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Pharmacokinetics of Iopamidol After Intrathecal Administration in Humans

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The kinetics of iopamidol, a new nonionic radiocontrast agent, were evaluated in 10 patients undergoing lumbar myelography. The doses of iopamidol administered intrathecally were 11 and 15 ml of a 200-mg iodine per ml solution in one and nine patients, respectively. Radiographs were made within 30 to 40 min and CTs were taken at about 1, 6, and 23 hr after iopamidol administration. The diagnostic quality and usefulness of the conventional and CT myelograms were considered excellent. In the lumbosacral subarachnoid space, the densitometry CT readings were maximal at 1 hr, whereas in the cervical subarachnoid space, peak CT values were reached at 6 hr. Plasma and urine samples were taken at frequent intervals up to 48 hr after the contrast agent was administered. Peak plasma levels of iopamidol were observed at 2.9 hr and were no longer detectable at 48 hr. The 48-hr urinary recovery for all patients averaged 66 ± 8% of the dose. In all but one patient, iopamidol was cleared almost completely from the CSF within 24 hr. Side effects after iopamidol administration were transient and minor, and were not related to the CT readings or its systemic clearance.

The use of nonionic iodinated contrast agents for myelography permits excellent visualization of anatomic structures [1–4]. Because these agents are water-soluble, they mix readily with CSF before their eventual transfer into the systemic circulation for elimination. A new nonionic agent, iopamidol, has been extensively evaluated in lumbar myelography and has been shown to be equivalent in efficacy to metrizamide, another nonionic contrast agent [5, 6]. Iopamidol has also been reported to have a more favorable side-effect profile than metrizamide [5–8].

Iopamidol has desirable pharmacokinetic properties for a myelographic agent [9]. In healthy subjects, iopamidol is not metabolized, is poorly protein-bound, and has a volume of distribution approximately equivalent to that of the extracellular fluid space. After intravenous administration, 90% or more of the dose is recovered in the urine within 1 day. The whole-body clearance of this agent is about 1.9 ml/min/kg and its elimination half-life is about 2 hr [9]. The kinetics of iopamidol after intrathecal administration in humans have not been explored and are the subject of this report.

Material and Methods

Ten patients (6 men and 4 women) were enrolled in this investigation. Exclusion criteria included a history of allergic reaction to iodinated contrast medium, convulsive disorder, hyperthyroidism, seizure disorder, a spinal puncture within the past month, impaired renal or liver function, use of medications within the past month that might lower seizure threshold, or clinical diagnosis of major psychiatric disorder, alcoholism, durg abuse, multiple sclerosis, or increased intracranial pressure. The mean age of these patients was 41 years (range: 27–57 years) and the average weight was 71.2 kg (range: 63.5–83.9 kg). Within 5 days before myelography, each patient gave a complete history; had physical, hematologic, and neurologic examinations; and were given a standard clinical laboratory battery, a complete urinalysis, and, for females, a urine chorionic gonadotrophin test for pregnancy. About 36–72 hr after

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injection of iopamidol, all physical, neurologic, and laboratory examinations, excluding pregnancy tests, were repeated. Blood pressure, pulse rate, temperature, and respiratory rate were obtained before and at frequent intervals after iopamidol administration. All patients were well hydrated and had ingested no solid food for 8 hr prior to and after the myelographic procedure. Written informed consent was obtained from each patient prior to entry into the study.

After intradermal local anesthesia (1–2 ml of 1% lidocaine), a narrow (20–22 gauge) needle was inserted under fluoroscopic control at either the L3 or L4 disk space. After the subarachnoid space was entered, 5 to 10 ml of CSF was removed for laboratory analysis. One patient received 11 ml of iopamidol (200 mg I/ml) and nine patients were given 15 ml of iopamidol (200 mg I/ml). After the radiographs were taken, patients were placed on a stretcher with their heads elevated (30°) and instructed to remain in a head-up position for at least 8 hr. Only clear liquids were given over the first 8 hr after the procedure. CTs were performed at the L3–L4 and C3–C4 disk space levels just prior to and at 1 hr (range: 0.5–2), 6 hr (range: 5–7), and 23 hr (range: 21–27) after iopamidol administration. The relative CT numbers were determined by a GE-8800 scanner for 5 × 5-mm pixel region of interest. The average number of pixels used to calculate the CT values was 25.

All radiographs and CTs were evaluated for technical and diagnostic adequacy by a neuroradiologist who did not perform or witness the procedure. These films were graded on a scale from 0 (no visualization) to 3 (superior visualization permitting easy diagnosis).

Venous blood samples (5 ml) were obtained aseptically from a suitable forearm vein using an appropriate heparinized Vacutainer tube before and at 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hr after the contrast agent was given. Urine was collected over the 0–12-, 12–24-, 24–48-, and 48–72-hr intervals after iopamidol administration. In patients who were scheduled for surgery soon after myelography, the 48- and 72-hr plasma and the 24–48-, and 48-72-hr urine samples were not obtained.

In all samples, iodine concentration was determined by fluorescent excitation analysis and then converted to iopamidol concentrations [10]. The following pharmacokinetic parameters were determined for individual patients by standard methods: maximum plasma concentrations (Cmax), time to maximum plasma concentration (Tmax), area under the plasma concentration-time curve (AUC) from 0–24 hr, and cumulative urinary excretion (0–48 hr). Systemic clearance was determined as dose administered/$AUC_{0\rightarrow\infty}$. It was assumed that all the iopamidol from the intrathecal space was absorbed into the systemic circulation because the AUC from a 15-ml dose given intravenously (917 ± 36 μg × hr/ml) in an earlier study [9] was not different from the AUC (931 ± 98 μg × hr/ml) obtained in the present study.

Results

The technical adequacy of the radiographs from each patient was considered excellent. The mean overall diagnostic adequacy of all the films was 3.0. The visualization of the subarachnoid space, the exiting roots and root sleeves, and the rootlets of cauda equina was rated excellent, and the conus margins were defined adequately or excellently. The diagnostic usefulness of the CTs with iopamidol was considered excellent and was similar to findings in other studies with this contrast agent [11].

Figure 1 gives the mean plasma levels of iopamidol after injection of 15 ml of this agent in nine patients. Cmax levels averaged 112.7 ± 15.4 μg/ml (mean ± standard error of the mean [SEM]) and were reached at 2.9 ± 0.5 hours (Table 1).

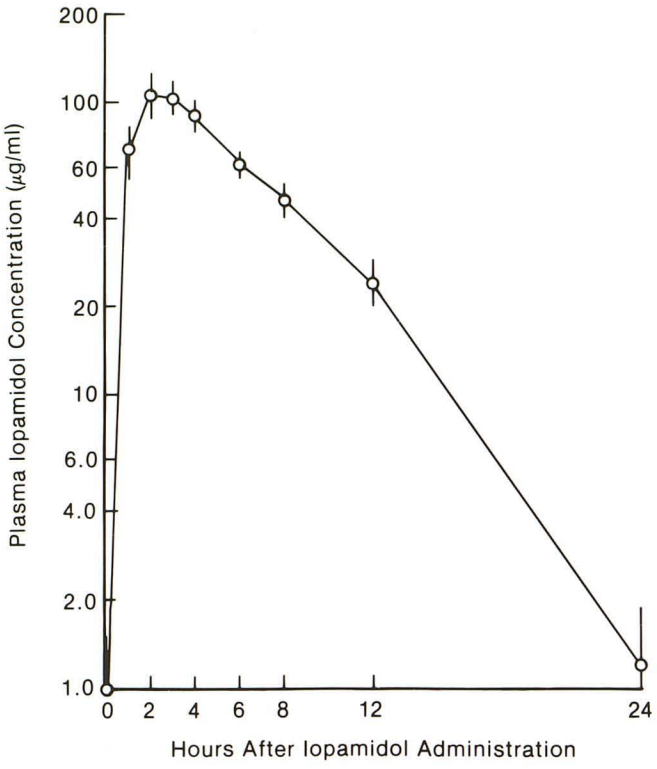

Fig. 1.—Mean (± SEM) plasma concentrations of iopamidol after intrathecal administration of 15 ml of iopamidol (200 mg I/ml).

The systemic clearance of iopamidol (both doses) was 1.35 ± 0.1 ml/min/kg. On average, almost half of the administered dose was excreted in the urine within the first 12 hr. In 48 hr 66.3 ± 8% (range: 29.3–100.9) of the dose was excreted. The wide range for urinary recovery was probably due to incomplete urine collections in some patients. In five patients for whom reasonable urine volumes were reported (i.e., ≥ 1 l/24 hr), 48-hr urinary recoveries ranged from 83–100% of the dose.

The average densitometry readings obtained from the CT scanner at various times after iopamidol administration are shown in Table 2. In the lumbosacral region, the highest readings occurred at the 1-hr interval and fell to a mean of 10% of those levels at 23 hr except in one patient whose value decreased to 42% of the 1-hr reading. Overall, the decrease in densitometry reading was proportional to time after drug administration ($r = 0.996, p < 0.001$). In the cervical region, peak iodine levels, as reflected by CT readings, were reached at about 6 hr, as the contrast medium moved rostral from the lumbar region. The CT readings recorded for the cervical cord tended to increase slightly over 24 hr for most patients.

No significant changes in blood pressure, pulse rate, temperature, respiratory rate, or clinical laboratory tests were observed after iopamidol administration.

Six patients experienced adverse reactions during the study, with multiple reactions reported for some patients. The

TABLE 1: **Systemic Iopamidol Kinetics After Intrathecal Administration**

Iopamidol Dose (ml)	No. of Patients	Cmax (μg/ml)	Tmax (hours)	AUC (μg × hr/ml)	Cl (ml/min/kg)	48-Hr Urinary Excretion (% dose)
11	1	141.5	2	1132	†	†
15	9	112.7[a]	2.9	931	1.35	66
		(15.4)[b]	(0.5)	(98)	(0.10)	(8)

Note.—Cmax = peak concentration of iopamidol in plasma; Tmax = time to reach peak concentration; AUC = area under plasma concentration vs time curve of iopamidol over 24 hr; Cl = systemic clearance of iopamidol.

† Since this parameter is independent of dose, the value for this patient is included in the results for the 15-ml dose.

[a] Mean value.

[b] Standard error of the mean.

TABLE 2: **Average CT Densitometry Values[a] After Iopamidol Administration**

Iopamidol Dose	No. of Patients	Lumbosacral SAS[b]			Cervical SAS			Cervical Cord		
		1 Hr	6 Hr	23 Hr	1 Hr	6 Hr	23 Hr	1 Hr	6 Hr	23 Hr
11	1	397[c]	113	31	50	31	12	5	4	3
15	9	408[d]	286	44	30	85	25	2	7	8
		(64)[e]	(79)	(18)	(10)	(20)	(11)	(1)	(3)	(5)

[a] Values (Hounsfield type), computed by a GE-8800 scanner, represent change in CT density from baseline values obtained before iopamidol administration. The average number of pixels used to compute these values was 25 for a 5 × 5-mm region of interest.

[b] SAS = subarachnoid space.

[c] Values for the one patient given the 11-ml dose.

[d] Average value (± SEM) for the nine patients given the 15-ml dose.

[e] Standard error of the mean for nine patients.

most common adverse effects, which were reported in four patients each, were moderate to severe headache and mild to moderate nausea and vomiting. The headaches lasted for 12–72 hr and nausea and vomiting lasted for 0.16–10 hr. Mild vasovagal reactions were reported in two patients and lasted for about 5 min after iopamidol was given. Three patients complained of either a stiff neck, back pain, or neck pain of moderate intensity, lasting from 7.5 to 48 hr after injection of iopamidol. Many of these reactions were considered to be due to the spinal puncture, but it could not be ascertained whether several incidences of headache, nausea, vomiting, and neck pain were due to the myelographic procedure or the iopamidol.

Similar adverse reactions have been reported with metrizamide [5]. Some reports have indicated that metrizamide may be more neurotoxic than iopamidol [6, 12].

Discussion

The results of this study indicate that iopamidol is readily cleared from the lumbar subarachnoid space into the systemic circulation. The tomogram readings for the lumbosacral area were maximal at 1 hr and had fallen approximately 10-fold by 23 hr. This is consistent with effective removal or clearance of iopamidol from this region of the subarachnoid space. By 6 hr the density in the cervical subarachnoid space had increased by nearly 3-fold from levels obtained at 1 hr. However, the density achieved was inadequate for a myelogram in this region.

The systemic plasma levels of iopamidol reflected the disappearance of the contrast material from the CSF, as assessed by radiographic procedures. Peak plasma levels were reached at nearly 3 hr and were at or near baseline levels at 24 or 48 hr. In a nonhuman primate study, maximal levels of iodine in serum were reached at 2.25 hr and only small amounts of iodine remained at 24 hr after the injection of a single intrathecal dose [13].

In healthy male subjects, a significant amount (~90% or more) of an intravenous dose of iopamidol is recovered in the urine within 24–96 hr [9]. In the present study, all patients had normal renal function, yet an average of only 66% of the dose was excreted in the urine. The failure of all patients to collect all their urine may have contributed to the lack of total recovery of the drug. Urinary recoveries of 83–100% of the dose were found in five patients who appeared to have reasonable 48-hr urine volumes. Our data for urinary recovery are similar to the results of another study, in which 72–85% of the dose was recovered in patients' urine within 72 hr after intrathecal administration of iopamidol [14]. The urinary recovery of metrizamide after intrathecal administration to patients averaged 59% of the dose administered in another study [15].

Interestingly, at 23 hr after injection of iopamidol, one patient in this study had only a 58% reduction in CT readings in the lumbosacral area and, in addition, had the lowest Cmax (38.8 μg/ml) and AUC (558 μg × hr/ml), and the highest Tmax (6 hr) of iopamidol, relative to the other patients. Ranges of 63.5–172.3 μg/ml (Cmax), 677–1523 μg × hr/ml (AUC), and 2–4 hr (Tmax) were observed for the other eight patients. The systemic clearance of iopamidol in this patient was consistent with that of the others; i.e., 1.41 ml/min/kg, compared

with an overall mean of 1.35 ml/min/kg for all 10 patients. The former patient had undergone a lumbar laminectomy 2 years before this study; thus, these results were most likely due to a slow release of iopamidol from the central nervous system. These postmyelography CT findings confirmed the presence of obstructive scarring in the lower lumbar sac. No adverse effects occurred in this patient.

In conclusion, iopamidol is cleared rapidly and efficiently from the intrathecal space. After intrathecal administration, iopamidol appeared in plasma within 1 hr and was essentially undetectable 48 hr later. The comparable serum/plasma AUC values for 15-ml doses given intravenously in an earlier study and intrathecally in the present study indicate that virtually all the iopamidol given intrathecally reached the systemic circulation within 24 hr.

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