

P613

ABCB1 2677T and 3435T polymorphisms are associated with cilostazol-induced headache in phase I clinical trials

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Background

Cilostazol, a phosphodiesterase type 3 inhibitor, induces headache by increasing cyclic adenosine monophosphate levels and dilating arteries. Multidrug resistance protein 1 (MDR1, encoded by the *ABCB1* gene) is expressed in vascular smooth muscle and involved in the transport of cilostazol. We investigated whether genetic variants of *ABCB1* are associated with differential incidence of cilostazol-induced headache

Methods

The study had two components. First, we examined whether single nucleotide polymorphisms of the human *ABCB1* gene are associated with the incidence of cilostazol-induced headache in 101 volunteers participating in six phase I cilostazol clinical trials. Second, using an *in vitro* functional analysis, we investigated whether cilostazol is a substrate of MDR1 and the genetic variants of MDR1 show different transport activity of cilostazol.

Results

ABCB1 c.2677G>T and c.3435C>T polymorphisms were associated strongly with the incidence of cilostazol-induced headache (G/A vs. T, $P=0.006$, OR=2.34; C vs. T, $P=0.0003$, OR=3.01; G/A2677T and C3435T, respectively). Logistic regression analysis with multiple clinical variables indicated that the presence of the T allele at the *ABCB1* c.3435C>T locus is an independent determinant of headache incidence. Functional analysis indicated that cilostazol is a substrate of MDR1 and 893Ser-MDR1 (c.2677T) failed to transport cilostazol effectively.

Conclusion

ABCB1 c.2677G>T and c.3435C>T polymorphisms are related to the incidence of cilostazol-induced headache. Large-scale clinical trials are needed to confirm this finding.