PK/PD ANALYSIS OF QT PROLONGATION CAUSED BY ARSENIC TRIOXIDE ADMINISTRATION IN RATS

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In recent years, arsenic trioxide has been used to treat patients with acute promyelocytic leukemia who experience relapse or who are refractory to all-trans retinoic acid. Arsenic causes various adverse effects, such as QT prolongation, hepatopathy and nephropathy. In particular, QT prolongation is a severe side effect. In this study, the relationship between arsenic plasma concentration and QT prolongation in rats was studied by using pharmacokinetic/pharmacodynamic analysis.

Male SD rats (8 weeks) were used. Arsenic trioxide was intravenously administered at doses of 2, 10 and 20 mg/kg under urethane anesthesia. Blood was sequentially collected while the heart was monitored by electrocardiogram. Plasma concentration of arsenic was determined by gas chromatography/mass spectrometry¹.

Plasma level of arsenic followed the 2-compartment model. QT prolongation was found to be dose dependent and was maximal at 30–60 minutes after administration. The relationship between plasma arsenic concentration and QT interval exhibited an anti-clockwise hysteresis-loop. These results suggest that arsenic levels at the site inducing QT prolongation may lag behind those in plasma.