An LC-MS/MS Method for the Simultaneous Quantification of Sarpogrelate and Its Active Metabolite, M-1, in Human Plasma and Its Pharmacokinetic Application

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Purpose
Sarpogrelate ((R, S)-1-[(2-[2-(3-methoxyphenyl)ethyl]phenoxy)-3-(dimethylamino)-2-propyl hydrogen succinate chloride), a highly specific 5-HT\textsubscript{2A} receptor antagonist, has been approved in Japan for peripheral arterial disease in 1993 and widely used in Japan, China, and South Korea. It inhibits serotonin-induced platelet aggregation and vasoconstriction on smooth muscle cells. Additionally, it has beneficial effects in restenosis after coronary stenting, pulmonary hypertension, angina pectoris, and diabetes mellitus. Sarpogrelate is metabolized to (±)-1-[(2-[2-(3-methoxyphenyl)ethyl]phenoxy)-3-(dimethylamino)-2-propanol hydrochloride (M-1), formed by hydrolysis from sarpogrelate. The M-1 is an active sarpogrelate metabolite, which has inhibitory effects exceeding those of sarpogrelate in vitro. Despite excellent pharmacological activities, to date, no analytical method for simultaneous determination of sarpogrelate and M-1 in biological fluids has been reported.

Methods
A rapid and simple liquid chromatography-tandem mass spectrometry method for simultaneous determination of sarpogrelate and its active metabolite, M-1, in human plasma was established. Sarpogrelate, M-1, and the internal standard, ketanserin, from 50 µL aliquot of biological samples were extracted by protein precipitation using acetonitrile. Chromatographic separation was carried out on an Agilent ZORBAX Eclipse Plus C\textsubscript{18} column (2.1 x 100 mm, 1.8 µm) using a gradient elution consisting of 10 mM ammonium acetate and acetonitrile (0.6 mL/min flow rate, 6.0 min total run time). Detection and quantification were performed using a mass spectrometer in selected reaction-monitoring mode with positive electrospray ionization at \textit{m/z} 430.4→135.1 for sarpogrelate, \textit{m/z} 330.3→58.1 for M-1, and \textit{m/z} 395.7→188.9 for the internal standard.

Results
The linear ranges of concentration for sarpogrelate and M-1 were 1-1000 and 0.5-500 ng/mL, respectively, with a lower limit of quantification of 1 and 0.5 ng/mL, respectively. The coefficient of variation for the assay’s precision was ≤ 14.9%, and the accuracy was 88.1-112%. All analytes were stable under various storage and handling conditions and no relevant cross-talk and matrix effect were observed.

Conclusion
Finally, this method was successfully applied to assess the pharmacokinetics of sarpogrelate and M-1 after oral administration of 100 mg sarpogrelate to healthy Korean subjects.