AJNR

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AJNR Am J Neuroradiol 1984, 5 (6) 801-803
http://www.ajnr.org/content/5/6/801

Safety of Contrast Media in Cerebral Angiography:
Iopamidol vs. Methylglucamine Iothalamate

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A randomized double-blind study was performed in 27 patients to compare the clinical safety, incidence of pain and warmth, and film quality produced by iopamidol and Conray-60 in selective cerebral angiography. No complications or adverse reactions occurred in either group. Iopamidol was significantly less painful than was methylglucamine iothalamate for common carotid artery injections and caused significantly less heat in both common carotid and internal carotid artery injections. Film quality and diagnostic accuracy were excellent in both groups. These results, when viewed in conjunction with laboratory data demonstrating the decreased neurotoxicity of nonionic contrast agents, suggest that iopamidol is an important advance in the development of angiographic contrast media.

The major risk of selective cerebral angiography is transient or permanent neurologic deficit resulting from improper technique, catheter manipulation, or contrast medium infusion. In addition, selective injections of hyperosmotic contrast materials into the common and external carotid arteries may cause pain, resulting in patient movement, decreased image quality, and increased patient discomfort. It is also well established that hyperosmotic contrast media injected into the vertebral or carotid arteries may produce transient disruption of the blood-brain barrier (BBB) with associated neurologic deficit or seizure [1–9]. In an effort to further decrease the incidence of patient discomfort and neurotoxicity associated with the ionic contrast agents currently used for cerebral angiography, a number of new, hydrosoluble, nonionic contrast media have been developed [10–18]. The purpose of our study was to compare one of these new nonionic agents, iopamidol (Isovue, Squibb, Princeton, NJ) with a widely used ionic agent, methylglucamine iothalamate (Conray-60, Mallinckrodt, St. Louis) for cerebral angiography in terms of clinical safety, patient tolerance, and film quality.

Subjects and Methods

The study was conducted as a randomized, double-blind comparison study using iopamidol (300 mg I/ml) or methylglucamine iothalamate (282 mg I/ml) in 27 alert and cooperative patients, 18 years of age and older, referred for cerebral angiography. There were 13 patients in the iopamidol group and 14 in the methylglucamine iothalamate group. To be included, patients were required to be alert, cooperative, and able to give informed consent. Those with a history of contrast allergy, acute stroke, bleeding disorder, anticoagulant therapy, renal failure, or other serious illness were excluded from the study. Patient evaluation included clinical observations (physical and neurologic examinations) and laboratory data (complete blood cell count, blood chemistry, urinalysis) before and at 24 and 72 hr after angiography. Vital signs were monitored before, during, and after the procedure. Electroencephalograms were obtained in six patients, three in the iopamidol group and three in the methylglucamine iothalamate group, before and 24 hr after angiography. Postangiographic computed tomographic (CT) scans were obtained in all patients and evaluated for abnormal contrast enhancement denoting BBB disruption.

Received January 25, 1984; accepted after revision June 1, 1984.

Presented at the annual meeting of the American Society of Neuroradiology, San Francisco, June 1983.

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AJNR 5:801–803, November/December 1984
0195–6108/84/0506–0801

The patients were not premedicated. Local anesthesia at the site of arterial puncture was obtained with 1% lidocaine. The standard transfemoral approach with selective injections was used in each case. Determinations of pain and heat sensations were made by the patient after each injection and graded on a 0–100 scale, with zero being no pain and 100 being the worst pain they had ever felt. Statistical analysis of the results was performed using the Wilcoxon rank sum test. The angiograms were evaluated for technical and diagnostic adequacy by a neuroradiologist not involved with the procedure.

TABLE 1: **Iopamidol and Methylglucamine Iothalamate for Selective Cerebral Angiography: Numbers and Locations of Injections**

Artery	No. of Injections	
	Iopamidol	Conray-60
Common carotid	31	33
Internal carotid	12	12
External carotid	2	0
Vertebral	0	8

Results

No angiographic complications, neurologic changes, laboratory abnormalities, adverse reactions, or electroencephalographic changes occurred in either group. None of the postangiographic CT scans showed evidence of BBB disruption attributable to the contrast agents.

Table 1 shows the numbers and locations of injections in both groups. The mean warmth rating with iopamidol was 52 in the common carotid artery and 30 in the internal carotid artery as opposed to 73 and 65, respectively, with methylglucamine iothalamate (table 2). The mean pain rating in the common carotid artery was zero with iopamidol and 30 with methylglucamine iothalamate. No patient in either group reported pain with internal carotid artery injections. The subjective, graded differences in pain and heat experienced with common carotid artery injections and heat with internal carotid artery infusion were statistically significant ($p < 0.05$). The numbers of external carotid artery and vertebral artery injections were insufficient for statistical comparison.

Film quality and diagnostic adequacy were rated as excellent in all patients in both groups. There was no correlation between subjective patient discomfort and image quality in this group of alert, cooperative patients.

TABLE 2: **Iopamidol and Methylglucamine Iothalamate for Selective Cerebral Angiography: Adverse Reactions**

Contrast Agent: Artery	Mean Score	
	Pain	Heat
Iopamidol:		
Common carotid	0	52
Internal carotid	0	30
Methylglucamine iothalamate:		
Common carotid	30	73
Internal carotid	0	65
Wilcoxon rank sum test:		
Common carotid	0.0230	0.0002
Internal carotid	...	0.0084

Note.—Pain and heat were evaluated on a scale of zero to 100, with 100 being the worst pain the patient had ever experienced in his or her life. In no patients were neurologic deficits, electroencephalographic abnormalities, or abnormal CT enhancement found.

Discussion

This randomized, double-blind comparison study demonstrated that nonionic iopamidol and ionic methylglucamine iothalamate are comparable in terms of image quality and clinical safety. The major difference between these two contrast agents was in patient tolerance, with iopamidol producing significantly less pain and heat with carotid injection than did methylglucamine iothalamate. Our results confirm previous studies in which iopamidol and other nonionic contrast media were compared with conventional ionic agents [11, 16–18]. As hyperosmolality seems an important factor in producing pain and warmth [19, 20], the improved patient tolerance with lower osmolality nonionic contrast agents is as expected.

The chemical structure of iopamidol consists of a tri-iodinated benzene ring with three highly hydrophilic side chains. It is stable in solution, and, at a suitable concentration for conventional cerebral angiography (300 mg I/ml), it has an osmolality of 616 mosmol/kg and a viscosity of 4.7 cP. At a concentration of 282 mg I/ml, methylglucamine iothalamate has an osmolality of 1440 mosmol/kg. Osmolality is one of the key factors in determining the toxicity of an intracarotid infusate to the BBB. Experiments in our laboratory [9] and others [1–6, 8, 10, 15] confirm a gradation in severity of disruption of the BBB directly proportional to the osmolality of the contrast medium injected in the carotid artery (fig. 1). Using trypan blue as a marker of barrier integrity, neither iopamidol nor saline controls produced barrier breakdown [8, 9]. It should also be noted that factors other than hyperosmolality play a role in the neurotoxicity of contrast media. Compounds of similar osmolality may cause varying degrees of barrier disruption. An additional important factor may be the inherent chemotoxicity of a contrast agent, which may lead to stimulation of capillary endothelial cell pinocytosis or increased viscosity and red cell clumping with prolonged capillary contact time.

In our series, CT scanning within 1 hr after angiography showed no evidence of abnormal contrast enhancement after infusion of either iopamidol or methylglucamine iothalamate. Although this suggests integrity of the BBB using methylglucamine iothalamate in clinical practice, CT may not be a sufficiently sensitive indicator of subtle barrier disruption, particularly in our study group, in whom generally less than 100 ml of iodinated contrast medium was infused intraarterially 1–3 hr before CT scanning.

The final issue arises as to whether the higher cost of nonionic contrast materials for intraarterial use makes them worthwhile "just" to decrease patient discomfort and possibly reduce the danger of neurotoxicity. This is more of a philosophic than a scientific question. Perhaps a general decision needs to be made as to which contrast agent should be used

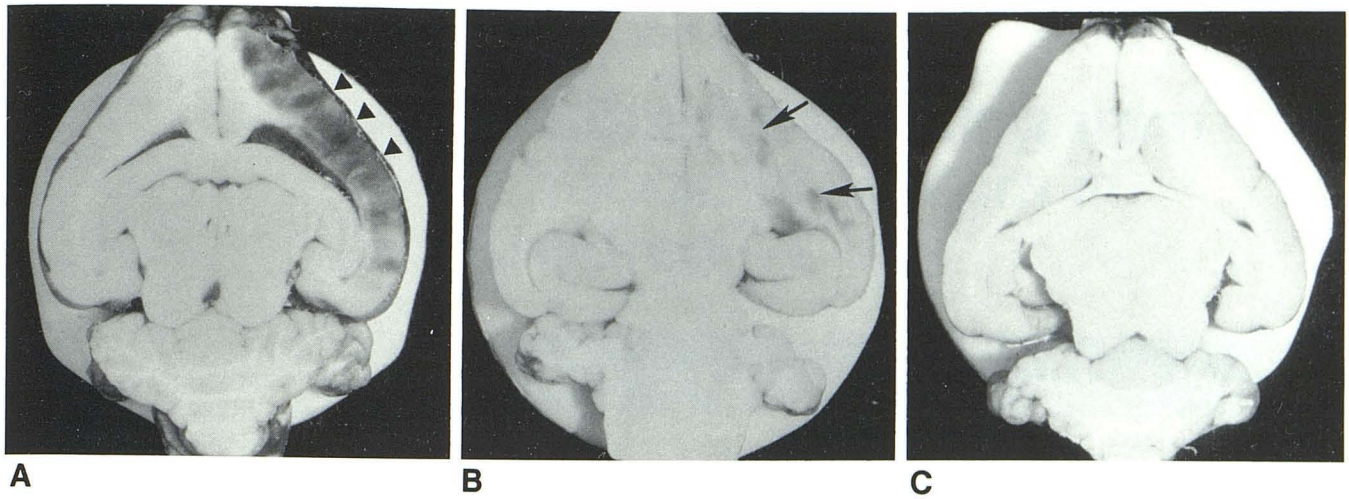

Fig. 1.—Comparative BBB disruption after intracarotid infusion of contrast media (0.3 ml/sec for 30 sec). Trypan blue injected intravenously was used to define integrity of BBB. Trypan blue extravasates into brain with intracarotid diatrizoate meglumine (**A**, *arrowheads*) and methylglucamine iothalamate (**B**, *arrows*), denoting BBB disruption that does not occur with iopamidol in rabbit (**C**) or in normal saline controls.

in a given clinical situation. For example, nonionic agents might be reserved for selective external carotid injections or a clinical situation of suspected vasospasm or BBB disruption. Whatever the ultimate applications, the data suggest that iopamidol is an important evolutionary advance in intraarterial contrast materials in terms of improved patient tolerance and theoretic decreased neurotoxicity.

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