Effects of Ionic and Nonionic Contrast Media on Cardiohemodynamics and Quality of Radiographic Image during Canine Angiography

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ABSTRACT. Cardiovascular responses and radiographic image quality during cerebral angiography, aortofemoral angiography and left ventriculography with nonionic ioxilan, iohexol or iopamidol were compared with those of ionic sodium meglumine diatrizoate in pentobarbital anesthetized dogs. Injection of all contrast media caused cardiovascular changes to a greater or lesser degree, e.g., hypotension, bradycardia, tachycardia, a decrease in left ventricular pressure (LVP) and its first derivative (dP/dt), and prolongation of the P-Q and Q-T intervals. Ionic diatrizoate had a greater effect on cardiovascular parameters than nonionic contrast media during angiography in all areas. Moreover, diatrizoate produced cardiac arrhythmias and prominent changes in blood rheology concerned with blood viscosity and deformability of the erythrocyte. The cause of various effects of contrast media seemed to lie mainly in osmolality, viscosity and partially ionic additives. The radiographic image quality of all of the contrast media used was similar, but nonionic ioxilan and iohexol with lower iodine content and low osmolality gave better radio opacity than ionic diatrizoate in cerebral angiography. These results suggested that nonionic contrast media should be recommended as a diagnostic tool for both animals and human patients in poor health.—KEY WORDS: angiography, blood rheology, cardiohemodynamics, contrast media, radiographic image quality.


Angiography is a useful diagnostic technique which detects the existence of diseases, such as intracranial tumors, malformation of organs and narrowing of the vascular bed. In clinical angiography as currently practiced in man, the classical ionic contrast media have been replaced by recently developed nonionic contrast media to some extent, because the nonionic contrast media elicit less vascular pain [19]. Moreover, a novel nonionic contrast medium, ioxilan ((±)-N-(2,3-dihydroxy-propyl)-N’-(2-hydroxyethyl)-5-[N-(2,3-hydroxypropyl)-acetamido]-2, 4, 6-triiodoiso-phthalamide), is shown to elicit less arrhythmias and ventricular fibrillation during coronary angiography than other nonionic contrast media in the canine model [13, 15]. The chemical structure of monomeric ioxilan, which aggregates as a dimer in solution to accomplish low osmolality, discriminates ioxilan from other nonionic monomeric contrast media [18].

The present study was therefore conducted to assess the cardiovascular effects and diagnostic radiographic image quality of ioxilan and to compare them with those of nonionic iohexol, iopamidol and ionic diatrizoate during angiography in anesthetized dogs. Also, the effect of contrast media on a blood rheological aspects was investigated.

MATERIALS AND METHODS

Eighteen male beagle dogs, weighing 9.5 to 13.5 kg, were anesthetized with an intravenous administration of 35 mg/kg sodium pentobarbital and then maintained at an infusion rate of 4 mg/kg/hr. Under spontaneous respiration, an incision of the skin was made to expose the artery. Puncture of the femoral or common carotid artery was performed by Seldinger’s technique [17] and a Bentzon type or Pig-tailed type catheter (ST60BM0.36PTB, Medikit) of adequate size was introduced into the internal carotid artery, abdominal aorta or left ventricle under fluoroscopic control. The physical properties of ioxilan (synthesized in our laboratories), iohexol (Omnipaque® 350, Daiichi Pharmaceutical), iopamidol (Iopamiron® 370, Nippon Schering) and Diatrizoate (Urografin® 76%, Nippon Schering) were measured with a vapor pressure osmometer (Type 5100C, Wescor), a cone plate viscometer (Model E, equipped with a 0.8° cone, Tokyo Keiki) and a pH meter (HM-30S, Toa Electronics) as listed in Table 1. Contrast media were prewarmed to 37°C and injected through the catheter by a power injector (M800, Nemoto Kyorindo), 5 ml/dog at a rate of 1 ml/sec for cerebral angiography, 20 ml/dog and 4 ml/sec for aortofemoral angiography or 20 ml/dog and 10 ml/sec for ventriculography. In cerebral angiography, the exposure of 0.05 sec at 110 kV and 50 mA was made by an X-ray system (DR-155, Hitachi Medical) and a rapid film changer (PUCK CM/C with SEP3, Siemens-Elema) every second. In aortofemoral angiography and left ventriculography, the exposure conditions were 0.1 sec, 70 kV and 50 mA, 0.02 sec, 120 kV and 100 mA, respectively.

Blood pressure and heart rate during angiography were recorded and compared with the responses to saline and commercially-prepared 20% mannitol solution (Nikken Kagaku). A polyethylene needle was inserted into the femoral artery and connected to a pressure transducer (DTX disposable transducer kit, Viggo-Spectramed) for measurement of systemic blood pressure. A-B lead ECG was recorded by a telemetry system (ZB-141G, Nihon Kohden), and used for monitoring of the heart rate throughout the experiments. In left ventriculography, a microtip catheter transducer (PC-350, Millar Instruments) was introduced into the left ventricle from the femoral artery for monitoring of LVP and dP/dt. For analysis of
the mechanism of cardiovascular changes during cerebral angiography, the responses induced by injection of contrast media into the external jugular vein (5 ml/dog, 1 ml/sec) were observed. Also, the effect of atropinization on the responses induced by internal carotid injection of contrast media was examined. In order to investigate the effects of osmolalities on blood pressure, 0.9 to 3.6% sodium chloride solution, 5 to 20% meglumine solution and 5 to 20% mannitol solution were injected under the same conditions as aortofemoral angiography.

The radiographic image quality of the original films taken at the end of injections was evaluated by density measurement. Evaluation by densitometer (DM-101, Maeda) was carried out for the following arteries: in cerebral angiography, the arterial circle of the brain, the middle cerebral and rostral cerebral arteries; in aortofemoral angiography, the femoral, popliteal and crural-tibial arteries; in left ventriculography, the left ventricle, aortic arch and abdominal aorta. The values were corrected, with each photodensity of axis, femur or lumbar on the film taken as “100%” in order to standardize each experimental result. Thus, good opacity was represented by a low value. For representation of the injected areas, subtracted films were made manually from the original films (Super HR-S, Fuji), subtraction print film (Cronex®, Dupont; X-omat®, Kodak) and a medical film printer (PSM 430DSP, Fuji). The subtracted films were printed as overlapping images of the original films and corresponding reversal images of the injected areas which were taken before each injection.

Measurement of red blood cell deformability was performed by the method of Aspelin [2] with a 5 μm filter and 15% cell suspension with or without contrast media in a volume ratio of 20%. Results were expressed as a deformability index calculated by dividing the flow rate of plasma by that of the blood sample. Whole blood viscosity was measured with a cone plate viscometer (Model E, Tokyo Keiki) at 37°C under a physiological shear rate (75 and 150 s⁻¹). The blood sample for the viscosity study consists of heparinized canine whole blood mixed with contrast medium in a volume ratio of 20%.

Results were expressed as the mean ± standard error. Comparison was made by use of Student’s t-test between the saline group and each contrast medium or mannitol group. Concerning rheological experiments, comparison was made between ioxilan and other contrast media or blood sample. Statistical differences were considered significant if p<0.05.

RESULTS

Cardiovascular responses in cerebral angiography: The injection of all contrast media caused hypotension and bradycardia. The decrease in blood pressure and heart rate peaked at 15 sec and 5 sec, respectively. With respect to the maximal decrease in mean blood pressure (MBP), diatrizoate had the greatest effect followed by iohexol and iopamidol, while ioxilan produced a lesser effect (Fig. 1A). Twenty percent mannitol produced less hypotension than all contrast media. For the maximal decrease in heart rate, diatrizoate produced the greatest (−79.2 ± 30.3%, p<0.05, vs saline) followed by 20% mannitol (−42.9±7.6%, p<0.05, vs saline), iohexol (−32.5±9.0%, p<0.05, vs saline), iopamidol (−26.5±10.7%) and ioxilan (−14.1±7.7%). The injection of contrast media into the external jugular vein did not affect blood pressure or heart rate. Atropinization nearly abolished bradycardia induced by an internal carotid injection of contrast media, whereas hypotension remained the same (Fig. 2).

Cardiovascular responses in aortofemoral angiography: Injection of contrast media caused a biphasic change in MBP; a transient rise (2.3 to 4.3 mmHg) within a few seconds after injection following by hypotension with a peak at 15 sec. With respect to the maximal decrease in MBP, diatrizoate had the greatest effect, followed by 20% mannitol, iopamidol and iohexol, while ioxilan was less potent (Fig. 1B). The heart rate was decreased by 8.8 to
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22.5 beats/min from the basal value in association with a transient rise in MBP (described above), followed by slight tachycardia (increase within 10 beats/min) in all test solutions, although there were no significant differences among them.

Cardiovascular responses in left ventriculography: Hypotension caused by contrast media and 20% mannitol reached a peak at 30 sec. With respect to the maximal percent changes in MBP, diatrizoate was severe, whereas nonionic contrast media and 20% mannitol were equally mild (Fig. 1C). Although all contrast media decreased the heart rate by approximately 10 beats/min at the end of the injection period, diatrizoate and 20% mannitol caused a marked increase within 45 sec from the beginning of an injection (33.2±11.5 beats/min (p<0.05, vs saline) and 26.8±5.4 beats/min (p<0.05, vs saline), respectively). All contrast media and 20% mannitol also decreased LVP, associated with a change in MBP. With regard to the degree of decrease in LVP, diatrizoate caused a greater change (−28.4±1.9%, p<0.05, vs saline) than the other media (−5.0 to 8.5%). Contrast media decreased dP/dt at 5 to 15 sec following by an increase at 30 to 60 sec. Diatrizoate produced a marked decrease (−680±198.5 mmHg/sec, p<0.05, vs saline) and increase (780±320.0 mmHg/sec), but nonionic contrast media produced no significant changes.

From the determination of ECG parameters, diatrizoate prolonged the P-Q and Q-T intervals (Table 2). In addition, atrial or ventricular arrhythmias were caused only by diatrizoate and mannitol.

Effects of sodium chloride, meglumine and mannitol on blood pressure: Each solution of sodium chloride, meglumine or mannitol caused hypotension in proportion to their osmolalities (Fig. 3). In comparison with their vasodilating effects at the same osmolality, meglumine produced the greatest effect even if equivalent to body fluid, followed by sodium chloride and mannitol.

Radiographic image quality of arteries: A subtracted radiographic image of each injected area is shown in Fig. 4. Although no clear differences between radiographic images were obtained by visual inspection, slight differences for each contrast medium were detected by measuring the radiodensity of the original films. In cerebral angiography, although almost the same values were obtained from original films for the arterial circle of brain, ioxilan and iohexol showed better radio opacity than diatrizoate in the middle and rostral cerebral arteries as shown in Table 3. On the other hand, iopamidol and diatrizoate were slightly better than ioxilan and iohexol in the left ventricle.

![Fig. 2. Bradycardia and hypotension induced by diatrizoate in cerebral angiography with or without atropine. A) control (n=1), B) atropinization: atropine sulfate administered 0.1 mg/kg, i.v. (bolus), 0.01 mg/kg/hr infusion (n=1). Each point represents a diatrizoate injection (5 ml, 1 ml/sec) into the internal carotid artery.](image)

![Fig. 3. Effects of sodium chloride, mannitol and meglumine solution on mean blood pressure (MBP, n=3), Mannitol (— ■ — ), NaCl (— ○ — ), Meglumine (— △ — ). Each solution was injected into the abdominal aorta (20 ml, 4 ml/sec).](image)

<table>
<thead>
<tr>
<th>Table 2. ECG changes during left ventriculography</th>
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<tbody>
<tr>
<td><strong>Contrast media</strong></td>
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<tr>
<td>---------------------</td>
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<tr>
<td><strong>P-Q interval</strong></td>
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<tr>
<td><strong>Q-T interval</strong></td>
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<tr>
<td><strong>T wave amplitude</strong></td>
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<tr>
<td><strong>Arrhythmia</strong></td>
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</table>

Values are expressed as a percentage of change at 10 sec after the beginning of injection to each initial ECG except arrhythmia represented as respond animal/animal used (n=5).

a) p<0.05, vs saline.
Fig. 4. Subtracted angiographic film of the brain (A), legs (B) and left ventricle (C) with nonionic contrast media in anesthetized dogs. A, ioxilan 5 ml (1 ml/sec); B, iopamidol 20 ml (4 ml/sec); C, iohexol 20 ml (10 ml/sec). Measuring points of the original films by densitometer are indicated in each subtracted film. A-1, arterial circle of the brain; A-2, middle cerebral artery; A-3, rostral cerebral artery; B-1, femoral artery; B-2, popliteal artery; B-3, cranial tibial artery; C-1, left ventricle; C-2, aortic arch; C-3, abdominal aorta.

Table 3. Density values for ioxilan, iohexol, iopamidol and diatrizoate

<table>
<thead>
<tr>
<th>Contrast media</th>
<th>Ioxilan</th>
<th>Iohexol</th>
<th>Iopamidol</th>
<th>Diatrizoate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodine (mg/l/ml)</td>
<td>350</td>
<td>350</td>
<td>370</td>
<td>370</td>
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<tr>
<td>Cerebral angiography (n=4)</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Arterial circle of brain</td>
<td>69.4±1.0</td>
<td>70.1±1.5</td>
<td>68.8±0.8</td>
<td>69.6±1.1</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>71.5±1.2</td>
<td>72.4±1.2</td>
<td>74.4±1.7</td>
<td>74.4±1.8</td>
</tr>
<tr>
<td>Rostral cerebral artery</td>
<td>72.0±1.4</td>
<td>74.6±1.0</td>
<td>76.1±2.1</td>
<td>76.1±1.8</td>
</tr>
<tr>
<td>Aortofemoral angiography (n=4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral artery</td>
<td>77.2±6.8</td>
<td>71.0±3.4</td>
<td>68.3±5.0</td>
<td>73.8±6.9</td>
</tr>
<tr>
<td>Popliteal artery</td>
<td>89.5±3.9</td>
<td>90.6±3.8</td>
<td>86.9±5.0</td>
<td>86.6±3.0</td>
</tr>
<tr>
<td>Cranial tibial artery</td>
<td>198.1±5.8</td>
<td>194.0±6.0</td>
<td>197.0±8.4</td>
<td>198.8±7.4</td>
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<tr>
<td>Left ventriculography (n=5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricle</td>
<td>74.8±10.7</td>
<td>73.1±6.6</td>
<td>69.9±8.2</td>
<td>71.7±7.9</td>
</tr>
<tr>
<td>Aortic arch</td>
<td>95.2±3.2</td>
<td>98.5±3.3</td>
<td>95.1±5.5</td>
<td>97.0±5.5</td>
</tr>
<tr>
<td>Abdominal aorta</td>
<td>88.3±4.8</td>
<td>91.5±5.0</td>
<td>88.5±5.4</td>
<td>90.8±5.7</td>
</tr>
</tbody>
</table>

Values are expressed as a percentage of density corrected with each photodensity of axis, femur or lumbar on the original film taken as 100%. a): p<0.05, vs diatrizoate.

Fig. 5. Effects of ioxilan, iohexol, iopamidol and diatrizoate on canine blood rheology. A) red blood cell deformability (n=5), B) whole blood viscosity (n=4). The deformability index was calculated by dividing the filtration time (flow rate) of plasma by that of the blood sample in the presence or absence of contrast media. Blood viscosity was measured with a cone plate viscometer. *: p<0.05, vs. ioxilan.
Rheological effects of contrast media in vitro: All contrast media decreased red blood cell deformability and increased the whole blood viscosity as shown in Fig. 5. In terms of the degree of change, diatrizoate showed a marked decrease in deformability and a significant increase in viscosity (p<0.05, vs ioxilan). Also, iopamidol significantly decreased blood deformability compared with that of ioxilan (p<0.05).

DISCUSSION

It is well known that the angiographic technique, e.g., catheter placement, volume and rate of the injection and selection of the injection site, is related to the hemodynamic changes. In the present study, we used Selnder's technique as a recent trend in the clinical field useful for maintaining peripheral blood flow. To assess the safety and toxicity of contrast media, we chose a relatively higher iodine content than the clinical dosage.

All contrast media and 20% mannitol caused hypotension and bradycardia during cerebral angiography. In this study, we observed the responses induced by the injection of contrast media into the external jugular vein to investigate whether these hemodynamic changes were concerned with the effect on the central nervous system or not. Since intravenous injection under the same conditions as internal carotid injection did not produce any change in hemodynamics, we considered that hypotension and bradycardia seen during cerebral angiography were related to the effect on the central nervous system, in accordance with the reports by Hayakawa et al. [6, 7]. Moreover, the result of atropinization indicated that the mechanism of hypotension is independent of the decrease in the heart rate. Although Hilal [8] and Lynch et al. [11] suggested that hypotension and bradycardia were mainly due to its osmolality, the cause of hypotension in the present study was not a simple osmolar mechanism.

In aortofemoral angiography and left ventriculography, contrast media and 20% mannitol solution induced hypotension in proportion to their osmolarities, in accordance with Hilal [8] and Kloster et al. [9]. As in left ventriculography, diatrizoate caused a particularly greater hypotension than that during cerebral angiography, so we conducted an experiment to clarify the effect on blood pressure of the ionic additives included in diatrizoate. Comparing the vasodilating effects of sodium chloride, meglumine and mannitol, meglumine produced remarkably higher hypotension even if in an equiosmolar condition similar to that of body fluid. Therefore, we reason that the drastic hypotension with diatrizoate, which contains 15.9% meglumine and 0.6% sodium hydroxide, may reflect not only the osmolality of the agent, but also the pharmacological effect of the ionic additives, e.g., meglumine-induced histamine release from systemic organs [3, 10]. Moreover, diatrizoate prominently induced a change in ECG and a decrease in dP/dt during left ventriculography. It is well known that high osmolar agents depress cardiac conduction [1], and cardiac contractility depends upon the sodium concentration of the contrast media [4, 14]. Sakamoto et al. [15] reported that the incidence of ventricular fibrillation was closely related to the sodium ion concentration. Accordingly, the cardiovascular changes produced with diatrizoate during left ventriculography might also be involved in direct actions on the heart.

In terms of radiographic image quality, we attempted to measure the density of each radiograph objectively by means of a densitometer. In consideration of the difference in the iodine content of the contrast media, it is understandable why diatrizoate and iopamidol would produce a better quality than ioxilan and ioxhol as shown in the left ventricle. Nonionic ioxilan and ioxhol, however, were more effective in cerebral angiography. To explain this contradiction, we note that hyperosmotic ionic contrast media affect red blood cell deformability and increase the resistance to blood flow through the capillaries [2, 12]. In fact, nonionic contrast media, especially ioxilan which was characterized by low osmolality and low viscosity, had a lesser effect on cell deformability and blood viscosity than did that of diatrizoate.

In conclusion, the physical properties of contrast media influence cardiohemodynamics. Osmolality, viscosity and ionic components of contrast media should be emphasized. The recently developed nonionic contrast media, especially ioxilan and ioxhol produced a good radiopacity and had much less effect on the cardiovascular system and blood rheology, compared with the classical ionic contrast media used. Moreover, they are shown to have much less effect on kidney function [20], endothelial cells [16] and the blood-brain barrier [5]. The nonionic type is therefore thought to be useful in ensuring the safety of animal and human angiography.

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