TICAGRELOR INDUCES ADENOSINE TRIPHOSPHATE RELEASE FROM HUMAN RED BLOOD CELLS

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The novel P2Y12 antagonist Ticagrelor inhibits ADP-induced platelet aggregation more rapidly and more potently than clopidogrel, and has been shown in the PLATO study to significantly reduce cardiovascular mortality in patients with acute coronary syndrome. Its side effects include dyspnea and asymptomatic ventricular pauses; the exact mechanisms for these are not known, but it is plausible that both effects are mediated by adenosine. Ticagrelor has been shown in vitro to inhibit adenosine reuptake by red blood cells, however other P2Y12 inhibitors (elinogrel, cangrelor) also report dyspnea, but are not known to affect adenosine reuptake. The purpose of the present study was to determine whether ticagrelor has other effects on red blood cells that could explain the side effects seen with Ticagrelor treatment.

Using a luciferase-based bioluminescence assay, we studied ATP release from human red blood cells collected from healthy volunteer donors. Human red blood cells responded to Ticagrelor in vitro by releasing substantial amounts of ATP in a dose-dependent manner (EC50 10μM). From a library of inhibitors, Ticagrelor-induced ATP release was found to be significantly reduced by the chloride channel blocker NPPB and the PKA inhibitor H89. Based on this inhibitory profile and in light of previous findings that suggest a role for the ABC transporter MDR-1 in ATP release, we performed lentiviral gene silencing of mdr-1 in a murine erythroblast cell line. Subsequent ATP release experiments showed complete absence of Ticagrelor-induced ATP release in silenced cells compared to control cells. This was confirmed in non-respondent CHO cells, which, after transfection with a plasmid containing mdr-1, responded with Ticagrelor-induced ATP release.

In conclusion, our data show that Ticagrelor induces ATP release from human RBCs via mechanisms involving the ABC transporter MDR-1. ATP released in this manner is degraded to adenosine, an effect that is independent and potentially additive to the known effects of Ticagrelor on adenosine reuptake. Further studies of other P2Y12 inhibitors are warranted to determine what role this mechanism may play in the clinical effects of these agents.