Mechanisms of antiplatelet and antithrombotic activity of midazolam in in vitro and in vivo studies

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摘要

Abstract

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. In this study, midazolam concentration-dependently (15 and 30 microM) inhibited platelet aggregation in washed human platelets stimulated by thrombin (0.05 U/ml). Midazolam (15 and 30 microM) also inhibited phosphoinositide breakdown and intracellular Ca(+2) mobilization in platelets stimulated by thrombin (0.05 U/ml). In addition, midazolam (15 and 30 microM) increased the formation of cyclic AMP but not cyclic GMP or nitric oxide. The thrombin-evoked increase in pHi was markedly inhibited in the presence of midazolam (15 and 30 microM). Rapid phosphorylation of a platelet protein of molecular weight (Mr.) 47,000 (P47), a marker of protein kinase C activation, was triggered by thrombin (0.05 U/ml). This phosphorylation was markedly inhibited by midazolam (15 and 30 microM). Midazolam (30 microM) did not significantly reduce the electron spin resonance signal intensity of hydroxyl radicals in activated platelets. In the vivo study, intravenous injection of midazolam (10 microg/g) significantly prolonged the latent period of inducing platelet plug formation in mesenteric venules. These results indicate that midazolam can significantly prevent thrombus formation in vivo. Its antiplatelet activity may be involved in the inhibition of the activation of phospholipase C and the Na(+)/H(+) exchanger and increased cyclic AMP formation. These lead to lower intracellular Ca(+2) mobilization and phosphorylation of P47.