

Iodixanol Pharmacokinetics in Children

W.H. Johnson, Jr.,¹ T.R. Lloyd,² B.E. Victorica,³ V.R. Zales,⁴ M.L. Epstein,⁵ R.D. Leff,⁶
R.H. Ardinger, Jr.,⁷ T.L. Slovis,⁸ J.A. Johnson,⁹ P.A. Marsters⁹

¹Department of Pediatrics, LM Barger Division of Pediatric Cardiology, University of Alabama at Birmingham, Birmingham, AL 35294, USA

²Department of Pediatrics, Division of Pediatric Cardiology, University of Michigan Medical Center, CS Mott Children's Hospital, Ann Arbor, MI 48109, USA

³Department of Pediatrics, Division of Pediatric Cardiology, University of Florida, Gainesville, FL 32610, USA

⁴The Deborah Heart and Lung Center, Browns Mills, NJ 08015, USA

⁵Division of Pediatric Cardiology, Children's Hospital of Michigan, Detroit, MI 48201, USA

⁶Departments of Pharmacy and Pediatrics, The University of Kansas Medical Center, Kansas City, KS 66160, USA

⁷Department of Pediatrics, Division of Pediatric Cardiology, The University of Kansas Medical Center, Kansas City, KS 66160, USA

⁸Department of Pediatric Imaging, Children's Hospital of Michigan, Detroit, MI 48201, USA

⁹Nycomed Inc., Wayne, PA 19087, USA

Abstract. The objective of this report was to study the elimination pharmacokinetics of iodixanol in children. Iodixanol (VISIPAQUE®, Nycomed Inc., Wayne, PA, USA) is a new iso-osmolar iodinated radiocontrast agent. We hypothesized that elimination of this agent would be dependent on age-related differences in renal clearance. Seven centers enrolled 43 patients. Cardiac catheterization was performed in 41 patients and cranial computed tomography in 2. Patients were entered into 5 age groups: newborn to <2 months, 2 to <6 months, 6 months to <1 year, 1 to <3 years, and 3 to ≤12 years. Plasma samples were obtained before and at 4 time periods after completion of iodixanol injection: 0.75–1.25 hours, 2–4 hours, 8–12 hours, and 16–32 hours. Plasma concentrations of iodixanol were determined using high performance liquid chromatography. The primary pharmacokinetic endpoint was the terminal elimination rate constant (k_{el}). Data were complete for 40 patients, showing mean k_{el} significantly lower in newborn to <2-month-old patients vs older patients: (h^{-1} , mean ± standard deviation [SD]): newborn to <2 months 0.185 ± 0.060 , 2 to <6 months, 0.256 ± 0.046 , 6 months to <1 year 0.299 ± 0.042 , 1 to <3 years 0.322 ± 0.058 , and 3 to ≤12 years 0.307 ± 0.071 ; with increasing age, excretion is more rapid, as shown by each age group's elimination half-life ($t_{1/2 \beta}$) (h) 4.14 ± 1.41 , 2.79 ± 0.55 , 2.36 ± 0.37 , 2.23 ± 0.51 , and 2.36 ± 0.52 , respectively. Iodixanol has elimi-

nation in children >6 months of age that is comparable to normal adults. Prolonged elimination in children <6 months of age is related to renal immaturity.

Key words: Angiography — Contrast media — Pharmacokinetics

Iodixanol (VISIPAQUE® Injection) is a dimeric, nonionic radiographic contrast medium, which, unlike traditional ionic and nonionic contrast agents, has an osmolality equal to blood. Iodixanol may offer advantages over conventional hypertonic media, particularly in children with renal and myocardial immaturity. The elimination of iodixanol in children has not been previously studied.

Clearance of contrast agents in adults occurs primarily by renal elimination [9]. Patients with renal impairment have delayed elimination and prolonged plasma levels of contrast agents, including iodixanol, that are linearly related to the glomerular filtration rate (GFR) [5]. We hypothesized that the same would be true of infants (aged 0–6 months), in whom normal renal function, as assessed by GFR, is less than adult values [8]; this would result in slower renal elimination of iodixanol and lower terminal elimination rate constants (k_{el}). This would also show that k_{el} in older children would be similar to those reported for adults.

We performed a multicenter study to test this hypothesis by determining the pharmacokinetic profile of iodixanol in pediatric patients undergoing contrast-enhanced diagnostic procedures.

Materials and Methods

Study Centers

Seven pediatric centers participated: the University of Alabama at Birmingham, Birmingham, AL, USA; CS Mott Children's Hospital, Ann Arbor, MI, USA; the University of Florida, Gainesville, FL, USA; the Deborah Heart and Lung Center, Browns Mills, NJ, USA; Children's Hospital of Michigan (the Division of Pediatric Cardiology and the Department of Pediatric Imaging operated as separate entities), Detroit, MI, USA; and the University of Kansas Medical Center, Kansas City, KS, USA.

Authors JAJ and PAM were employed by the study sponsor, Nycomed, Inc. Other than the support provided by Nycomed, Inc. to each center for conducting this study, the other authors have no commercial interest in Nycomed, Inc.

Patients

Newborn infants (≥ 36 weeks gestational age and ≥ 2000 g body weight at time of enrollment) to children ≤ 12 years of age, referred for an iodinated contrast-enhanced intravascular diagnostic procedure, were eligible. Patients undergoing interventional procedures (biopsy, balloon atrial septostomy, coil embolization, balloon dilation of aortic or pulmonary valves, or coarctation) were included.

Prior approval by each center's human subjects Institutional Review Board was received, and written informed consent was obtained from the parent or legal representative of each patient. No incentives were offered; iodixanol was provided by Nycomed at no cost.

Radiographic Use

Iodixanol (5,5'-[(2-hydroxy-1,3-propanediyl)bis(acetylimino)]-bis[N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide]) was supplied by Nycomed Inc. (Wayne, PA, USA) as a 652 mg/ml solution, equivalent to 320 mgI/ml. Patients received iodixanol in identical fashion to approved contrast agents, without modification of dose or administration method. Pharmacokinetic samples were obtained at baseline (preinjection) and at four time periods after injection: 0.75–1.25 hours, 2–4 hours, 8–12 hours, and 16–32 hours. Blood samples were collected in potassium oxalate/sodium fluoride Vacutainer™ tubes (Becton Dickinson, Rutherford, NJ, USA) and were spun immediately. The plasma was separated, was frozen to $\leq -20^\circ\text{C}$, and was shipped to Nycomed Inc. for analysis.

Iodixanol Assay

Plasma iodixanol assays were performed by Nycomed Inc. using size-exclusion, high-performance liquid chromatography with ultraviolet detection [4]. The assays were modified as follows: reference standard concentrations ranged from 1.5–1000 $\mu\text{g/ml}$. The assay was validated to a minimum quantifiable level of 1.5 $\mu\text{g/mL}$. Triplicate quality-control samples at three concentrations were included in each analytical run.

Pharmacokinetic Analysis

Based on data for adults, the concentration vs time curve is best estimated by a one-compartment model with a first-order elimination rate.

In adults, the distribution phase for intravascular administration is of small magnitude and occurs rapidly, so this term was assumed to be zero. The terminal elimination rate constant (k_{el}) was computed by linear regression of the natural logarithm of the plasma iodixanol concentration as a function of time:

$$c(t) = c_0 e^{-k_{el}t}$$

where $c(t)$ is the concentration at time t , c_0 is the concentration at time 0, and t is the time after the end of the administration of iodixanol (defined as time zero). Preinjection sample times were set to zero and actual times were used for all postinjection samples. Elimination half-life was calculated as $t_{1/2} = 0.693/k_{el}$.

Study Design and Statistical Analysis

Male and female patients were enrolled by age into 5 age groups: birth to < 2 months, 2 to < 6 months, 6 to < 12 months, 1 to < 3 years, and 3 to ≤ 12 years. Analysis of interinstitutional differences was not performed because no more than 10 patients were enrolled per center.

The relationship between k_{el} and age for individual patients was modeled using a linear-plateau model [2, 6] (details available from the authors). k_{el} was analyzed for dose (continuous) and age-group (class) effects using a general linear model, because the dose of iodixanol varied from patient to patient in each group. Sample size was selected with the expectation that k_{el} in the youngest and oldest age groups could be distinguished from one another, based on published renal elimination rates [8]. We chose age-group intervals corresponding to these published data. Statistical tests were performed with a level of significance set at 0.05.

Results

Patient Demographics

Forty-three patients were enrolled, ranging from 2–10 patients per center. All patients completed the trial. The data from 40 patients were used in the pharmacokinetic analyses. Two patients had incomplete pharmacokinetic sampling data; their pharmacokinetic data were excluded. Two additional patients were enrolled as replacements in the same respective age groups. A third patient was excluded from pharmacokinetic analyses because of abnormal renal function before participation in the trial. One patient, entered in error as the ninth patient in the 6 month to < 1 year of age group, was included in the analyses.

The majority of the patients were boys (63%) and Caucasian (60%); the median age was 0.56 years (range 0–10.4) and median body weight 6.6 kg (range 3–40) (Table 1). The majority of patients (56%) had more than one diagnosis; the most common was ventricular septal defect (40%), followed by patent ductus arteriosus (19%), aortic stenosis (16%), tetralogy of Fallot (14%), atrial septal defect (14%), pulmonary stenosis (14%) and aortic hypoplasia (12%).

Table 1. Patient demographics and iodixanol dose

Patient group	<2 months	2 to <6 months	6 to <12 months	1 to <3 years	3 to ≤12 years	All patients
Number of patients	8	9	10	8	8	43
Age	2 days 12 hours–59 days	0.29 years 0.17–0.41 years	0.67 years 0.51–0.90 years	1.84 years 1.06–2.96 years	6.46 years 3.16–10.41 years	0.56 years 0–10.41 years
Weight kg	4 3–5	4.9 3–6	7.3 6–11	11.3 7–14	19.1 14–40	6.6 3–40
Dose gI/kg ^a	1.5 0.7–3.2	1.5 1.0–2.9	1.3 0.8–2.7	1.2 0.3–3.0	0.8 0.3–1.3	1.3 0.3–3.2
Dose volume ml/kg	4.8 2.0–10.0	4.8 3.3–9.0	4.2 2.4–8.5	3.9 1.1–9.2	2.4 1.0–4.0	4.0 1.0–10.0
Number of injections	2.5 1–5	3 2–5	3 1–4	3 1–8	2 1–2	2 1–8

Data are median and range.

^a g iodine/kg body weight.

Type of Study, Dose, and Mode of Iodixanol Delivery

Two patients who underwent head and/or neck CT scanning received intravenous iodixanol, whereas all other patients had injection during angiocardiology. The mean (\pm SD) dose of iodixanol 320 mgI/ml was 1.49 ± 0.75 gI/kg and the mean total volume was 4.67 ± 2.34 ml/kg. Median and range of dose data are presented in Table 1. The mean duration of the procedure was 30 ± 29 minutes (range 0–102) and the median number of injections was 2 (range 1–8).

The median dose per kg of iodixanol 320 mgI/ml and median total volume per kg was similar for the four patient groups less than 3 years of age. The median dose per kg and median total volume per kg for patients ≥ 3 years of age were approximately half that for patients < 3 years of age (Table 1). Patients < 3 years of age received an average of approximately 3 injections per patient; patients ≥ 3 years of age averaged 1.6 injections per patient.

Concurrent Medications and Drug Interaction

Concurrent medications (from 24 hours before the start of the radiographic procedure until up to 32 hours postinjection) were received by 36 (84%) of patients; the majority (63%) received cardiovascular medications (e.g., digoxin, diuretics). Premedication/procedural medications were received by all patients. These medications included sedatives, anesthetics, and analgesics by 98% of patients, cardiovascular drugs (e.g., inotropes, vasodilators, prostaglandin) by 74% of patients, and antithrombotic drugs and/or intravenous solutions by 61%. No drug interactions were identified.

Pharmacokinetics

The highest plasma iodixanol levels were found during the first sampling period (0.75–1.25 hours) after injection,

and ranged from 970–11,102 μ g/ml, with a median of 4718 μ g/ml.

The mean k_{el} was significantly lower in the newborn to < 2 month age group than in any of the three oldest age groups ($p \leq 0.0001$). Mean k_{el} for the 2 to < 6 month age group (0.256/h) was intermediate between that of the newborn to < 2 month age group (0.185/h) and those of older patients (0.299/h to 0.322/h). Total dose was not a significant independent variable ($p = 0.08$). The mean k_{el} in the youngest age group (0.185/h) represented approximately 55% of the adult mean k_{el} value of 0.336/h [1] (Table 2).

A segmented linear regression model (Fig. 1) showed increasing k_{el} from birth to approximately age 0.55 years (95% CI: 0.36 to 0.75 years). The model also showed estimated k_{el} for patients over 0.55 years as 0.313/h (corresponding to an elimination $t_{1/2}$ of 2.21 h). The predicted k_{el} at birth was 0.169/h (95% CI: 0.131 to 0.208/h, or a $t_{1/2}$ of 4.1 h). This model accounted for almost 97% of the observed age-related variability in k_{el} .

Laboratory Data

Preinjection serum creatinine values ranged from 0.1–1.1 mg/dl and did not correlate with age. Renal function was considered normal-for-age in all but the one patient who was excluded from the analyses. One day postinjection, 2 patients had increases in serum creatinine to levels above the 95% CI for age, yet no creatinine value exceeded 1.1 mg/dl in any patient. No patient showed clinical evidence of renal insufficiency, except for the patient excluded because of preexisting renal insufficiency. No patient had evidence of structural renal abnormalities.

Discussion

Pharmacokinetic data regarding contrast media in children is limited [3, 7]. However, the pharmacokinetic pro-

Table 2. Iodixanol elimination rate constant (k_{el}) and elimination half-life ($t_{1/2}$) by age group

Age group	N	k_{el} (h^{-1})		$t_{1/2}$ (h)	
		Mean	SD	Mean	SD
Newborn to <2 months	8	0.185	0.060	4.14	1.41
2 to <6 months	8	0.256	0.046	2.79	0.55
6 months to <1 year	9	0.299	0.042	2.36	0.37
1 to <3 years	7	0.322	0.058	2.23	0.51
3 to \leq 12 years	8	0.307	0.071	2.36	0.52

files of several iodinated radiographic contrast agents are well described in adults [5, 9, 10, 11]. In a single-dose study of iodixanol administered to 40 healthy adult men [9], approximately 97% of iodixanol was excreted unchanged in the urine within 24 hours. Elimination was independent of dose and was similar to other nonionic agents.

We found iodixanol elimination rates in children older than 6 months ($t_{1/2}$ β 2.32 hours), similar to those reported for healthy adults ($t_{1/2}$ β 2.05 hours) [9]. In adults with renal impairment, renal elimination of iodixanol and iohexol is via glomerular filtration only [5]. In our patients <2 months of age, we demonstrated prolonged clearance of iodixanol. This corresponds to this age group's lower, yet normal-for-age, GFR as published [8]. Infants in the 2 to 6-month age group had elimination intermediate between our youngest infants and patients older than 6 months. Our data confirm our hypothesis of an age-dependent renal elimination of iodixanol.

Our findings suggest that in pediatric patients, the renal elimination of iodixanol should be similar to conventional contrast media. We speculate that safety of

iodixanol in children should not be related to its elimination pharmacokinetics.

In adult patients, clinical trials of iodixanol demonstrated similar efficacy, safety, and pharmacokinetics as compared with other nonionic agents [1]. Iodixanol solution is hypotonic at iodine concentrations adequate for imaging. Sodium and calcium are added to obtain a plasma-isoosmolal solution. The presence of sodium and calcium ions in iodixanol, and its osmolality, may result in fewer side effects. However, higher viscosity, as compared with other agents, may be a relative disadvantage.

More experience is needed in infants and children to determine if the chemical properties of iodixanol confer safety advantages over conventional nonionic agents.

Study Limitations

Our study is limited by the absence of a comparison group of pediatric patients receiving a conventional, non-ionic agent. Although our patients had normal indicators of renal function for age, we did not measure creatinine clearance or GFR. The performance of these studies in pediatric patients is no less problematic today than when the widely accepted renal clearance data, upon which we based our hypotheses, were first measured decades ago [8]. It is possible that concurrent drugs could have altered iodixanol clearance by altering renal blood flow (e.g., inotropes) or by a direct effect on renal filtration (e.g., prostaglandin). However, our patient numbers were too small for analysis of a specific drug's possible effect. Although we found no relation of iodixanol dose to elimination rate, it is possible that a dose effect might be evident in the youngest patients, given a larger sample size.

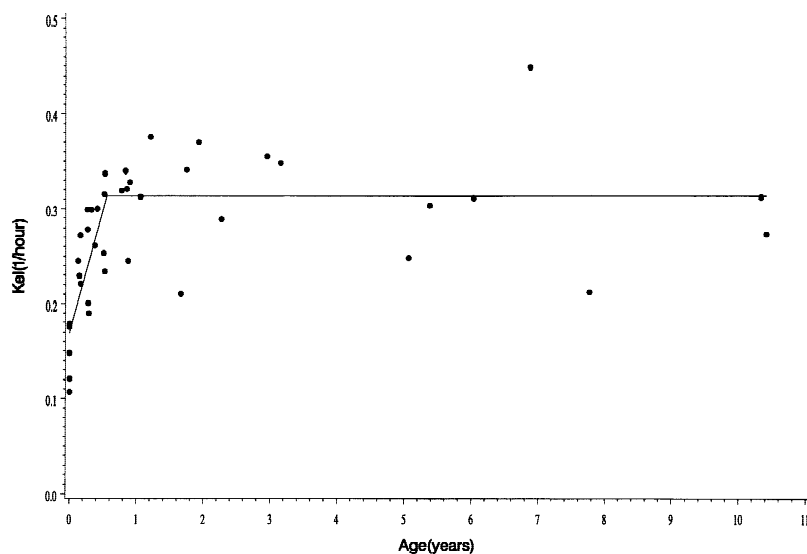


Fig. 1. Analysis of k_{el} vs age for iodixanol. The terminal elimination rate constant, k_{el} (h^{-1}) is plotted against age (years) for each individual patient (closed dots). Using a segmented linear regression model, k_{el} increases with increasing age from birth to a value of 0.313/h at 0.55 years, according to the regression $k_{el} = 0.169 + 0.26(\text{age})$; at ages older than 0.55 years, k_{el} is relatively constant, represented by a horizontal line with y-intercept of 0.313/h.

Conclusion

Our study demonstrates that iodixanol injection (320 mgI/ml), when used as a radiographic contrast agent in pediatric patients undergoing angiography or CT scanning, is eliminated in a fashion similar to that in adults. The elimination is dependent on the age-related degree of renal maturity.

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