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Bolus Injection of MR Contrast Agents: Hemodynamic Effects Evaluated by Intracerebral Laser Doppler Flowmetry in Rats

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PURPOSE: To determine the effects on arterial blood pressure and cerebral blood flow of intravenous bolus injection of three MR contrast agents: gadopentetate dimeglumine, polylysine-Gd-DTPA, and superparamagnetic iron particles (SPIO). **METHODS:** A single-fiber laser Doppler flowmetry probe was placed intracerebrally in 56 anesthetized rats. Cerebral blood flow and mean arterial blood pressure were measured before (baseline), during, and up to 30 minutes after intravenous bolus administration of the three contrast agents: 0.1 mmol/kg and 0.3 mmol/kg gadopentetate dimeglumine (n = 18 per group), 0.3 mmol/kg polylysine-Gd-DTPA (n = 10), and 0.03 mmol/kg SPIO (n = 10). **RESULTS:** Neither the higher nor lower dose of gadopentetate dimeglumine had any statistically significant effect on cerebral blood flow, and there was no change in blood pressure during administration of either dose of gadopentetate dimeglumine. Administration of polylysine-Gd-DTPA caused a transient drop in blood pressure in two animals, marked in one (decrease to 21% of baseline values) and mild in the other (84% of baseline). After administration of SPIO, a significant decrease in blood pressure occurred in one animal (41% of baseline). Despite this decrease in mean arterial blood pressure, there were no statistically significant changes in cerebral blood flow after administration of polylysine-Gd-DTPA or SPIO. **CONCLUSION:** Our results suggest that bolus injection of these contrast agents at clinically relevant doses causes no significant alteration in cerebral blood flow. We conclude that gadopentetate dimeglumine is well suited for cerebral MR perfusion imaging without inherent influence on cerebral blood flow and that the same is probably true for polylysine-Gd-DTPA and SPIO.

Index terms: Cerebral flood flow; Contrast media, effects; Ultrasound, Doppler; Animal studies

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Fast gradient-echo and echo-planar imaging allow for real-time sequential imaging in subseconds and, combined with bolus application of susceptibility contrast media, enable quantitation of blood flow by measuring the temporal changes in image intensity (1). Bolus injection is required to show the initial blood flow–dependent enhancement pattern of various organs and pathologic lesions and to achieve optimal contrast (2, 3).

Gadopentetate dimeglumine is an ideal agent for use in the diagnosis of lesions that compromise the blood-brain barrier. Its short blood half-life and rapid extravasation into the extravascular space, however, limit the usefulness of low-molecular-weight gadopentetate dimeglumine as a perfusion agent. Several macromolecular agents have been developed to assess tissue perfusion, such as the new paramagnetic agent polylysine-Gd-DTPA, which remains largely confined to the intravascular space, causes persistent enhancement of the blood pool, and is cleared from the body relatively quickly thereafter (4, 5). As an alternative to macromolecular complexes, ultrasmall superparamagnetic iron particles (SPIO), studied extensively for their potential to improve detection of liver tumors (6–10), may also be useful as blood pool or perfusion agents. In the presence of an external magnetic field, they induce higher local signal inhomogeneities than would paramagnetic substances. Thus, these particles are very effective T2 relaxants, and they can be

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used as negative contrast agents by locally decreasing signal intensity (11).

We conducted an experimental study to evaluate the effects of intravenous (IV) bolus injection of three different magnetic resonance (MR) contrast agents on cerebral blood flow (CBF) and blood pressure in an animal model. We used two doses of gadopentetate dimeglumine: 0.1 mmol/kg, which represents the usual clinical dose, and 0.3 mmol/kg, a dose that is three times that used clinically. Polylysine-Gd-DTPA was used at a dose of 0.3 mmol/kg, and SPIO was administered in doses of 0.03 mmol/kg.

To measure CBF, we used laser Doppler flowmetry with an especially designed and intracerebrally placed single-fiber probe. This method has an extremely high temporal resolution, thus permitting detection of even subtle changes in CBF shortly after IV injection.

Material and Methods

Animal Preparation

Care and maintenance of experimental animals were in strict agreement with the guidelines established by the local animal protection committee. Adult male Wistar rats, weighing 250 to 350 g, were allowed free access to food and water before the procedure and were anesthetized with pentobarbital sodium (40 mg/kg, intraperitoneally). Each rat was allowed to breathe spontaneously. Rectal temperature was recorded and maintained at 37 ± 0.5°C with a heating pad. The left femoral artery was cannulated with a PE-50 catheter with a PE-10 tip for continuous monitoring of mean arterial blood pressure (MABP) and blood sampling for blood gas analysis (Radiometer, Copenhagen, Denmark). A tail vein catheter was used for IV injection of contrast medium.

Cranial Window Technique

The animals were immobilized in a stereotactic frame, the skull was exposed with a midline sagittal incision, and a craniectomy (burr hole diameter, 2 mm) was performed at 3 mm to the right and 4 mm anterior to the lambda suture. During drilling, care was taken to preserve a thin bone layer to avoid physical injury to the cortex. Gentle rinsing with saline (0.9%, 25°C) over the drilling site prevented thermal injury to the cortex. The bone layer was then carefully removed with forceps without disrupting the dura. The dura was pierced and an especially designed single-fiber laser Doppler flowmetry probe, mounted on a micromanipulator, was placed 1.5 mm into the cerebral cortex of the animal.

Laser Doppler Flowmetry

Use of laser Doppler flowmetry for the measurement of CBF is a novel technique, and thus its principles and technical features, which have been described in detail elsewhere (12–17), are reviewed here briefly. We used a Moor blood perfusion monitor (MBF 3D, Moor Instruments, Axminster, England) with a low-power (1.6 mW) laser diode as the source of coherent light. The laser emits an infrared light with a wavelength of 820 nm that is directed to the tissue through an optical fiber. We used a new single-fiber probe with a diameter of 0.1 mm, which allows CBF measurements to be made not only on the cortical surface but also within deep brain structures without causing much tissue damage. Since the single-fiber probe was attached to the micromanipulator of the stereotaxic frame, all measurements were obtained with the tip of the probe in identical topographic positions.

As light enters the tissue, photons are scattered randomly both by moving red blood cells and stationary tissue cells. Light scattering by moving red blood cells results in a Doppler frequency shift, while light scattered by stationary tissue does not change frequency. A portion of the light is reflected back into the single-fiber probe and returned to a photodetector. The electrical signal, generated by the backscattered light on the surface of the photodetector, contains frequency and power information. Frequency information is related to blood cell velocity, the power information is related to the blood volume. Parameters were measured within an estimated tissue volume of 0.4 mm^3. The flow signal was averaged with a time constant of 0.5 seconds. Validation of laser Doppler flowmetry for quantitative measurements of CBF changes had been carried out in an earlier study by Reith et al (18).

The laser Doppler flowmetry monitor allows output of blood flow values to be measured as a percentage level. Preinjection (baseline) value was set at 100% (relative laser Doppler flowmetry values) because the study was designed to evaluate changes in CBF after administration of a contrast agent. Arterial blood pressure measurements were also expressed in relative values as a percentage of MABP with baseline set at 100%.

Drug Administration (MR Contrast Media)

Three MR contrast agents (all manufactured by Schering AG, Berlin, Germany) were used in this study.

Gadopentetate Dimeglumine

Gadopentetate dimeglumine is a stable, clear, colorless, aqueous solution that contains the di-*N*-methylglucamine salt of diethylenetriamine pentaacetic acid (DTPA) at a concentration of 0.5 mol/L (0.5 mmol/mL), corresponding to an osmolality of 1.96 osmol/kg H_2O (at 37°C). The solution also includes 0.39 mg/mL of dimeglumine and 0.15 mg/mL of DTPA. A detailed description of the pharmacokinetic and paramagnetic properties has

been published (19). This contrast agent was administered in doses of 0.1 mmol/kg and 0.3 mmol/kg.

Polylysine-Gd-DTPA

Gd-DTPA complexed with polylysine is a new intravascular MR contrast agent. Polylysine-Gd-DTPA was synthesized by covalently binding Gd-DTPA molecules to a linear polymer of lysine molecules. We dissolved this compound in 0.9% saline at a concentration of 20 mmol Gd^{3+}/L. The average molecular weight of this compound is 48 000, the T1 relaxivity as measured at 39°C and 0.47 T is 13.1 $mmol^{-1}Gdsec^{-1}$ (Speck U, Schering AG, Berlin, Germany, personal communication). The polylysine-Gd-DTPA complex is composed of amino group 312 and gadolinium 60 per molecule, with a molecular weight of 4 to 5 kd. Pharmacokinetic studies with rats and rabbits have shown a bifunctional wash-out: a short phase of 2 to 4 minutes and a longer lasting phase of a 150-minute half-life. Although polylysine-Gd-DTPA is a macromolecular agent, it is small enough to be eliminated by the kidneys. The median lethal dose of this agent in mice is 15 mmol of gadolinium per kilogram of body weight, which, on a molar basis, is 2.7 times higher than gadopentetate dimeglumine (5.6 mmol Gd/kg) (20).

Superparamagnetic Iron Particles

The median diameter of the iron particles used was 40 nm, as measured by laser light scattering. The average molecular weight was 300 000 to 500 000 d; T1 relaxivity was 25 $mmol^{-1}Fesec^{-1}$, T2 relaxivity was 157 $mmol^{-1}Fesec^{-1}$, obtained with a 0.47-T nuclear MR spectrometer at 39°C.

The T2 relaxivity of 0.03 mmol/kg SPIO, the dose administered in our study, is equivalent to the relaxivity of 0.3 mmol/kg gadopentetate dimeglumine (the dose used in our perfusion studies). The paramagnetic iron particles used in our study do not correspond to the preparation SHU 555A (Resovist).

Study Design and Experimental Protocol

The animals were divided into four experimental groups according to type/dose of contrast agent administered: gadopentetate dimeglumine, 0.1 mmol/kg (n = 18); gadopentetate dimeglumine, 0.3 mmol/kg (n = 18); polylysine-Gd-DTPA, 0.3 mmol/kg (n = 10); and SPIO, 0.03 mmol/kg (n = 10).

In the first part of the study, we evaluated the effects of gadopentetate dimeglumine at doses of 0.1 mmol/kg and 0.3 mmol/kg, respectively, on CBF and MABP in 18 animals each. Subsequently, we performed the same study with the new contrast agents polylysine-Gd-DTPA and SPIO in 10 animals each, since this number of animals was statistically sufficient.

After surgical preparation, animals were allowed to equilibrate for at least 20 minutes, during which time baseline values of CBF and MABP were acquired to assure their stability prior to drug administration. The animals then received the contrast agent (gadopentetate dimeglumine 0.1 mmol/kg or 0.3 mmol/kg, polylysine-Gd-DTPA 0.3 mmol/kg, or SPIO 0.03 mmol/kg) as an IV bolus injection by hand via a tail vein catheter. Injection volumes administered ranged from 0.07 to 0.2 mL. Injection rates were 0.1 mL/sec. Laser Doppler flowmetry values and MABP were continuously monitored before, during, and up to 30 minutes after drug administration; data were recorded every 30 seconds.

Statistical Analysis

Measured values are expressed as the mean plus or minus the standard error of the mean. Values at various specified time intervals after drug administration were compared with preinjection (baseline) values (100%) by using a paired *t* test and ANOVA. A probability (*P*) value of less than .05 was considered to be significant.

Results

No statistically significant differences were noted among the four groups for any of the physiological parameters measured at baseline. Throughout the study period the average body temperature for all animals was 36.9 ± 0.5°C (mean ± SD). There were no significant changes in arterial blood gases (Po_2 = 126 ± 37 mm Hg, Pco_2 = 33 ± 3.2 mm Hg, pH = 7.4 ± 0.02).

The baseline laser Doppler flowmetry values were highly sensitive to probe positioning and showed a wide variability (range, 23 to 487 arbitrary units). Hence, absolute laser Doppler flowmetry readings carry little information with respect to CBF. During measurement, care was taken to avoid small displacements of the probes or the animals that could artifactually change the laser Doppler flowmetry reading.

Neither application of gadopentetate dimeglumine (0.1 mmol/kg or 0.3 mmol/kg) had any statistically significant effect on CBF. There were no changes in blood pressure during administration of gadopentetate dimeglumine at either dose level (Figs 1 and 2). *P* values at specified time intervals were greater than .05 for 20 minutes after drug administration. Standard deviation for both dose levels at specified time intervals was low (<10%).

Administration of polylysine-Gd-DTPA (0.3 mmol/kg) caused a transient drop in blood pressure in two animals, which was marked in one animal (maximum blood pressure drop to 21% of preinjection values) and mild in the other (maximum drop to 84% of preinjection values).

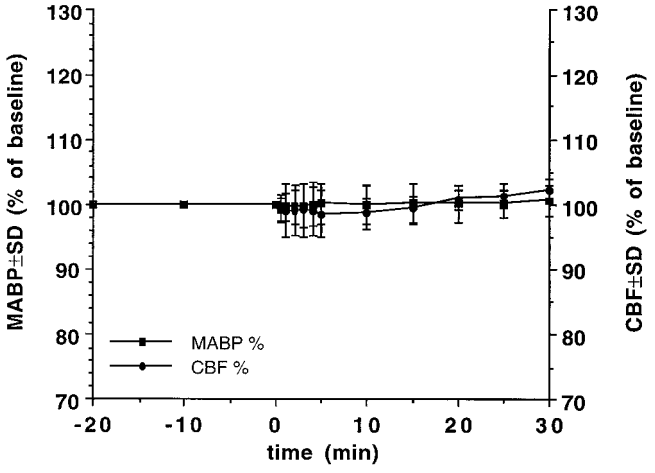

Fig 1. Mean values of CBF and MABP ± SD at various specified time intervals after administration of 0.1 mmol/kg gadopentetate dimeglumine.

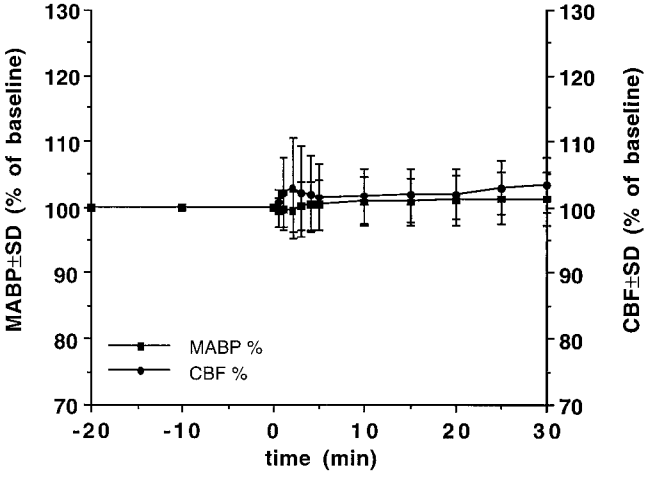

Fig 2. Mean values of CBF and MABP ± SD at various specified time intervals after administration of 0.3 mmol/kg gadopentetate dimeglumine.

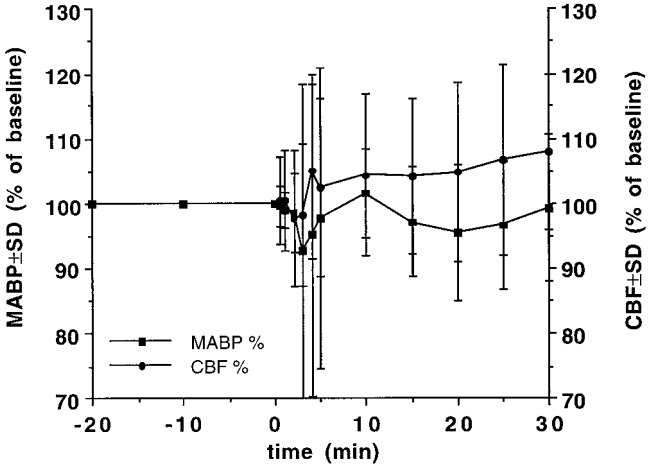

Fig 3. Mean values of CBF and MABP ± SD at various specified time intervals after administration of 0.3 mmol/kg polylysine-Gd-DTPA.

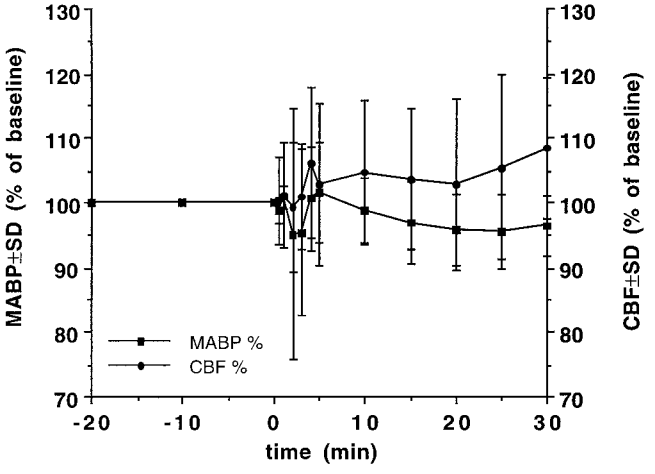

Fig 4. Mean values of CBF and MABP ± SD at various specified time intervals after administration of 0.03 mmol/kg SPIO.

After administration of SPIO (0.03 mmol/kg), a significant decrease in blood pressure occurred in one animal (maximum drop to 41% of preinjection values). The onset of these hemodynamic effects was observed within 3 minutes after injection. All hemodynamic parameters returned to baseline within 2 minutes. There were no statistically significant changes in CBF after administration of polylysine-Gd-DTPA or SPIO (Figs 3 and 4). *P* values at specified time intervals were greater than .05.

The average decrease in mean arterial blood pressure 3 minutes after drug administration was 7% (from 100% to 93%) for polylysine-Gd-DTPA and 4.6% (from 100% to 95.4%) for SPIO (Figs 3 and 4).

As compared with gadopentetate dimeglumine, the standard deviation at specified time intervals after drug administration was higher when injecting polylysine-Gd-DTPA or SPIO, especially within the first 5 minutes.

Discussion

The use of laser Doppler flowmetry for CBF measurements was described by Riva et al (21), who studied blood flow in retinal vessels. So far, the technique has been used in different designs for blood flow recordings in various tissues (17). Comparisons of this method with other, more direct blood flow techniques, such as hydrogen clearance, xenon-133 clearance, or autoradiog-

raphy, have shown linear relationships (13–15, 18). Laser Doppler flowmetry has proved to be a valuable, valid, and reliable technique for online measurement of blood flow under experimental conditions (15, 17, 22). Laser Doppler flowmetry also has an excellent spatial resolution, allowing recognition of CBF changes in small tissue samples of about 1 mm^3.

Laser Doppler flowmetry has certain disadvantages, however; for example, the lack of quantitation. This limitation is not inherent in the technique but rather depends on the lack of acceptable alternatives to calibrate the laser Doppler flowmetry signal against an independent measure of blood flow in the region of interest (23). Absolute flow values are highly dependent on probe placement and position; that is, minor changes in probe position ($<$100 μm) sometimes result in major artifactual changes in CBF values ($>$50%). There are no data available on direct effects of MR contrast agents on the laser Doppler flowmetry measurement. We cannot exclude the possibility that administration of contrast agents might cause artifacts during injection. Therefore, mechanical stability of the probe attachment is of great importance for obtaining accurate results over long periods of observation. We tried to minimize these motion artifacts by using a stereotactic probe holder.

In our study, bolus injection of gadopentetate dimeglumine at doses of 0.1 and 0.3 mmol/kg into the tail vein of rats caused no statistically significant alterations in CBF and no changes in blood pressure. Recently, Mühler et al (24) showed acute dose-dependent hemodynamic effects of gadopentetate dimeglumine if administered as a rapid bolus injection in the right atrium of rats in incremental doses (0.1, 0.3, 0.5 mmol/kg). Changes in blood pressure were significant at all doses beginning at 0.1 mmol/kg. Rapid injection of the high dose (0.5 mmol/kg) produced a transient decrease in arterial blood pressure (systolic, −34%; diastolic, −39%; mean, −32% aortic pressure), which returned to baseline values within 1 minute after injection. Bolus injection of equivolumetric and equiosmotic control material showed no statistically significant hemodynamic effects. The decrease in blood pressure is thought to be unrelated to volumetric or osmotic effects; instead, it is considered to have a direct influence on the peripheral vascular resistance rather than a direct effect on the contractility of the myocardium (25). Injection volumes administered in our study ranged from 0.07 to 0.2 mL, so that volumetric effects can be ruled out.

Hong-Tai et al (26) compared the hemodynamic effects of incremental doses (0.1, 0.3, 0.5 mmol/kg) of nonionic gadodiamide and ionic gadopentetate dimeglumine in rats with acute myocardial infarction. Gadodiamide produced no significant hemodynamic effects at any of the doses. However, gadopentetate dimeglumine caused significant alterations in hemodynamic parameters in a dose-dependant fashion; after bolus injection of gadopentetate dimeglumine in doses of 0.1, 0.3, and 0.5 mmol/kg in the jugular vein, mean arterial blood pressure decreased by 98 $\pm$ 1.1%, 83 $\pm$ 5%, and 52 $\pm$ 5.4%, respectively.

Peters and Shaw (27) also compared the hemodynamic effects of gadopentetate dimeglumine and gadodiamide administered by IV bolus injection in the inferior vena cava at doses of 1.0 and 1.5 mmol/kg in anesthetized dogs. They reported that mean aortic pressure was maximally decreased 30 seconds after administration of gadopentetate dimeglumine. Gadopentetate dimeglumine injections administered at doses of 1.0 and 1.5 mmol/kg resulted in a maximum fall in pressure of about 41% and 47%, respectively.

These results are contrary to our findings. A possible explanation for the drop in blood pressure in these studies might be the injection site. All investigators used a central site, injecting the contrast agent via the jugular vein or inferior vena cava into the right atrium. The hemodynamic alterations induced by contrast media depend on the site of administration: peripheral intravenous injection (tail vein) tends to cause fewer or perhaps even insignificant hemodynamic alterations compared with intracardiac injection (28). We used a tail vein catheter for injection of the contrast agent.

Sullivan et al (25), in a study in anesthetized mongrel dogs, showed a small but statistically significant hemodynamic effect of gadopentetate dimeglumine when administered as a rapid bolus injection (within seconds) in the femoral vein only in a high dose (0.5 mmol/kg), with a transient decrease in systolic (−13%), diastolic (−23%), and mean (−19%) aortic pressure occurring 30 seconds after bolus injection. They concluded that this decline was most likely a direct result of gadopentetate dimeglumine on the peripheral vascular resistance ves-

sels. Application of usual clinical doses of gadopentetate dimeglumine (0.1 mmol/kg) in a rapid bolus (10 seconds) or an infusion (1 minute) or a slow infusion of the higher dose (0.5 mmol/kg) had no influence on heart rate, left ventricular end diastolic pressure, or central venous pressure. This is consistent with our results.

The time at which the maximum changes from baseline occurred in our hemodynamic measurements was approximately 30 seconds to 3 minutes after injection and is consistent with that observed with iodinated contrast agents, suggesting that part of the response may be mediated by reflex vasodilatation (29, 30).

In a placebo-controlled study in healthy volunteers, Kashanian et al (31) observed no clinically significant changes of hemodynamic parameters compared with baseline after rapid bolus injection of gadopentetate dimeglumine (0.2 mL/kg). Niendorf et al (32) reviewed the safety profile of gadopentetate dimeglumine after more than 5 million applications. Fast bolus injections were also tolerated without additional risk (33–35). Kanal et al (36) evaluated the frequency and type of adverse events following bolus administration of gadopentetate dimeglumine in 4260 patients and observed only one episode of hypotension.

Bolus administration of gadopentetate dimeglumine at doses of 0.1 mmol/kg and 0.3 mmol/kg was not associated with significant changes in CBF. We conclude that perfusion studies of CBF after bolus injection of gadopentetate dimeglumine should be possible without having the result influenced by the contrast agent itself. To avoid cardiodepressive effects, a peripheral injection site (cubital vein) should be used. Studies with patients are needed to support specific clinical recommendations.

Administration of polylysine-Gd-DTPA (0.3 mmol/kg) caused a transient drop in blood pressure in two animals. After administration of SPIO (0.03 mmol/kg), a significant decrease in blood pressure occurred in one animal. Blood pressure values returned to baseline within 2 minutes. The average decrease in MABP (3 minutes after drug administration) was 7% for polylysine-Gd-DTPA and 4.6% for SPIO. In acute stroke patients in whom brain autoregulation is altered, even transient changes in MABP may result in significant consequences, and reduced blood flow may exacerbate cerebral ischemia. Despite an isolated decrease in MABP in some animals there were no changes in CBF after administration of polylysine-Gd-DTPA and SPIO in our study.

Recently, a study in rats has shown that IV injection of polylysine-Gd-DTPA (0.05 mmol/kg over 30 seconds) is not associated with any significant effects on left ventricular function, heart rate, or systemic blood pressure, respectively (20). Similarly, no adverse effects were observed after injection of 0.6 mmol/kg polylysine-Gd-DTPA in mice (37).

Dextran-coated iron oxide particles (the initial formulation of AMI-25) have been administered at the high dose of 40 mmol/kg to humans in phase II and III studies (7). However, because of hypotension (in about 70% of patients) and lower back pain after injection of AMI-25, the clinical trials were stopped and the formula had to be changed before further investigations were undertaken in patients (7, 9, 38, 39). Hypotension might have been related to the dose injected (greater than 40 μmol/kg), to the infusion rate (greater than 1000 μmol/min), or to both; however, the exact mechanism underlying this adverse reaction remains undetermined.

After a short interruption of clinical trials brought on by the adverse reactions, investigations were continued with different formulations of SPIO at different doses and injection rates (40, 41). Subsequent clinical trials have shown predominantly minor side effects in approximately 10% to 15% of patients (eg, facial flush, rash, dyspnea, and lumbar pain) (42). In a study of 20 patients with liver metastases, Bellin et al (10) observed no change in heart rate or blood pressure and concluded that AMI-25, infused slowly in dextrose solution at a dose of 15 μmol/kg, is well tolerated and safe. The same results have been reported by Halavaara et al (43) and Grangier et al (44) in similar studies with Endorem (Labaratoire Guerbet, Paris, France), a reformulation of AMI-25.

To further improve contrast-enhanced MR imaging of the liver, Resovist, a new liver-specific SPIO was developed. In a phase II trial in 33 patients, Reimer et al (42) observed no significant changes in cardiovascular parameters after slow injection (0.5 to 1.0 mL/min) of Resovist at doses of 4, 8, and 16 μmol of iron per kilogram of body weight. These investigators also believe Resovist to be suited for perfusion studies of the brain or heart. In perfusion studies

in experimental stroke in rats, Minematsu et al (45) observed no effect on blood pressure after rapid bolus injection of 0.05 mmol/kg SPIO.

Duewell et al (46), in a study with dogs, observed a precipitous drop in blood pressure to almost zero, which lasted for several minutes after high-dose (0.1 to 0.3 mmol/kg body weight) bolus application of ionic ferrioxamine-B, a chelate of iron. This reaction seems most likely to have been the result of a negative inotropic effect of ferrioxamine-B.

The macromolecular polylysine-Gd-DTPA and the very effective T2 relaxant SPIO are promising contrast agents for assessing tissue perfusion. Owing to their macromolecular structure, these agents remain intravascular. After bolus injection of polylysine-Gd-DTPA (0.3 mmol/kg) and SPIO (0.03 mmol/kg), we noted no significant changes in CBF. Perfusion studies of CBF in which the result is not influenced by the contrast agent itself should therefore also be possible with polylysine-Gd-DTPA and SPIO. However, in our study, administration of each of these contrast agents caused a transient drop in blood pressure in two animals, with return to baseline within 2 minutes.

Administration of gadopentetate dimeglumine at doses of 0.1 mmol/kg and 0.3 mmol/kg, polylysine-Gd-DTPA at a dose of 0.3 mmol/kg, and SPIO at a dose of 0.03 mmol/kg was not associated with significant changes in CBF. We conclude that perfusion studies of CBF should be possible without having the result influenced by the contrast agent itself, at least with gadopentetate dimeglumine and probably also with polylysine-Gd-DTPA and SPIO.

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