REDUCED VARIABILITY TO ASPIRIN ANTIPLATELET EFFECT BY THE CO- ADMINISTRATION OF STATINS IN HIGH-RISK INDIVIDUALS FOR CARDIOVASCULAR EVENTS

1)Tacconelli S. 2)Dovizio M. 3)Di francesco L. 4)Meneguzzi A. 5)D'agostino I. 6)Evangelista V. 7)Manarini S. 8)Capone ML. 9)Porreca E. 10)Di febbo C. 11)Levantesi G. 12)Fava C. 13)Minuz P. 14)Patrignani P.

G. D'Annunzio University

Several processes triggered by cardiovascular(CV) disease might interfere with the complete and persistent suppression of thromboxane(TX)A2 biosynthesis by low-dose aspirin necessary for cardioprotection, thus leading to variability in drug response(Patrono et al.2005; Patrignani et al.1982).

The objectives of the present study were to verify, in high-risk individuals for CV events chronically treated with enteric coated (EC)-aspirin (100mg daily), the possible influence of CV risk factors, such as diabetes mellitus, dyslipedimia or previous CV events, and co-treatments, such as statins, on residual platelet TXA2 generation in serum. Serum TXB2(the hydrolysis product of TXA2) levels were assessed in 182 patients with coronary heart and cerebrovascular disease treated with low-dose EC-aspirin and in a control group of 13 individuals with comparable age, gender, incidence of hypertension, but without other CV risk factors and/or previous vascular events. In both groups, low-dose aspirin was administered under supervision for 7 days and then blood samples were collected for biomarker assessment(Patrono et al.1980) at 12h after the last dose of aspirin to minimize the influence of platelet turnover to aspirin's antiplatelet effect.

In control individuals, complete inhibition of platelet COX-1 activity by aspirin was associated with a residual serum TXB2 levels of 1.5±1.2(mean±SD)ng/ml. We defined the upper limit value of serum TXB2 for an adequate response to aspirin, as the mean value+2SDs, 3.9ng/ml: thus, we selected a value of 4ng/ml as cutoff point to identify individuals with appropriate vs inappropriate inhibition of platelet COX-1. Median value of residual serum TXB2 levels in CV patients was not significantly different from that detected in control individuals [1.1(0.02-155.5) vs 0.84(0.2-3.7)ng/ml, median(range),respectively]. However 14% of CV patients(n=25) had higher serum TXB2 values than the cutoff value. In CV patients, the addition of an excess of aspirin in vitro(50□g/ml) caused a significant(P<0.01) reduction of median serum TXB2 levels; only 2% of patients showed serum TXB2 levels >4ng/ml. These results show that in a small number of high-risk individuals for CV events, low-dose aspirin did not appropriately inhibit platelet COX-1-dependent TXA2 biosynthesis. Then we studied the influence of demographic, clinical factors and pharmacological co-treatments on residual serum TXB2 levels in CV patients treated with EC-aspirin. Linear multiple regression analysis of log10-transformed data of residual serum TXB2 levels detected in these patients showed that, among demographic and clinical factors, only a previous myocardial infarction(MI) was an independent predictor of residual serum TXB2 levels(□=0.19,SEM=0.06;P=0.001). The % of patients with serum TXB2 values >4ng/ml were significantly lower in the group of patients with a previous MI (6.5% vs 24%,P<0.01). Moreover, the linear multiple regression analysis of log10-transformed data of residual serum TXB2 levels detected in these patients showed that, among the pharmacological co-treatments, only statins

were an independent predictor of residual serum TXB2 levels (□=0.11,SEM=0.05;P=0.038). Interestingly, the group with a previous MI was characterized by higher use of statins vs those without a previous MI (72.9% vs 53.9%, respectively,P<0.001). Median serum TXB2 levels were significantly(P<0.01) higher in patients without statins vs those who were co-administered with statins [1.88(0.15-96.7) vs 0.82(0.015-155.5),respectively]; the % of patients with serum TXB2 values >4ng/ml were significantly lower in statin users vs non-users (9.3% vs 20.3%, P<0.01).

In conclusion, our results showed that the co-administration of statins improved the inhibitory effect of low-dose EC-aspirin on platelet TXA2 biosynthesis ex vivo. These findings may be explained by an effect of statins to enhance the capacity of aspirin to reach the target (ie platelet COX-1) and to acetylate it.

References

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