

Mechanisms involved in the antiplatelet activity of midazolam in human platelets.

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Abstract

BACKGROUND: Midazolam is widely used as a sedative and anesthetic induction agent. The aim of this study was to systematically examine the inhibitory mechanisms of midazolam in platelet aggregation. **METHODS:** The inhibitory mechanisms of midazolam in platelet aggregation were explored by means of analysis of the platelet glycoprotein IIb-IIIa complex, phosphoinositide breakdown, intracellular Ca²⁺ mobilization, measurement of membrane fluidity, thromboxane B₂ formation, and protein kinase C activity. **RESULTS:** In this study, midazolam dose-dependently (6-26 microm) inhibited platelet aggregation in human platelets stimulated by agonists. Midazolam also dose-dependently inhibited phosphoinositide breakdown and intracellular Ca²⁺ mobilization in human platelets stimulated by collagen. Midazolam (6-26 microm) significantly inhibited thromboxane A₂ formation stimulated by collagen in human platelets. Moreover, midazolam (15 and 26 microm) dose-dependently decreased the fluorescence of platelet membranes tagged with diphenylhexatriene. Rapid phosphorylation of a platelet protein of Mr 47,000 (P47), a marker of protein kinase C activation, was triggered by collagen (2 microg/ml). This phosphorylation was markedly inhibited by midazolam (26 microm). **CONCLUSIONS:** These results indicate that the antiplatelet activity of midazolam may be involved in the following pathways: the effects of midazolam may initially be caused by induction of conformational changes in platelet membrane, leading to a change in the activity of phospholipase C, and subsequent inhibition of phosphoinositide breakdown and thromboxane A₂ formation, thereby leading to inhibition of both intracellular Ca²⁺ mobilization and phosphorylation of P47 protein.