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Comparative Double-Blind Investigation of Meglumine Metrizoate, Metrizamide, and Iohexol in Carotid Angiography

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The new nonionic contrast medium iohexol (Omnipaque) was compared with its predecessor metrizamide (Amipaque) and with the conventional ionic medium meglumine metrizoate (Isopaque Cerebral) in carotid angiography using a double-blind crossover technique. The results indicated that iohexol and metrizamide caused less discomfort than the ionic medium. The circulatory effects of the three media were generally mild, and the diagnostic effectiveness was comparable when the iodine concentration was kept in the range of 280–300 mg I/ml.

The research concerned with contrast media for vascular use during recent years has focused on the synthesis of nonionic monomeric compounds. The prototype for these compounds is metrizamide (Amipaque), which is now extensively used in many different diagnostic procedures. However, this medium has two definite drawbacks: it has a very high production cost, and it is packaged as a lyophilic powder that has to be dissolved separately for every examination. Iohexol (Omnipaque), a recently synthetized compound, does not have these disadvantages.

The principal aim of this study was to compare the safety, tolerance, and usefulness of metrizamide and iohexol in carotid angiography with the conventional standard medium meglumine metrizoate (Isopaque Cerebral, referred to in this paper as metrizoate). Another objective of the study was to compare the two nonionic media in order to find out if iohexol might replace metrizamide as safely as animal studies [1] and phase II noncomparative trials [2] seem to indicate. For these reasons a test model was designed that allows for high sensitivity and cross-checking of results while at the same time being easily applicable to routine angiography.

Subjects and Methods

Among patients referred for cerebral angiography, 110 fully conscious and cooperative adults were selected. All patients except one agreed to participate after thorough explanation of the test, which was performed as a double-blind crossover investigation. The patients were split into three groups. The first 52 patients (group 1) were given meglumine metrizoate (280 mg I/ml) and metrizamide (280 mg I/ml); the next 30 (group 2) meglumine metrizoate (280 mg I/ml) and iohexol (300 mg I/ml); and the last 28 (group 3) metrizamide (300 mg I/ml) and iohexol (300 mg I/ml). (The iodine concentration was not the same in all groups for production reasons.) Group 1 consisted of 26 men (mean age 52 years, range 17–70) and 26 women (mean age 42 years, range 17–69); group 2 consisted of 13 men (mean age 42 years, range 26–64) and 17 women (mean age 45 years, range 25–74); and group 3 of 12 men (mean age 47 years, range 37–64) and 16 women (mean age 47 years, range 26–73). The diagnoses are listed in table 1.

In each patient the two different contrast media being used were administered at the beginning of the angiographic procedure. Rapid serial exposures in the lateral view were added in order to assess circulation time. The order of the injections was randomized according to a code list and remained unknown to the examining physician and to the patient.

Premedication was 0.5 mg atropine and 10 mg diazepam. The examinations were carried out under local anesthesia. Catheterization was performed via the femoral route in most cases, although a few patients were examined after direct puncture of the internal carotid artery. With few exceptions the contrast media injections were made with the tip of the catheter in the internal carotid artery (table 2). In this artery 8 ml of contrast medium was injected, while for injections of the common artery 10 ml was used. The media were at room temperature at injection. Average injection times for the different media and groups were: group 1: 1.1 sec for both metrizoate and metrizamide; group 2: 1.2 sec for metrizoate and 1.3 sec for iohexol; and group 3: 1.2 sec for both metrizamide and iohexol.

The electrocardiogram (ECG) was recorded on an ink-writer from extremity lead II, and was monitored before, during, and up to 60 sec after every injection. On parallel channels of the ink-writer the injection times and the exposures were recorded. The bradycardial effect was defined as the difference in milliseconds between the longest R-R interval before and after injection [3]. One patient who suffered from atrial fibrillation could not be evaluated in this respect. The heart rate was also determined before and 60 sec after the injection. There was no continuous monitoring of blood pressure. Manometer recordings from a brachial cuff were performed at the beginning and end of each examination. Circulation time was determined as the time interval between maximum contrast medium filling in the carotid siphon and maximum filling of the parietal veins [4].

The patients were questioned in a standardized way about adverse reactions immediately after each injection, with the radiologist

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TABLE 1: **Diagnoses of Patients Referred for Cerebral Angiography and Contrast Media Used**

Diagnosis	No. Patients/Contrast Group		
	Metrizoate/ Metrizamide	Metrizoate/ Iohexol	Iohexol/Metrizamide
Subarachnoid hemorrhage	17	13	10
Arteriovenous malformation	4	2	2
Tumor	21	8	8
Transitory ischemic attacks	3	7	4
Other	7	...	4
Totals	52	30	28

TABLE 2: **Injection Sites in Patients Referred for Cerebral Angiography and Contrast Media Used**

Branch of Carotid Artery	No. Patients/Contrast Group		
	Metrizoate/ Metrizamide	Metrizoate/Iohexol	Iohexol/Metrizamide
Right internal	27	14	12
Right common	3	2	4
Left internal	22	10	12
Left common	...	4	...

taking information according to a protocol that was designed for the investigation. The intensity of adverse reactions was estimated according to a four grade scale (0, 1, 2, and 3).

All measurements, interpretation of films, and tabulations were made before breaking the study code.

Results

The most striking difference between tested pairs of media was that the sensation of warmth or heat was significantly more pronounced with metrizoate than with the two nonionic contrast agents. This symptom appeared more often (table 3) and was of a higher intensity in the majority of cases following injection of metrizoate. Many patients felt the heat after injection of metrizoate as pain. This was especially true for injections in the common and internal carotid arteries, where a reflux also filled the external artery. The four grade scale used for assessment of sensation of heat gave a score of 2.3 for the metrizoate injections and a score very close to 1.0 for the other contrast media.

A marked difference between the nonionic media and the ionic reference compound was also demonstrated by analyzing the replies obtained on the direct question put to every patient after the injections: "Which injection caused more discomfort?" In group 1, 75% felt more discomfort from the metrizoate injection than the metrizamide; 10% felt equal discomfort; and 15% felt more discomfort from the metrizamide injections ($p < 0.001$). In group 2, in which metrizoate was compared with iohexol, the same discomfort figures were 80%, 10%, and 10%, respectively ($p < 0.001$). In group 3, in which iohexol and metrizamide were compared, there was no clear preference. Metrizamide was reported to cause more discomfort than iohexol by 39% of the patients; iohexol more than metrizamide by 32%; and 29% reported they caused equal discomfort.

Other adverse reactions were visual phenomena (i.e., bright spots, lightning, colors, stars, etc.), which were infrequently reported (not more often than 10% for any group or medium tested). The frequency of this reaction did not differ significantly among the groups or contrast media tested.

A few patients reported headache and a few nausea in all three series, but there was no pattern to these complaints that would allow any conclusion to be made regarding these media and these reactions. Except for a few single reactions (like metallic taste shortly after the injection) no other symptoms or signs appeared, and all angiographic procedures were uneventful.

The circulation times estimated from the serial carotid angiograms are listed in table 4. In group 1 there is a statistically significant difference between metrizoate and metrizamide. There was no significant difference between iohexol and metrizoate in group 2 or between iohexol and metrizamide in group 3.

The mean values for maximal prolongation of the heart cycle are listed for the different groups and different contrast media in table 4. The greatest difference is recorded in group 1 ($p = 0.05$). However, statistically significant differences are not to be found between the media in any of the other groups. No correlation was found between circulation time and bradycardial effect. The changes in heart rate were small and insignificant in all patients. No difference could be recorded between the different media in the three groups, nor could any difference be found in their blood pressure as estimated by simple manometer readings. Neither were there differences to be recorded in density of arteries, capillary blush, or venous filling as studied with the naked eye on routine subtraction films from the different phases of the angiograms. Various anatomic structures could be studied with the same degree of accuracy independent of medium used.

Discussion

The test model used—the double-blind crossover technique—includes double recordings of the parameters under study, so that the reactions obtained from the test compound and from the refer-

TABLE 3: **Frequency of Sensations of Warmth, Heat, or Pain after Cerebral Angiography by Contrast Medium Used**

Group No.: Contrast Medium (mg I/ml)	No. Patients (%)
1 ($n = 52$):	
Meglumine metrizoate (280)	49 (94)
Metrizamide (280)	43 (83)
Probability	$p > 0.05$
2 ($n = 30$):	
Meglumine metrizoate (280)	30 (100)
Iohexol (300)	23 (77)
Probability	$p = 0.05$
3 ($n = 28$):	
Iohexol (300)	21 (75)
Metrizamide (300)	21 (75)
Probability	$p > 0.05$

TABLE 4: **Mean Values of Media Tested during Cerebral Angiography for Circulation Time and Bradycardia Effects**

Group No.: Contrast Medium	Mean Circulation Time in sec (SD)	Mean Prolongation of Heart Cycle in msec (Maximum)
1 ($n = 52$):		
Metrizoate	4.71 (0.80)	43 (82)
Metrizamide	4.37 (0.67)	18 (40)
Probability	$p < 0.001$	$p = 0.05$
2 ($n = 30$):		
Metrizoate	4.84 (1.11)	26 (40)
Iohexol	4.71 (1.05)	18 (37)
Probability	$p > 0.05$	$p > 0.05$
3 ($n = 28$):		
Iohexol	4.66 (0.87)	28 (49)
Metrizamide	4.73 (0.90)	22 (42)
Probability	$p > 0.05$	$p > 0.05$

ence compound are consequently compared in an unbiased way under almost identical conditions, each patient acting as his own control. That the yield of this high sensitivity test was "poor"—that there are such great difficulties in separating one medium from another by the available methods—may also be taken as a proof of the success research has enjoyed over the last 20 years in providing contrast media that are well tolerated and of low toxicity.

The results of the present investigation are largely in accordance with the results obtained in earlier double-blind tests comparing metrizamide [5, 6] and iohexol [7–9] with conventional ionic media. All earlier investigators have found small or insignificant cardiovascular effects of the nonionic compounds.

A significantly shorter circulation time was demonstrated in group 1 for metrizamide compared with metrizoate. This is consistent with earlier observations in lung circulation [10, 11], and is also in accordance with earlier findings by Skalpe et al. [6] (who could not, however, demonstrate a significant difference in their two group parallel study of the same media). The time for the passage of a contrast bolus through the brain is determined by factors such as flow and pressure of the systemic circulation, autoregulation of the brain, nerve reflexes, composition of blood, and so forth. Almén and Aspelin [12] have drawn attention to the effects of contrast media on the rheology of the red blood cells. They have demonstrated that the conventional high osmolar ionic media increase the rigidity of the erythrocytes more than the nonionic media do [13–16], which tends to delay the passage of the corpuscles through the capillary bed. This offers a plausible explanation for the observed difference in circulation time between metrizamide and metrizoate. However, the same difference was not demonstrated for iohexol as compared to metrizoate. The reason for this is not clear. The difference in viscosity of the media (11.6 mPa·s for iohexol versus 9.7 mPa·s for metrizamide) is considered too small to account for any difference in circulation time. Again, it seems more probable that osmolarity (higher for iohexol than for metrizamide, table 5) plays a role via the same mechanism as described above. Iohexol has been compared with another ionic medium (Conray meglumine) in a similar cross-over study [8]. The circulation time was found to be equal or slightly longer for iohexol as compared with the ionic medium.

The bradycardial effect was generally small. Only a low degree of significance differentiates metrizoate from metrizamide in this respect. This agrees with Skalpe et al. [6] who found an even higher degree of significance in their two group investigation of the same media. The study of this parameter seems unrewarding in the evaluation of the toxicity of nonionic compounds.

The present investigation clearly shows that the sensation of heat is much more pronounced after injection of metrizoate than after injections of nonionic media. The difference is not dramatic, however, as is shown by the fact that it was not recognized in an earlier double-blind two group study [9]. The difference is more pronounced when injection is made in the common or external carotid artery. This may be of importance for correct interpretation of the films, as the sensation of heat may induce patient movement, which precludes a subsequent subtraction film of high quality.

The comparison of the two nonionic media did not show any differences in adverse reactions. The use of metrizamide is impractical and expensive; this medium can be replaced by iohexol in all respects.

TABLE 5: **Viscosity and Osmolality of the Contrast Media Solutions Used in Cerebral Angiography**

Contrast Medium (mg I/ml)	Viscosity (mPa·s)	Osmolality (mol/kg H_2O)
Meglumine metrizoate (280)	7.2	1.46
Metrizamide (280)	9.7	0.46
Metrizamide (300)	12.7	0.48
Iohexol (300)	11.6	0.69

REFERENCES

1. Iohexol. A non-ionic contrast medium. Pharmacology and toxicology. Lindgren E, ed. *Acta Radiol [Suppl]* (Stockh) **1980**;362
2. Amundsen P, Dugstad B, Presthus Y, et al. Cerebral angiography with iohexol, a new non-ionic contrast medium. A phase II multicentre clinical trial. *Acta Radiol [Diagn]* (Stockh) (in press)
3. Greitz T, Törnell G. Bradycardial reactions during cerebral angiography. A comparison of Isopaque sodium, Isopaque B, Hypaque, and Urografin. *Acta Radiol [Suppl]* (Stockh) **1967**;270:75–86
4. Greitz T. Normal cerebral circulation time as determined by carotid angiography with sodium and methylglucamine diatrizoate (Urografin). *Acta Radiol [Diagn]* (Stockh) **1968**;7:331–336
5. Amundsen P, Dugstad G, Slettebö M. Clinical testing of Amipaque for cerebral angiography. *Neuroradiology* **1978**;15:89–93
6. Skalpe IO, Lundervold A, Tjörstad K. Cerebral angiography with non-ionic (metrizamide) and ionic (meglumine metrizoate) watersoluble contrast media. A comparative study with double blind technic. *Neuroradiology* **1977**;14:15–19
7. Ahlgren P. Ioxhexol compared to Urografin Meglumine in cerebral angiography. A randomized, double blind cross-over study. *Neuroradiology* **1982**;23:195–198
8. Ingstrup HM, Hauge P. Clinical testing of iohexol, Conray meglumine and Amipaque in cerebral angiography. *Neuroradiology* **1982**;23:75–79
9. Nakstad P, Sortland O, Aaserud O, Lundervold A. Cerebral angiography with the non-ionic water-soluble contrast medium iohexol and meglumine-ca-metrizoate. A randomized double blind parallel study in man. *Neuroradiology* **1982**;23:199–202
10. Almén T, Aspelin P, Levin B. Effect of ionic and non-ionic contrast medium on aortic and pulmonary arterial pressure. An angiocardiographic study in rabbits. *Invest Radiol* **1975**;10:519–525
11. Almén T, Aspelin P, Nilsson P. Aortic and pulmonary arterial pressure after injection of contrast media into the right atrium of the rabbit. Comparison between metrizoate, ioxaglate and iohexol. *Acta Radiol [Suppl]* (Stockh) **1980**;362:37–41
12. Almén T, Aspelin P. Cardiovascular effects of ionic monomeric and ionic dimeric and non-ionic contrast media. Effects in animals on myocardial contractile force, pulmonary and aortic blood pressure and aortic endothelium. *Invest Radiol* **1975**;10:557–563
13. Aspelin P. Effect of ionic and non-ionic contrast media on morphology of human erythrocytes. *Acta Radiol [Diagn]* (Stockh) **1978**;19:675–687
14. Aspelin P, Stöhr-Liessen M, Almén T. Effect of iohexol on human erythrocytes. I. Changes of red cell morphology in vitro. *Acta Radiol [Suppl]* (Stockh) **1980**;362:117–122
15. Aspelin P, Birk A, Almén T, Kiesewetter H. Effect of iohexol on human erythrocytes. II. Red cell aggregation in vitro. *Acta Radiol [Suppl]* (Stockh) **1980**;362:123–126
16. Aspelin P, Teitel P, Almén T. Effect of iohexol on red cell deformability in vitro. *Acta Radiol [Suppl]* (Stockh) **1980**;362:127–130