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The pharmacokinetic profile, tolerability and safety of the iodinated, non-ionic, dimeric contrast medium Iosimenol 340 injection in healthy human subjects

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Abstract

Background: Iosimenol 340 injection is a new isotonic iodinated contrast medium for X-ray angiography.
Purpose: To investigate the pharmacokinetics and biotransformation, tolerability, and safety of Iosimenol 340 in healthy human subjects.
Material and Methods: Twenty-four subjects were enrolled and randomized to receive either Iosimenol 340 (0.5, 1.5 or 3.0 mL/kg) or placebo (0.9% saline). In each dosing group, six subjects received Iosimenol 340 and two subjects received placebo. Safety was assessed by physical examination, vital signs, electrocardiography, and laboratory tests. Adverse events were recorded throughout the study up to 14 days after dosing. Blood samples were collected from 10 min before until 48 h after the start of dosing and urine samples were collected from 15 min before until 96 h after the start of dosing. Iosimenol was quantified in plasma and urine by measuring iodine concentrations with X-ray fluorescence. High-performance liquid chromatography was used to assess iosimenol biotransformation.
Results: Mean half-lives (mean ± standard deviation [SD]) of iosimenol were 0.17 ± 0.08 h (10.2 ± 4.8 min) and 2.01 ± 0.32 h for distribution and terminal elimination phases, respectively. The apparent volume of distribution was 0.27 ± 0.05 L/kg, indicating distribution to the extracellular fluid volume. Iosimenol was excreted within 24 h without any sign of metabolic transformation. Thirty-two adverse events were observed in 14 subjects. All were mild or moderate, and were transient in nature.
Conclusion: Iosimenol was not metabolized, had a distribution volume corresponding to the extracellular space, and was rapidly excreted through the kidneys by glomerular filtration. The area under the plasma concentration curve and the peak plasma concentration was proportional to dose, while clearance was independent of dose. Iosimenol 340 was well tolerated.

Keywords
Iosimenol, pharmacokinetics, safety, phase I, iodinated contrast media

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Introduction

Since the first chance observation of iodine's X-ray opacity, iodinated contrast media (CM) have become a mainstay in imaging of all kinds of internal bodily structures (1). More than 80 million doses of iodinated intravascular CM were administered in 2003 (2). The molecular structure of these compounds has undergone significant changes since their introduction in clinical practice, with changes being aimed primarily at increasing tolerability. Most modern CM are non-ionic (i.e. they do not dissociate in solution), but vary with regard to iodine content and physicochemical properties. They are all based on

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tri-iodinated benzene molecules and are either mono- or dimeric (i.e. based on one or two benzene rings). The viscosity and, in particular, the osmolality of CM has been considered as important for renal tolerance (3–6). The osmolality of monomeric CM is higher than that of the dimeric CM, which can be formulated as iso-osmolar relative to human plasma (approximately 290 mOsm/kg) at concentrations suitable for clinical use (7). Visipaque^{TM} (iodixanol) (GE Healthcare; Amersham, United Kingdom) is currently the only iso-osmolar, dimeric CM commercially available for intravascular use. The viscosity of iodixanol, however, is considerably higher than that of most other CM, making it less suited for injection in very thin catheters (3,8) and it has been suggested that the high viscosity to some degree might counteract the beneficial effects of the low osmolality (1,4). Iosimenol 340 injection is a non-ionic, dimeric CM, under development for use in cardiac angiography. It is iso-osmolar but exhibits a lower viscosity than iodixanol at the same concentration (9). This Phase 1 (first-in-man) study was designed to investigate the pharmacokinetics and metabolism, safety and tolerability, of intravenously administered Iosimenol 340 in healthy human subjects.

Material and Methods

This randomized, double-blind, placebo-controlled, single dose-escalating Phase 1 study was performed at the Parexel International GmbH Institute in Berlin, Germany from May 2002 to August 2002. Written informed consent was obtained from each subject prior to their participation in the study. The study was approved by an Independent Ethics Committee at the Chamber of Physicians, Berlin (Registration no: Eth-837-119/02) and was conducted in accordance with Good Clinical Practice guidelines of the International Conference on Harmonization, the German Drug Law and the 1964 Declaration of Helsinki and subsequent updates.

Study population

In total, 24 healthy Caucasian men, between 18 and 43 years of age and with normal body weight (body mass index [BMI], 20–27 kg/m^2), were enrolled. Good general health was determined at screening by medical history, physical examination, vital signs, electrocardiography (ECG), and laboratory findings.

Study drug administration

Iosimenol 340 (containing 340 mg /mL, as 660.2 mg/mL iosimenol drug substance) was provided by Koehler Chemie, Bensheim, Germany (manufactured by Interpharma Praha [Prague, Czech Republic]). Six subjects per group were randomly assigned to receive one of three doses of Iosimenol 340 (0.5, 1.5, or 3.0 mL/kg, equivalent to approximately 0.2, 0.5, or 1.0 gI/kg) while two subjects in each group were assigned to receive placebo (0.9% saline solution). Study drug and placebo were administered intravenously with an injection rate of 3 mL/s to dosing groups in ascending order with intervals of 7 days after each group. Investigators and subjects were blinded to treatment assignment. Subjects were confined from the afternoon before dosing until the day after dosing under conditions of controlled fluid and food intake.

Pharmacokinetic and biotransformation sampling

Blood (10 mL) was sampled 10 min prior to dosing (predose; t = 0 h) and then 1, 2, 5, 10, 30, and 45 min, and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 h after dosing. Urine aliquots (10 mL) were obtained from spot urine at least 15 min before dosing and from pooled urine collected during each of the following collection intervals: 0–2, 2–4, 4–6, 6–8, 8–10, 10–24, 24–48, 48–72, and 72–96 h after dosing. Blood samples for biotransformation (40 mL) were collected 10 min prior to dosing, and at 1 and 4 h after dosing; urine aliquots (10 mL) were taken from spot urine 15 min before dosing and from pooled urine from each of the following intervals: 0–2, 2–4, and 10–24 h.

Knowing the size of the Iosimenol 340 molecule, the high water solubility and the lack of protein binding, the results of animal experiments and the clinical experience from similar compounds, there was no reason to expect any significant fecal elimination, hence no fecal sampling was done (10,11).

Bioanalytics

Iosimenol was quantified by measuring iodine using X-ray fluorescence (Labor Dr. Limbach und Kollegen; Heidelberg, Germany) in plasma and urine samples. The limit of quantification (LOQ) was 0.15 mg iodine/mL, which was considered sufficient, given the high amount injected of the compound and the expected rapid renal excretion, with consequent high concentrations in plasma and urine samples. Serum was heated for 10 min at 100°C, centrifuged and the resulting supernatant was analyzed. Urine samples were filtered using a Whatman 12 kD filter. A control experiment was conducted with high-performance liquid chromatography (HPLC) and liquid chromatography/ mass spectrometry (LC/MS) to ensure that iodine only occurred organically bound to iosimenol.

Pharmacokinetic evaluation

The following pharmacokinetic variables were determined: C_{max}, t_{max}, $AUC_{0\rightarrow t}$, $t_{½}$, Ae, CL, CL_R, and V_z, where C_{max} [mg iodine/mL], was the highest plasma concentration observed after Iosimenol 340 administration at time t_{max}. The area under the plasma concentration time curve (AUC) from time zero to time t of the last plasma concentration above the LOQ ($AUC_{0\rightarrow t}$) was calculated using the log/linear trapezoidal rule from baseline concentrations to time t. The apparent terminal elimination half-life ($t_{½}$) was calculated as $\ln(2)/\lambda_z$ and total clearance (CL) as the ratio between dose and AUC. For the determination of pharmacokinetic parameters, only concentrations above the LOQ were used. The volume of distribution (V_z) was calculated as CL/λ_z and renal clearance (CL_R) as Ae/AUC, where Ae was the cumulative amount excreted in urine.

Safety assessments

Safety was assessed during the study by recording of adverse events (AEs), physical examination, vital signs (blood pressure and pulse rate), ECG recordings, safety laboratory parameters: hematology, clinical chemistry including alpha-1-globulin, alpha-2-globulin, beta globulin, gamma globulin, complement (CH100, urine analysis, coagulation tests and thyroid hormones at screening, at baseline, at regular intervals during the day of treatment, and between Days 2 and 5 and at the end-of-study visit 14 days after dosing. AEs were recorded throughout the study (daily up to 5 days and at the follow-up visit about 14 days after dosing). The intensity of AEs was graded as follows: mild (no limitation of usual activities), moderate (some limitation of usual activities), severe (inability to carry out usual activities). AEs are coded per MedDRA 15.1 (Medical Dictionary for Regulatory Authorities, version 15.1). Abnormal laboratory values and significant deviations from baseline within the range of normal were monitored and recorded until they returned to normal or baseline values.

Statistical analysis

$AUC_{0\rightarrow t}$ and C_{max} were tested for dose-proportionality with the following regression model: $\text{Log}(Y_{ik}) = \alpha + \beta^{*}\log(\text{Dose}_k) + \varepsilon_i$, where Y_{ik} represented the selected pharmacokinetic parameter for subject i on dose level k, α represented the intercept, β represented the slope, $k = 1, 2, 3$ were the three dose levels and ε_i was the normal error deviate. Dose-proportionality was concluded when the 95% confidence interval of the slope parameter β included the value 1. Demographic and safety data were summarized for the complete study population and for individual treatment groups using descriptive statistics (N, mean, standard deviation [SD], min, max, median). Changes from baseline were also calculated and summarized for safety data. All statistics and analyses were performed with SAS (Statistical Analysis System; Cary, NC, USA).

Results

Subjects

This study included 24 healthy Caucasian men between 18 and 43 years of age, the dose groups were similar with respect to height, weight, and BMI. The mean age was 32.0 ± 8.9 years at the time of dosing (29.2 years in the 1.5 mL group to 34.3 in the placebo group). The overall BMI was 23.3 ± 1.9 (22.3 in the placebo group to 23.8 in the 1.5 mL group). None of the subjects withdrew consent or were withdrawn by the investigator.

Pharmacokinetics and biotransformation

The highest plasma concentrations of iosimenol were obtained 2 min post-dose for the two lower dose groups and at 1 min post-dose for the highest dose group. Two minutes after intravenous administration of Iosimenol 340, $39.6 \pm 3.3\%$ (mean of all subjects $\pm$ SD) of the dose was detected in the total plasma volume, corresponding to iosimenol concentrations of 3.18 ± 1.42 mg/mL, 7.94 ± 2.76 mg/mL, and 16.41 ± 3.61 mg/mL for the three different doses (0.2, 0.5, or 1.0 gI/kg), respectively. For the highest dose group, mean plasma levels declined to less than 1.0% of the dose in total plasma volume 8 h after administration. Plasma levels for the two lower dose groups were quantifiable up to 3 and 4 h post-administration only. Individual differences in plasma concentrations showed an approximately two-fold inter-subject

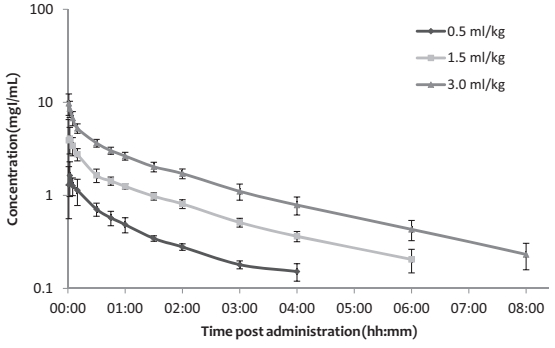

Fig. 1. Mean $\pm$ SD iosimenol plasma concentrations (mg iodine/mL) over time (hours after start of initial administration) per dosing group.

variability. As shown in Fig. 1, mean plasma concentration *versus* time curves suggest a dose-proportional increase. No urine was collected during the 2 to 4 h interval from two subjects. Most of the injected iosimenol was excreted renally within the first few hours after administration. Six hours after dosing, 76.7 ± 10.4% of iosimenol (over all concentrations) was recovered in urine, with 89.0 ± 11.4% after 24 h and 90.5 ± 11.4% after 96 h. Renal excretion was observed to be the major elimination route and 89% of iosimenol was excreted via this route within 24 h (Fig. 2). The elimination rate was independent of dose. C_{max} was reached within 1–2 min after the beginning of dosing, with the exception of two subjects where C_{max} was observed 5 min after dosing. Mean C_{max} and $AUC_{0\rightarrow t}$ increased proportionally to dose, with C_{max} values increasing from 1.80 mg iodine/mL to 9.63 mg iodine/mL, depending on dose. The 95% confidence intervals of the slope parameters for C_{max} and $AUC_{0\rightarrow t}$ were all between 0.80 and 1.25, which is consistent with the assumption of a dose-proportional increase within the tested dose range of 0.5–3.0 mL equivalent to approximately 0.2–1.0 gI/kg. There was a rapid initial distribution phase of approximately 10 min, followed by a more prolonged terminal phase. Iosimenol's elimination half-life was 2.01 h and the apparent volume of distribution was 0.27 L/kg (body weight). Mean pharmacokinetic parameters are summarized in Table 1. No metabolites were detected in plasma or urine.

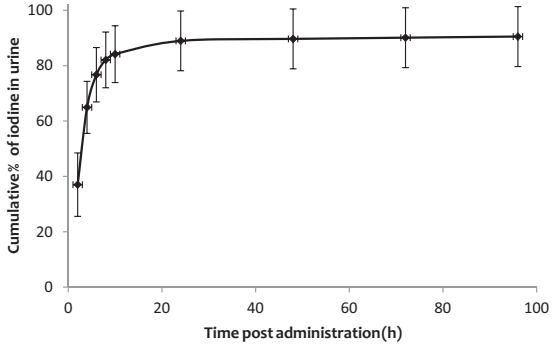

Fig. 2. Mean ± SD accumulated fraction of iosimenol dose excreted via urine, combined for all three dosing groups.

Safety and tolerability

There were no reports of deaths, serious adverse events, or clinically significant abnormalities of laboratory parameters. Fourteen (58%) of the 24 subjects experienced a total of 32 AEs, all of which were judged possibly or probably related to drug treatment (Table 2). Of these 32 AEs, 26 were mild and six were rated as moderate by the investigator (1 subject in the 0.5 gI/kg group experienced a skin rash, 1 subject in the 1.0 gI/kg dose group dizziness, 3 subjects experienced rashes and 1 pruritus in the 1.0 gI/kg dose group). Three subjects, one in the 0.5 gI/kg and two in the 1.0 gI/kg dose groups, received medical treatment (anti-histamines or corticosteroids treatment). All AEs resolved without sequelae before the end of the study. No AEs occurred in the placebo group. Most AEs (56%) occurred on the day of treatment and were of short duration. Twelve subjects reported a feeling of warmth (coded in MedDRA as ''feeling hot''), none reported pain, and five subjects reported rash and pruritus (Table 3). The pulse rate increased slightly with dose immediately after dosing, but the observed changes in vital signs were not considered to be of clinical significance. There also were no

Table 1. Summary of pharmacokinetic parameters.*

	Iosimenol 340 Dose		
Parameter	0.5 mL/kg (0.2 gI/kg, $n = 6$)	1.5 mL/kg (0.5 gI/kg, $n = 6$)	3.0 mL/kg (1.0 gI/kg, $n = 6$)
C_{max} (mg iodine/mL)	1.80 ± 0.78	4.77 ± 2.15	9.63 ± 2.73
t_{max} (h)	0.03 (0.02–0.08)	0.03 (0.02–0.08)	0.02 (0.02–0.03)
$AUC_{0\rightarrow t}$ (mg iodine *h/mL)	1.41 ± 0.23	4.50 ± 0.54	10.43 ± 1.49
Initial phase half-life ($t_{1/2,\lambda 1}$) (min)	7.2 ± 3.6	13.2 ± 7.2	10.2 ± 3.6
Terminal phase half-life ($t_{1/2,\lambda z}$) (h)	1.64 ± 0.27	2.23 ± 0.38	2.17 ± 0.30
$Ae_{,6h}$ (%) (cumulative amount excreted at 6 h)	75.0 ± 3.8	82.8 ± 5.9	72.3 ± 15.7
$Ae_{,4d}$ (%) (cumulative amount excreted at 4 days)	90.9 ± 5.0	95.3 ± 2.9	86.1 ± 19
CL (L/h)	7.40 ± 1.14	7.81 ± 1.53	6.86 ± 0.53
CL_R (L/h)	6.54 ± 0.70	7.44 ± 1.51	5.93 ± 1.25
V_z (L/kg)	0.22 ± 0.03	0.31 ± 0.02	0.29 ± 0.04

*All data are presented using the arithmetic mean ± SD, except for t_{max}, which is presented using median and range.

Table 2. Treatment of emergent AEs.*

Parameter	Iosimenol 340 dose		
	0.5 mL/kg (0.2 gI/kg, $n=6$)	1.5 mL/kg (0.5 gI/kg, $n=6$)	3.0 mL/kg (1.0 gI/kg, $n=6$)
Subjects with AEs†	4	5	5
AEs (*n*)	9	9	14
AE relationship to study drug			
Related	9	9	14
Not related	0	0	0
AE intensity			
Severe	0	0	0
Moderate	0	1	5
Mild	9	8	9

*"Related" summarizes events with "highly probable", "probable", and "possible" relationship to drug, while "Not related" refers to all events "unlikely" or "not related" to drug.
†Subjects who received placebo did not experience any AEs.

Table 3. AEs by MeDRA system organ class and preferred term.

Parameter*	Iosimenol 340 dose		
	0.5 mL/kg (0.2 gI/kg, $n=6$)	1.5 mL/kg (0.5 gI/kg, $n=6$)	3.0 mL/kg (1.0 gI/kg, $n=6$)
Gastrointestinal disorders	**2**	**1**	**1**
Glossodynia	1	0	0
Hypoesthesia oral	0	1	1
Nausea	1	0	0
General disorders and administration site conditions	4	5	4
Feeling hot	3	5	4
Infusion site rash	1	0	0
Nervous system disorders	3	1	1
Dizziness	1	0	1
Dysgeusia	0	1	0
Headache	2	0	0
Respiratory, thoracic, and mediastinal disorders	0	0	1
Throat irritation	0	0	1
Skin and subcutaneous tissue disorders	0	2	7
Pruritus†	0	1	3
Rash	0	1	2
Rash generalized†	0	0	2

*Data are presented per MedDRA (Medical Dictionary for Regulatory Authorities), system organ class (SOC), and preferred term (PT).
†All individuals who had rash also reported pruritus, one individual in the highest dose group reported two episodes of rash.

clinically relevant changes in ECG morphology, atrioventricular conduction or ventricular repolarization. QTc prolongation ≥30 ms were evenly distributed between subjects that received treatment and placebo. Two subjects had QTc prolongation ≥60 ms, one after receiving placebo and one after receiving Iosimenol 3.0 mL/kg.

Discussion

A control experiment with HPLC demonstrated the absence of metabolites in the urine and serum samples, hence the only source of iodine was non-metabolized iosimenol. With a consequent direct proportionality between the concentration of iodine and the concentration of iosimenol, pharmacokinetic calculations could therefore be based on measurements of iodine concentrations. Iosimenol 340 showed pharmacokinetic characteristics very similar to those of other available CM, such as iohexol, iopentol, ioversol, iodixanol, or iomeprol (11–16). Plasma concentrations of iosimenol increased dose proportionally and showed only little inter-subject variability. Maximal serum concentrations were detected 1–5 min after the beginning of dosing. The mean distribution half-life was approximately 10 min. Reported variations between approximately 10 and 30 min can, with such short alpha half-lives, be expected due to differences in the experimental set-up, primarily injection rates and sampling time-points. The concentration-time curves for iosimenol demonstrated characteristics of a first-order elimination process from plasma. Iosimenol was cleared from plasma at a rate similar to creatinine; therefore, creatinine clearance may be expected to be predictive for CL_R of iosimenol. Approximately 72–83% of the administered dose was recovered in urine within 6 h, similar to the proportion reported for other CM (11,16). The mean recovery rate was somewhat reduced by an outlier in the highest dose group, for whom the calculated recovery was only 42.2% after 6 h and was consistently low at all time-points. This was most likely due to incomplete urine collection. Taking into account losses in urine collection, the small proportion of extra renal excretion known from other iodinated CM and the limitations of the analytical method, the estimated recovery after 4 days indicates complete excretion (12,14,16). Similarly to previous findings in animals, iosimenol was not metabolized in humans (10). This lack of biotransformation is comparable to that reported for iodixanol administration (11). There were no clinically relevant findings from laboratory tests, ECG, or other monitoring of vital signs. The

increase in heart rate in the highest dose group immediately after dosing (10.2 beats per minute) is comparable to what has been described in the literature (17). AEs observed after administration of iosimenol were mild or moderate, and were transient. The most frequently experienced AE was a feeling of warmth (12 subjects), followed by rash and pruritus (five subjects), and headache and abnormal taste (two subjects each). The nature of AEs also seems similar to those observed with other CM (18,19). Overall all three doses of Iosimenol 340 were well tolerated and larger studies can be justified. In summary, the pharmacokinetic properties of Iosimenol 340 are similar to those of other currently used CM, confirming findings in preclinical testing (10–16).

There are potential weaknesses of the trial. As this was the first human experience with the compound, focus was on exploring the pharmacokinetic profile and gaining necessary experience to ensure adequate subject safety in larger comparative trials. The sample size was limited and there was no active control. Definite conclusions regarding the safety profile of iosimenol are therefore limited by the nature of the trial. The trial only included healthy male volunteers. Although no gender differences are expected with this type of compound, inclusion of both men and women would have been preferable.

In conclusion, the data presented demonstrate that iosimenol is well tolerated and safe to use in healthy human subjects, exhibiting an adverse event profile similar to that of other commonly used CM. Iosimenol is not metabolized, its distribution is exclusively extracellular, it is cleared by glomerular filtration and is eliminated by renal excretion.

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