Enhanced Oral Absorption of Paclitaxel by Novel P-glycoprotein Inhibitor
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Purpose
Since P-glycoprotein (P-gp) has been reported to be a barrier for intestinal absorption of various drugs, P-gp inhibitors have been studied to improve oral absorption of P-gp substrate drugs. It has been reported that AC-603 (Methyl-3-(2-(4-(3-((2-(pyrrolidin-1-yl) ethyl amino) methyl) adamant-1-yl) phenoxy) acetamido) benzoate) inhibited P-gp activity in a P-gp over expressing MDR sarcoma cell line, MES-SA/DX5. In this study, the effect of AC-603 on oral bioavailability of paclitaxel, a P-gp substrate, was examined following oral co-administration in rats.

Methods
A high performance liquid chromatographic (HPLC) assay was used to determine paclitaxel in rat plasma. For the pharmacokinetic study, two groups of rats were received paclitaxel intravenously (2 mg/kg) or orally (25 mg/kg), as control groups. In the other groups, paclitaxel (25 mg/kg) was orally co-administered with verapamil (0.5 and 5 mg/kg), a positive control, and AC-603 (0.5 and 5 mg/kg), respectively.

Results
The validated HPLC-UV method was applied to evaluate the pharmacokinetics of paclitaxel following intravenous and oral administration to rats. The absolute bioavailability of paclitaxel in rats was only 2.52%. After oral co-administration of paclitaxel with AC-603 at the doses of 0.5 and 5 mg/kg, the relative bioavailability of paclitaxel was increased to 165 and 181%, respectively. The mean area under the plasma concentration-time curve (AUC) and maximum plasma concentration (Cmax) of paclitaxel were also significantly increased. These values were greater than those obtained from the groups co-administered with paclitaxel and verapamil, a well-known P-gp inhibitor.

Conclusion
The pharmacokinetic parameters of paclitaxel were significantly affected by a novel compound, AC-603. In addition, oral bioavailability of paclitaxel was significantly improved by co-administration with AC-603.