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Neuroangiography with Iohexol

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Iohexol is a new, nonionic water-soluble contrast agent undergoing early clinical trials in the United States. Using a double-blind, parallel format, iohexol was compared with meglumine iothalamate (60 patients) for selective cerebral angiography, and with sodium meglumine diatrizoate (40 patients) for arch aortography. Iohexol produced significantly less pain than meglumine iothalamate or sodium meglumine diatrizoate. There were no significant differences in terms of heart rate, blood pressure, or electrocardiogram (ECG) changes. Both produced a transient tachycardia and hypotension after arch aortography, but significantly less so with iohexol. No significant complications occurred. Film quality was comparable between contrast agents except for diminished motion artifacts with iohexol. Iohexol appears to be a superior neuroangiographic contrast agent to current ionic drugs.

Neuroangiography, involving the selective injection of carotid and vertebral arteries as well as flush injections of the aortic arch, follows myelography as the most frequent "invasive" neuroradiologic procedure performed. About 250,000 cerebral angiograms are obtained yearly in the United States with the following complication rate: minor complications, 5%; significant morbidity, 0.5%; and mortality, 0.1% [1, 2]. Adverse effects resulting from this procedure can be attributed to the contrast media injected and/or technical, mechanical factors such as arterial damage and emboli. Essentially all neuroangiographic procedures are now performed with "modern" ionic contrast agents using a meglumine salt of either diatrizoate or iothalamate. The adverse effects produced by these compounds are due to the extreme hyperosmolality of the ionic contrast media and the inherent neurotoxicity of the drugs [3, 4]. These factors, plus patient discomfort during the procedure, significantly limit the acceptability of the technique to selected patients. The recent development of water-soluble nonionic contrast agents has provided potentially less neurotoxic and painful media.

The purpose of this paper is to present the results of our clinical evaluation of one of these new nonionic agents, iohexol. Iohexol is a neutral, nonionic, water-soluble, hydrostable contrast medium with a molecular weight of 821 (iodine content 46.4%). Iohexol has previously been shown to have a low order of neurotoxicity in animal studies and to be clinically acceptable in preliminary European studies [5].

Subjects and Methods

Selective Cerebral Angiography

Sixty adult patients were randomly assigned to receive either iohexol (30 patients) or meglumine iothalamate (30 patients). Each

patient received only one contrast medium for his neuroangiographic workup. The contrast medium was placed in the injector by an assistant, so that the agent used was unknown to the investigator and patient. The patients were premedicated with atropine (0.4 mg) and nonnarcotic sedatives, usually Valium 2.5–7.5 mg intravenously. To be included in the study, a patient required selective carotid and/or vertebral angiography on clinical grounds, was 18 years of age or older, and was not pregnant. Patients who were incapable of judging pain, allergic to iodine-containing drugs, previous recipients of contrast injection within 48 hr, had serum creatinine levels of greater than 3 mg/dl, or required emergency procedure were excluded from the study.

Serum creatinines were obtained 24 hr and immediately before cerebral angiography and 24 hr after the procedure. Vital signs including oral temperature, pulse rate, and supine blood pressure were recorded 30 min before the first injection and 15 min, 3 hr, and 24 hr after the final contrast injection. A brief neurologic examination was also performed at these times. Neurologic status was also evaluated after each injection with motor function, vision, and speech specifically tested.

Clinically appropriate selective injections were made with doses of 10–20 ml for common carotid, 10 ml for internal carotid, 5–8 ml for external carotid, and 6–12 ml for vertebral injections. Another 50 ml of contrast agent was used for those patients requiring an aortic arch flush injection. While the aortic injections were performed, they were not specifically evaluated in these results due to the limited number of injections. The iohexol had a concentration of 300 mg I/ml while the meglumine iothalamate had a concentration of 290 mg I/ml.

Immediately before and for 1 min after each injection, strip recordings of the electrocardiogram (ECG) and arterial blood pressure were made. The blood pressure was obtained through the injection catheter. Systolic and diastolic blood pressure, pulse rate, Q-T intervals, ST segment, and T-wave amplitudes were specifically evaluated for change.

After each injection, the patient was asked to describe the type of discomfort experienced (heat, pain, etc.) and the degree of discomfort on a scale of 1–4 (1 = no reaction; 2 = slight discomfort; 3 = definite but tolerable discomfort; 4 = severe excruciating discomfort). The radiologist performing the injection also evaluated the patient's response on a scale of 1–4 (1 = no response; 2 = slight discomfort with mild visible and/or audible signs of discomfort; 3 = moderate discomfort with definite visible and audible signs; 4 = severe with evidence of definite patient distress). The radiologist performing the procedure also evaluated the imaging effectiveness on a scale of 1–4 (1 = no visualization; 2 = poor visualization; 3 = good visualization; 4 = excellent visualization).

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The final radiographic diagnosis was also recorded. The various factors evaluated were statistically compared between the two populations using a *t* test.

The purpose of this protocol was to compare the discomfort associated with injections of iohexol with that of meglumine iohalamate as well as to compare the imaging effectiveness and safety of the two compounds.

Arch Aortography

Forty adult patients were selected using basically the same criteria as on the selective cerebral angiography protocol, except that they required two aortic arch injections rather than selective cerebral injections. Most of these patients also received additional vascular injections for visualization of the abdominal aorta and/or lower extremity vessels. These additional injections were not specifically evaluated, except that any complications from the procedure as a whole were noted. The first two injections performed were of the aortic arch and proximal brachiocephalic vessels with the patient first in the right posterior oblique and then the left posterior oblique position. The type of contrast medium used for each injection was determined by a computer-generated randomized code. Contrast agents used were iohexol at a concentration of 350 mg/l/ml and sodium meglumine diatrizoate at a concentration of 370 mg/l/ml. The patients were subdivided into four groups (table 1). Any additional injections used were of commercially available sodium meglumine diatrizoate.

Immediately before and for 2 min after each injection, intraarterial blood pressure was monitored as was the ECG. Specifically, systolic and diastolic blood pressure, Q-T interval, ST segment, T-wave amplitudes, and heart rate were analyzed. After each injection a brief neurologic examination was performed, which included testing motor function, vision, and speech.

After each injection, the patient was asked to rate the intensity of the reaction on a scale of 0 (no discomfort) to 10 (severe or excruciating discomfort). After both test injections had been performed, the patient was asked to report which injection was the most uncomfortable. The radiologist performing the procedure rated the patient's response on a scale of 1-4 as with the previous protocol and also rated the imaging effectiveness on a similar scale. Final radiographic diagnosis was noted.

The primary purpose of this protocol was to compare the discomfort associated with iohexol with that of sodium meglumine diatri-

zoate, as well as compare the imaging effectiveness and safety of the two compounds.

Results

Selective Cerebral Angiography

None of the 60 patients receiving iohexol or meglumine iohalamate suffered any significant change in their neurologic status during or after the procedure. No significant changes in serum creatinine were noted. There were 106 selective injections in the iohexol patients and 106 selective injections in the meglumine iohalamate patients. For statistical purposes, each injection was handled as a separate unit. Using the *t* test, no significant change from baseline occurred with either contrast agent in terms of pulse rate, systolic or diastolic blood pressure, heart rate, or the ECG parameters measured.

There were statistically significant differences in the patients' discomfort response between the two contrast agents (table 2). Significantly more patients (19 versus four) reported more severe heat with meglumine iohalamate than iohexol, as well as more severe pain (12 versus five). More patients (33 versus 19) reported no heat after injection with iohexol than with meglumine iohalamate. While these figures are statistically significant ($p < 0.05$), there was no statistical difference between patients reporting mild to moderate heat, no pain, or mild to moderate pain.

The radiologist's evaluation of imaging efficacy was not statistically significant between the two groups. The radiologist performing the procedure did report a significantly greater number of patients with observable motion after meglumine iohalamate (26 versus three); however, this did not obviously denigrate the quality of the examinations.

In summary, these results indicate no statistical differences in the two patient populations in the parameters measured, except for patient discomfort and patient motion. Iohexol produced less of each.

Arch Aortography

As outlined in the protocol, 10 patients received both aortic injections with iohexol, 10 had both injections with sodium meglumine diatrizoate, and 20 had one injection of iohexol and the other of sodium meglumine diatrizoate. Twenty of these patients received iohexol in the first injection while the other twenty received sodium meglumine diatrizoate as the first injection. Of the various parameters statistically evaluated in the protocol, only those measurements related to patient discomfort, blood pressure, and heart rate showed significant differences. There was no significant difference in the numeric rating of discomfort in those patients receiving iohexol or sodium meglumine diatrizoate only. However, in those patients who received both contrast agents, there was a significantly lower discomfort response (3.75) with iohexol than with sodium meglumine diatrizoate (5.05). Furthermore, in these patients, 15 reported sodium meglumine diatrizoate to be more painful or hot

TABLE 1: Injection Protocols of Four Groups of Patients Studied with Arch Aortography

Group No.	Contrast Medium	
	Injection 1	Injection 2
1	iohexol	Diatrizoate
2	Diatrizoate	iohexol
3	iohexol	iohexol
4	Diatrizoate	Diatrizoate

TABLE 2: Patient Responses to Contrast Media after Cerebral Angiography

Contrast Material	No. Patients	No. Injections	Heat			Pain			Patient Motion
			1	2-3	4	1	2-3	4	
iohexol	30	106	33	69	4	89	12	5	3
Meglumine iohalamate	30	106	19	68	19	93	11	12	26

Note.—Patient responses were graded as: 1 (no reaction); 2 (slight reaction); 3 (definite but tolerable discomfort); and 4 (severe excruciating discomfort).

than iohexol; three indicated similar discomfort; and two reported iohexol to be more uncomfortable.

Both contrast agents resulted in significant lowering of systolic and diastolic blood pressure as compared with baseline. However, the average diminution in blood pressure ($-31.6/-21.0$) observed after sodium meglumine diatrizoate injection was significantly greater than that observed with iohexol ($-15/-7.8$ mm Hg).

Hypotension occurred within 30 sec after contrast injection with blood pressure returning toward baseline levels by 2 min. There were no obvious clinical correlates with this hypotension.

Heart rate within the first 2 min after contrast injection was slightly increased with iohexol (3.86, which is not statistically significant). However, the greater increase in pulse rate (11.46) seen after sodium meglumine diatrizoate injection was statistically significant from baseline and greater than the iohexol response.

Discussion

From these results alone, no significant difference in systemic neurotoxicity can be demonstrated between iohexol and the ionic contrast agents. This is not unexpected, due to the limited number of patients and the low expected incidence of such adverse side effects. One might anticipate, however, that with adequate statistical sampling, there would be no more, and perhaps slightly diminished, neurologic side effects due to the presumed lower neurotoxicity of iohexol as compared with the ionic contrast agents. Lower neurotoxicity might be expected from lower osmolality and direct neurotoxicity of iohexol as reported in prior animal and clinical studies [5].

Iohexol does appear to have less associated patient discomfort than the ionic contrast agents. This probably relates to its lower osmolality. Similar results have been reported with other nonionic contrast agents, including metrizamide and iopamidol [6-8]. This lower level of associated discomfort is more obvious in the selective cerebral angiography protocol than in the arch aortography protocol. This is probably because of the greater local pain with selective injection than with aortic flush injection. While not statistically evaluated due to the limited number of patients, this benefit of iohexol is most clinically obvious in those patients who receive selective external carotid injections, is where the degree of pain was obviously much less than with meglumine iothalamate.

The flush aortogram study reveals mild transient hypotension and tachycardia, as has been reported with arch aortography using many contrast agents [2, 9]. This is also probably due to the hyperosmolality of the solution as compared with serum and the vasodilatory effect of the compounds. This effect is less marked with iohexol. The tachycardia may also relate to patient discomfort, which is also less with iohexol.

These results suggest that the new nonionic water-soluble contrast agent, iohexol, is a superior neuroangiographic contrast agent with no greater, and perhaps less, neurotoxicity, less patient discomfort, and fewer systemic cardiovascular effects than current ionic contrast agents.

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