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Three New Low-Osmolality Contrast Agents: A Comparative Study of Patient Discomfort

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Relative patient discomfort resulting from carotid injections of three new low-osmolality contrast agents was assessed in 78 patients. Omnipaque-300 (iohexol), Isovue-300 (iopamidol), and Hexabrix (ioxaglate) were sequentially injected into both common carotid arteries of each patient. Patients were asked to rank the relative intensities of the three injections on each side. Mean patient rankings revealed that Hexabrix was preferred most often, Omnipaque-300 next, and Isovue-300 the least. The differences are statistically significant.

We conclude that while patients usually tolerated all intracarotid low-osmolality contrast agents rather well, the agent preferred most often was Hexabrix.

The recent introduction into the United States market of three new low-osmolality contrast agents (LOCAs) has caused much interest among radiologists. All three, Omnipaque (iohexol; Winthrop-Breon, NY), Isovue (iopamidol; E.R. Squibb, New Brunswick, NJ), and Hexabrix (ioxaglate sodium meglumine; Mallinckrodt, St. Louis), have been shown to have decided demonstrable and theoretical advantages over the older, conventional agents [1–3]. The tremendously higher cost of the new LOCAs, however, has kept them from replacing the older agents in most practices, except possibly among "high-risk" patients or for procedures in which extreme discomfort is likely.

Although the LOCAs have been shown to produce much less discomfort than conventional agents, all three usually produce some degree of discomfort. To best assess the differences between the agents, it was decided to give each patient identical amounts of all three agents. Since, at our institution, patients studied angiographically for possible cerebral ischemia routinely receive three selective injections of contrast agent into each common carotid artery, we were able to assess the effects of the three agents without subjecting patients to an increased number of injections. Patient assessment of the discomfort resulting from these injections forms the basis for this report.

Materials and Methods

Seventy-eight patients undergoing arch aortography with carotid arteriography for possible extracranial cerebral vascular disease were selected for study. Several other patients were excluded from the study because of origin occlusion of a common carotid artery. There were 41 men and 37 women, ranging in age from 42 to 86 years (mean, 68 years). Each patient was premedicated with 5 mg of diazepam orally, 0.4 mg atropine intramuscularly, and 10 mg dexamethasone intramuscularly.

After a pigtail catheter was placed into the mid-ascending aorta, several ml of Conray-60 (iothalamate meglumine; Mallinckrodt) was hand injected to fluoroscopically verify the catheter tip position. Arch aortography was performed using 39 ml of a 40% solution of Renografin-76 (diatrizoate sodium meglumine; E.R. Squibb) with digital subtraction imaging. Subsequently, a selective catheter was placed into the right common carotid artery. Three small test injections of Conray-60 were made with the head positioned first in the right posterior

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oblique then left posterior oblique and then neutral positions. Fluoroscopic observations of these three test injections were used to determine which projection demonstrated the common carotid bifurcation the best. Ten ml (8 ml/sec) of Omnipaque-300, Isovue-300, and Hexabrix were sequentially injected with conventional cut filming of the head in the anteroposterior and lateral projections and of the neck in the projection previously determined to be optimal. The catheter tip was not changed between injections. The tip was then placed into the left common carotid artery, where this process was repeated, but with the sequence of the three agents reversed. There were six possible sequences in which the three LOCAs could be injected in the right carotid artery matched by the reverse sequence in the left carotid artery. These sequences were altered for each patient so that a set of all six sequences was repeated 13 times in the 78 patients. The syringe of the power injector was rinsed with saline when the contrast agent was changed. All contrast agents were warmed to 37°C prior to the examination; admittedly, however, their temperatures likely migrated somewhat toward room temperature before all the injections were completed.

After the second common carotid injection on each side, the patients were asked, "Could you perceive a difference in the intensities of those two injections; if so, which one was more intense?" After the third injection into each artery, they were asked, "Could you perceive a difference in the intensities of those three injections; if so, rank them from most intense to least." The right and left sides were assessed independently from one another; no attempt was made to compare the intensities perceived on the right side with those on the left. Because the questioner was not blinded to the contrast agent used, bias was minimized by phrasing the question identically to each patient.

If a patient could perceive a difference in the three agents on a side, the least intense agent received a score of 1, the intermediate agent a 2, and the most intense a 3. If all three injections on a side were indistinguishable, each agent was given a score of 2. If two injections were perceived as identical and less intense than the third, those two agents were each given a score of 1.5; the most intense agent was given a 3. If two injections were indistinguishable and more intense than the third, those two agents were each given a score of 2.5; the least intense agent was given a 1. The total score on each side always added up to 6. For each patient, the right- and left-sided scores of each agent were averaged, and then the three agents were reranked for both sides taken as a whole. No patient was informed that different contrast agents were being used. Any procedural or postprocedural (< 6 hr) complications were recorded. Many of these studies were performed on outpatients, with 6 hr of observation prior to discharge. The data were analyzed using multiple comparison tests based on ranks.

Results

A total of 468 injections (156 injections of each LOCA) were made into 156 common carotid arteries in 78 patients. No procedural or immediately postprocedural (< 6 hr) evidence of cerebral ischemia, cardiovascular insult, or "idiosyncratic" contrast reaction was observed. Specifically, no vertigo, confusion, blindness, focal neurologic deficit, cardiac arrhythmia, or hypotension occurred. Two of the 156 carotid arteriograms performed with Hexabrix produced brief nausea and vomiting (two patients). None of the carotid arteriograms using Omnipaque-300 or Isovue-300 produced nausea or vomiting. This difference is not statistically significant.

Figure 1 shows the patients' perceptions of the relative

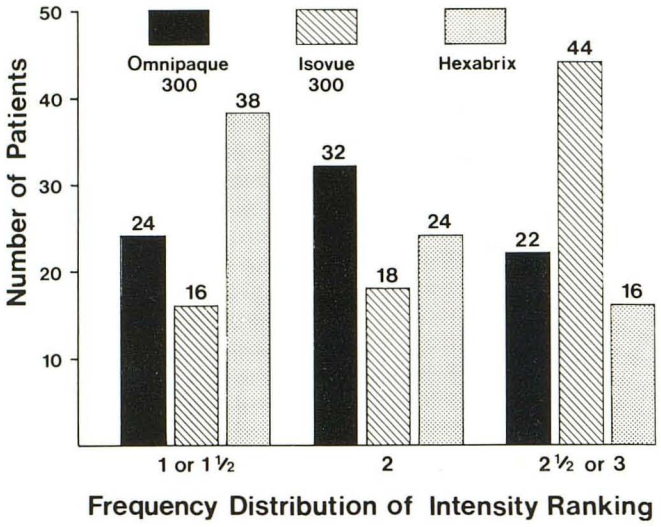

Fig. 1.—Summary of patient rankings of perceived intensity of carotid injection of three contrast agents.

intensities of the three agents that were injected into each carotid artery. Hexabrix received the assessment of 1 (least intense) or 1.5 (tied for least intense) more often than the other two agents. Isovue-300 received a 1 or 1.5 assessment least often. The mean scores (after each patient's right and left scores for each agent were averaged and subsequently reranked) were Omnipaque-300 1.97, Isovue-300 2.33, and Hexabrix 1.71. These means were compared via paired t-tests. The resulting p values were multiplied by 3 to compensate for the multiple comparisons that were made. These differences are all statistically significant (Hexabrix vs Isovue-300 [$p < .001$], Hexabrix vs Omnipaque-300 [$p < .05$], and Omnipaque-300 vs Isovue-300 [$p < .01$]). The interaction between side and contrast agent was not significant; the mean intensities had the same ordering on the right and left sides.

The sequence of carotid injections was altered to eliminate the effect of order. Analysis of the data reveals that the order in which an agent was injected did not influence the patient's perception of its intensity. Age and sex also did not influence patient ranking of contrast agent intensities.

Discussion

While much data has been published showing that all three new LOCAs are better tolerated than the older agents, it is difficult to find data comparing the three agents with one another. In a study of 50 patients, two of these agents, Isovue-300 and Hexabrix, were compared during cerebral arteriography [4]. Isovue produced a slightly greater sensation of warmth than Hexabrix did. However, no significant difference in pain was perceived. In our experience, patients frequently have difficulty in precisely categorizing the exact type of discomfort they experience from contrast injections during arteriography. We did not ask our patients to distinguish

between heat, pain, burning, pressure, or cramping. We only asked them to assess the difference, if any, in the intensity of the sensations perceived from each contrast injection.

We initially considered a study design in which an especially painful procedure, like aortoiliofemoral arteriography, would be used to assess patient preference to these LOCAs. However, we could not justify injecting each femoral runoff patient three times in order to make this determination. Although common carotid arteriography is rather well tolerated by most patients, conventional contrast agents do produce an intense enough sensation to be easily perceived, usually being mildly to moderately uncomfortable. Our routine procedure in performing most carotid arteriograms is to give three contrast injections in each common carotid artery, which makes carotid arteriography an ideal procedure with which to compare three contrast agents.

Although both Omnipaque and Isovue have more than one concentration, we chose Omnipaque-300 and Isovue-300 because their osmolalities are the closest to ioxaglate (672 mOsm/kg, 616 mOsm/kg, and 600 mOsm/kg, respectively). If osmolality were the sole determinant of the discomfort that patients experienced, one would expect Hexabrix (600 mOsm/kg) to be best tolerated and Omnipaque-300 (672 mOsm/kg) least. Although Hexabrix was given the best ranking, the agent with the intermediate osmolality, Isovue-300 (616 mOsm/kg), was the one with the worst patient ranking. The differences among the three agents were statistically significant.

It is not surprising that there were no serious complications resulting from the 468 common carotid artery injections in the 78 patients. Large series of carotid arteriograms performed with older conventional agents reveal very few serious complications [5], and the new agents hold the promise to be even safer [6].

Discomfort from arteriography continues to be a major concern for both the patients and the referring physicians. Performing arteriographic procedures with the least amount of discomfort possible, while not compromising safety, should be the goal of every angiographer. All three new agents were tolerated rather well by most of our patients, with Hexabrix being perceived most often as the least intense. It remains to be determined if the patients' rankings of these three agents is transferable to cerebral arteriography in a younger patient population or to procedures usually associated with considerable discomfort (e.g., extremity arteriography).

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