7 (70%)
Dyslipidemia	5 (50%)
Diabetes	1 (10%)
Current smoker	4 (40%)
Prior MI/PCI	1 (10%)
PAD	1 (10%)
CKD	0 (0%)

Procedural characteristics	
Clinical presentation	
STEACS	6 (60%)
NSTEACS	4 (40%)
Vessel treated	
LAD	3 (30%)
LCx	6 (60%)
RCA	1 (10%)
>2 stents	0 (0%)

Abbreviations: CCS, chronic coronary syndrome; CKD, chronic kidney disease; LAD, left anterior descending artery; LCx, left circumflex; MI, myocardial infarction; NSTEACS, non-ST segment elevation acute coronary syndrome; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEACS, ST-segment elevation acute coronary syndrome.

Figure 1. Maximal aggregation by LTA and Multiplate at baseline and 30 min from loading dose with and without ex-vivo escalating ticagrelor regimens.

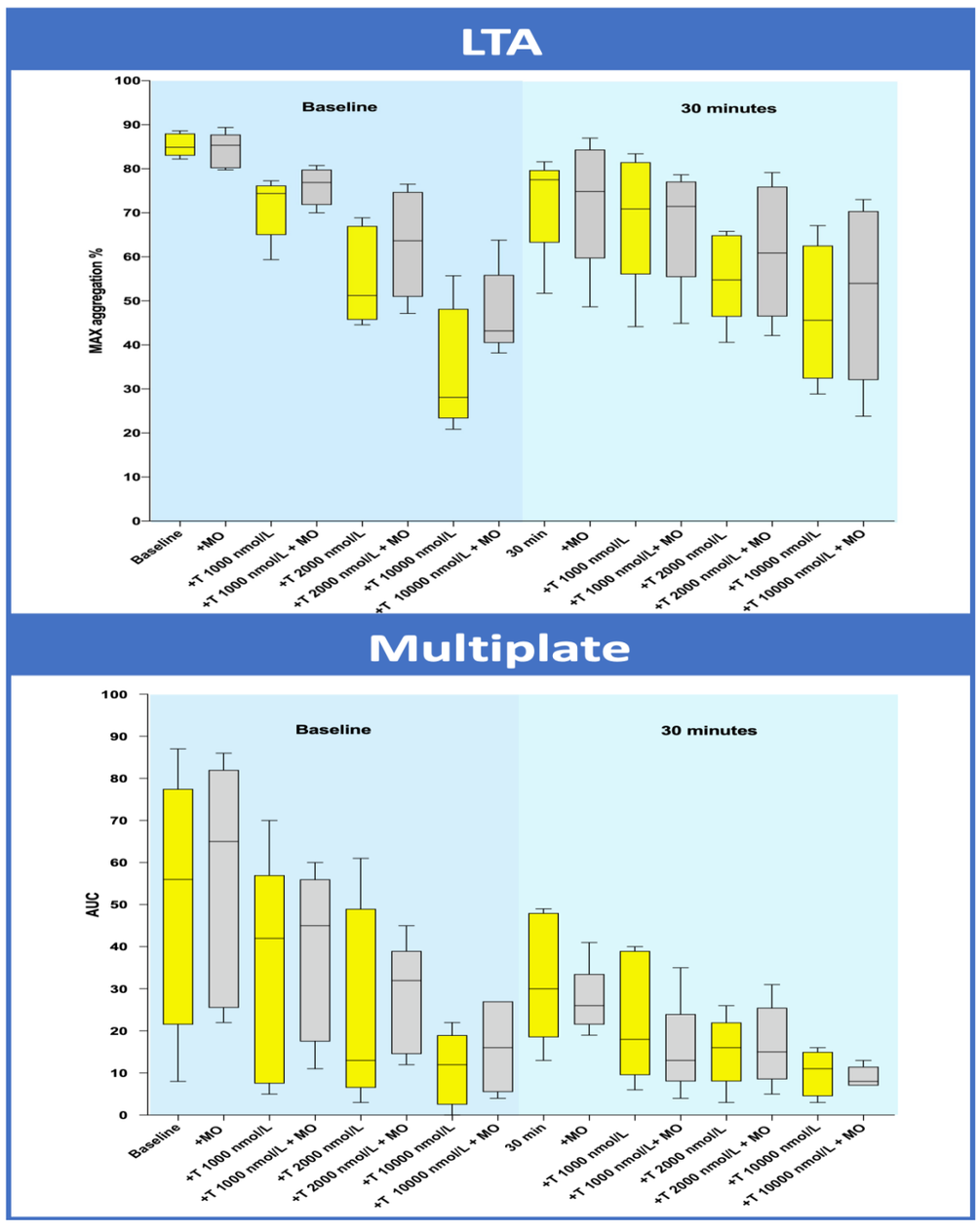
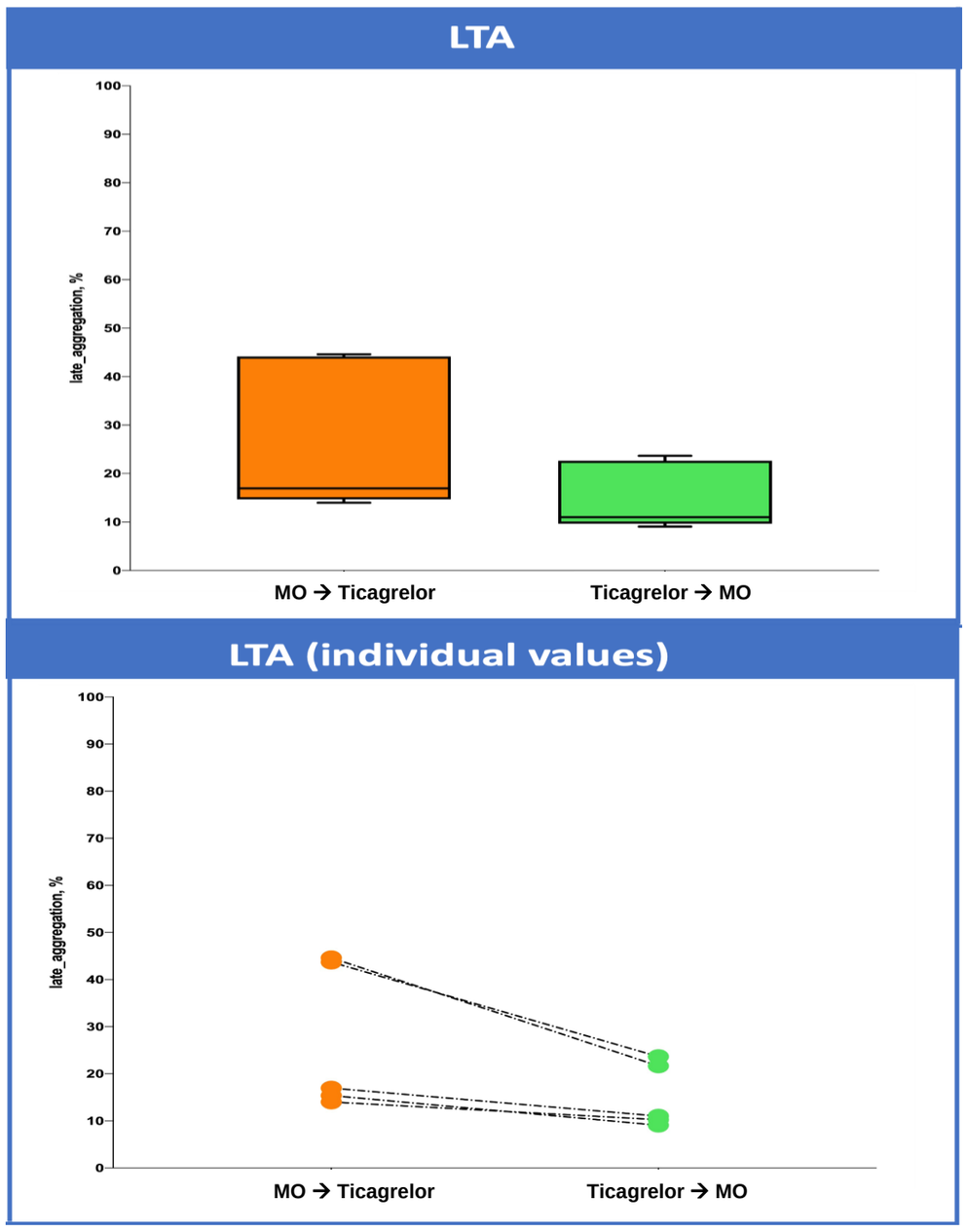


Figure 2. Maximal aggregation by LTA and Multiplate at baseline and 30 min from loading dose with and without ex-vivo escalating ticagrelor regimens. *Abbreviation: MO, morphine.*



CONCLUSIONS

Incremental ex-vivo ticagrelor concentrations achieved step-wise inhibition of PA. We observed for the first time a direct morphine effect on ticagrelor-mediated $P2Y_{12}$ receptor inhibition when added before but not after ticagrelor exposure, which may carry clinical implications.