Pharmacokinetics of gadocoletate trisodium (B22956/1), a new intravascular contrast agent for MR coronary angiography, in healthy volunteers

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Background: Magnetic resonance coronary angiography requires the use of very fast sequences during only a portion of the cardiac and respiratory cycles. A high relaxivity intravascular contrast agent would improve the clinical utility of MRCA. Gadocoletic acid trisodium salt (B-22956/1) is a new intravascular, protein binding, low molecular weight contrast agent consisting of a Gd-DTPA moiety linked to a deoxycholic acid substituent. Pre-clinical and preliminary clinical studies suggest that B22956/1 is well suited for high-resolution imaging of the coronary arteries (1-4). We conducted a single center, double-blind, placebo-controlled, parallel group pharmacokinetic (PK) evaluation of B22956/1 to determine the PK profile of this agent in healthy subjects.

Methods and Materials: Seventy-two subjects were randomized to one of four dose groups. Three groups of 18 subjects each received 0.25 M B22956/1 (Bracco Imaging, Milan) at doses of 0.025, 0.075 or 0.15 mmol/kg administered by power injector at 10 mL/min followed by a 20 mL saline flush. Control subjects received physiologic saline at 0.1, 0.3 and 0.6 mL/kg. Blood samples were obtained 5 min before injection of B22956/1 and at 1, 5, 10, 15, 30 min and 1, 2, 4, 6, 8, 12, 16, 20, 24, 48, 72, 96, 120 and 144 h after the injection. Pooled urine was collected –24 to 0 h predose and 0-24, 24-48, 48-72, 72-96, 96-120, and 120-144 h after injection. Fecal samples were collected –24 to 0 h predose, and at 0-24, 24-72 and 72-144 h after injection. Plasma, urine and fecal samples were assayed for Gd by ICP-AES. Selected samples were also analyzed for the B22956 ion by HPLC. Plasma concentration-time data were analyzed by non-compartmental and two-compartment methods. Determinations were made of T_{max} and C_{max}, the terminal-phase elimination rate constant (λ_z), the terminal-phase half-life ($t_{1/2}\lambda_z$), the area under the plasma concentration-time curve [AUC (0-t)], clearance (CL, Dose/AUC (0-inf)), and the steady-state volume of distribution (V_{ss}). Descriptive statistics were provided for observed and computed parameters and the relationship of dose to PK parameters was investigated by regression analysis. Compartmental analysis determined values for distribution and elimination half-lives from the fitted rate constants α and β.

Results: Mean baseline demographic variables were comparable between dose groups. For compartmental analysis (Table I), AUC, C_{max}, and V_{ss} showed a statistically significant dose-related increases. V_{ss} of from 11% to 15% of body weight indicated that B22956/1 is distributed in plasma and in part of the extracellular spaces. The plasma elimination half life of up to 4.13h is consistent with a prolonged residence in plasma of the protein-bound compound. Non-compartmental analysis (Table II), including AUC, C_{max}, $t_{1/2}\lambda_z$, mean residence time (MRT), and V_{ss} showed statistically significant dose-related increases. In both analyses, plasma clearance showed a trend of increase with dose, whereas the renal clearance increased substantially with increasing dose. At 48h, Gd was not detectable in plasma. Urinary excretion (Table II) increased with dose, while fecal excretion data varied widely and decreased with dose. Dose-dependent differences in the rate and route of elimination are most likely related to protein binding. Increased renal excretion may indicate saturation of the biliary excretion route at higher doses.

TABLE I. PK PARAMETERS, COMPARTMENTAL ANALYSIS

PK variable ±SD	0.025 mmol/kg	0.075 mmol/kg	0.15 mmol/kg
AUC (mmol×h/L)	1.10 ±0.381	3.11 ±0.669	5.76 ±1.645
CL (L/h/kg)	0.0255 ±0.0061	0.0253 ±0.0059	0.0277 ±0.0069
V_{ss} volume (L/kg)	0.11 ±0.012	0.13 ±0.015	0.15 ±0.052
α half-life (h)	0.31 ±0.205	0.25 ±0.125	0.24 ±0.176
β half-life (h)	3.55 ±1.210	3.95 ±0.846	4.13 ±1.203

TABLE II. PK PARAMETERS, NON-COMPARTMENTAL ANALYSIS

PK variable ±SD	0.025 mmol/kg	0.075 mmol/kg	0.15 mmol/kg
$AUC_{(0\text{-inf})}$ (mmol×h/L)	1.19 ±0.401	3.33 ±0.754	6.29 ±1.993
Terminal half-life λz (h)	6.02 ±1.283	7.74 ±1.917	11.99 ±5.474
CL (L/h/kg)	0.0225 ±0.0051	0.0237 ±0.0058	0.0256 ±0.0064
MRT (h)	6.35 ±1.585	7.30 ±1.594	8.65 ±2.878
V_{ss} volume (L/kg)	0.14 ±0.015	0.17 ±0.022	0.21 ±0.067

TABLE III PERCENT GADOLINIUM EXCRETED IN URINE & FECES

Dose (mmol/kg)	Mean Cumulative % excretion ± SD (0-144 h)		
	Urinary	Fecal	Total
0.025	6.0% ±2.2% (N=17)	67.2% ±25.7% (N=17)	73.2% ±25.7% (N=17)
0.075	15.0% ±5.4% (N=18)	59.3% ±17.4% (N=18)	74.3% ±17.7% (N=18)
0.15	25.9% ±7.6% (N=17)	35.6% ±17.0% (N=17)	61.5% ±17.0% (N=17)

Conclusions: After intravenous injection, B22956/1 is distributed in plasma and in part of the extracellular space and is eliminated completely from plasma within 48h. The serum albumin binding properties of B22956/1 result in a long plasma half-life and partial vascular confinement. Unmetabolized B22956/1 is eliminated through both the urinary and biliary routes. Renal and hepatic clearances appear to change with the dose according to the saturation of serum albumin binding sites and to the saturation of biliary uptake. This study demonstrates that the partial intravascular distribution, the reduced loss by glomerular filtration owing to the strong binding of B22956/1 to serum albumin, and the substantial liver uptake and bilary excretion of this agent produce a slow decay of the plasma concentration over the period of interest for coronary angiography.

References

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