Notes on Radiographic Contrast Agents

BASIC PRINCIPLES

The use of radiographic contrast agents dates almost from the discovery of X-Rays. In 1896 Becher opacified the gastrointestinal tract of the guinea pig using lead subacetate.

The basic principle is that contrast agents are administered in such a way as to alter the absorption of x-rays by specific anatomic structures in relation to their surroundings. Contrast agents may be positive (iodine or barium compounds, for example), or negative (gases).

Gaseous contrast agents absorb fewer x-rays than tissues because of their low density, even though the effective atomic number may be higher. On the other hand, positive contrast agents absorb more x-rays than tissues because of their high density and higher atomic number.

1 IODINE COMPOUNDS AS CONTRAST AGENTS

Almost all radiological examinations performed with injected contrast agents involve the administration of iodine-containing compounds.

The use of iodine compounds was initially related to low toxicity and excellent radio-opacity rather than physical considerations. However, it was also fortunate that iodine compounds possess physical properties which make them better contrast agents than compounds with higher atomic number.

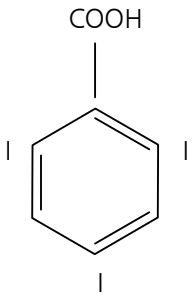
The K-edge of iodine is 33.2 keV. At photon energies slightly above this, iodine actually has greater attenuating properties for x-rays than the same mass of lead.

The location of this K-edge for iodine has practical implications. Obviously the maximum contrast in radiographic studies using iodine compounds would be obtained by using a monochromatic beam of radiation of energy just above 33.2 keV. This is not practicable, however, but what can be done is to select the peak kilovoltage (kVp) for the examination which will give a high proportion of the photons in the 33-40 keV range. This is achieved when a relatively low kVp is used.

Therefore, for contrast examinations using iodine compounds, optimum technique requires a kVp in the 60-80 range.

1a) IONIC WATER-SOLUBLE AGENTS HANDLED BY RENAL EXCRETION

These are sodium or methylglucamine salts of 2,4,6 tri-iodobenzoic acid:



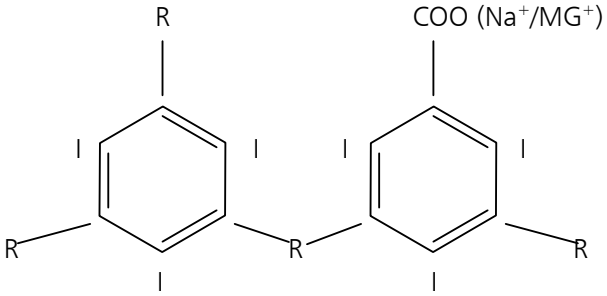
Positions 3,5 are substituted with side chains which increase solubility and decrease toxicity.

Contrast media of this type include:

- Diatrizoate (Urografin, Angiografin)
- Iothalamate (Conray)
- Metrizoate (Isopaque)
- Iodamide

These compounds vary only in the side chains at positions 3,5. All of these agents dissociate in solution to produce two ionic particles for each three iodine atoms. They are therefore referred to as RATIO 1.5 AGENTS. Commercial preparations of these agents may be pure methylglucamine or pure sodium compounds, or a mixture of both.

A relatively recent addition to this group of ionic agents is a mixture of the sodium and methylglucamine salts of ioxaglic acid (Hexabrix).



This agent is a monoacidic dimer. It dissociates in solution to produce two ionic particles for each six iodine atoms. Therefore, it is a RATIO 3 *AGENT,* a property which it shares with the non-ionic agents to be discussed later.

ADMINISTRATION

These compounds are not absorbed in significant amounts from the normal gastrointestinal mucosa. Therefore, they are mainly administered by the intravenous or intra-arterial routes. They are not suitable for intrathecal administration.

If ionic compounds are used for urography, 50ml of a 76% (w/v) diatrizoate preparation or equivalent is satisfactory for an average size patient with good renal function. This dose, however, can reasonably be doubled for large patients.

In angiography, the dose per injection varies with the vessel injected. The total dose is of some importance when multiple injections are made. Although there is no clearly recognised dose limit, with ionic agents it is wise to consider terminating the examination when 300ml of a 76% diatrizoate preparation or equivalent has been injected.

SELECTED IMPORTANT PHYSICAL PROPERTIES

OSMOLALITY

Normal serum osmolality is approximately 300 mosm/kg water. The osmolalities of some of the commoner RATIO 1.5 AGENTS and Hexabrix are:

	mosm/kg water
Urografin 76%	1690
Angiografin 65%	1530
Conray 280	1220
Hexabrix	580

The RATIO 1.5 AGENTS are high osmolality preparations. The undesirable effects of injection of high osmolality compounds include:

- Pain on arterial, and sometimes venous, injection.
- Endothelial damage.
- Large fluid shifts between the intravascular and extravascular compartments.
- Red cell deformation.
- Osmotic diuresis limiting concentrating ability.

A major benefit of the RATIO 3 AGENTS is reduced osmolality for the same iodine content.

VISCOSITY

Viscosity is obviously of considerable importance in angiography, where the injection rate through a catheter can be of critical importance. Viscosity may be measured in centipoise (cP). The viscosity of water at 20 degrees Centigrade is approximately lcP. Viscosity depends on a number of factors which include the size and shape of the solute particle, as well as temperature.

The viscosities of some of the common RATIO 1.5 AGENTS and Hexabrix are:

	cP @ 25 degrees	cP @ 37 degrees C
Urografin 76%	13.8	8.5
Conray 280	5.9	4
Hexabrix	15.7 (@ 20 degrees C)	7.5

Viscosity is obviously temperature dependent. Contrast media are approximately twice as viscous at 20 degrees C as at body temperature. Warming the contrast agent to body temperature may be of considerable importance in angiography in achieving required flow rates within the limitations of catheter pressure tolerances.

Note that sodium compounds are generally less viscous than methylglucamine compounds. On the other hand, it is generally considered that methyglucamine compounds are less irritating to vascular endothelium and end-organs such as the brain.

PLASMA CONCENTRATION & DISTRIBUTION AFTER INJECTION

These substances are carried free in plasma, less than 5% of an injected dose is protein bound.

The plasma concentration just after injection is strongly related to the dose and the injection rate. The larger the dose and faster the injection, the higher the plasma level. Immediately after injection, however, contrast: agent begins to diffuse into the extravascular space and water is drawn from the latter into the intravascular compartment by the increased osmolality due to the contrast agent. At five minutes, the concentration in the intravascular and extravascular compartments is virtually identical and 80% of the contrast agent is outside the intravascular compartment.

The exceptions are in the brain, other neural tissues and the testes, where the tight junctions of the endothelial cells do not allow the diffusion of the contrast agent molecules outside the vascular compartment. There is a "blood-brain barrier" which confines contrast agent to the vascular compartment in neural tissues.

There are important consequences of the above for the conduct of computed tomographic examinations. In scanning non-neural tissues, normal and abnormal tissues may often be differentiated by different degrees of vascularity and capillary permeability. These differences are best shown by early scanning after a bolus of contrast agent. Delayed scans, after equilibration has taken place, may show little or no abnormality.

On the other hand, when scanning neural tissues, a bolus injection is often of no particular merit but delayed scans may be most helpful as they will show accumulation of contrast agent over time in areas of blood-brain barrier breakdown, eg in tumours and demyelinating plaques.

Note that these agents cross the placenta as shown by studies of foetuses obtained during legal abortions after prior injection of the mother with radionuclide labelled diatrizoate. There have been reports of confirmation of renal function in the foetus by computed tomography after maternal intravenous injection of contrast agent.

EXCRETION

In the normal patient, excretion is almost entirely via the renal route. These compounds are handled by the kidney in the same fashion as inulin, ie there is glomerular filtration and concentration by tubular resorption of water. There is an insignificant amount of tubular secretion but this is said to be somewhat greater with iodamide than with other members of this group. It is doubtful if this is of clinical importance.

When the glomerular filtrate begins its course through the proximal tubule, it has the same iodine concentration as plasma. Under normal (non-urographic) conditions, 85% of the filtered water is absorbed in the proximal tubule (obligatory reabsorption). With large amounts of non-reabsorbable foreign molecules such as contrast agent present, this is no longer possible and only about half the filtered water can be reabsorbed. This reabsorption is independent of the state of hydration of the patient.

The amount of water reabsorption in the collecting tubule, however, is under the influence of ADH. The level of serum ADH is related to such factors as stress and dehydration. The effect of ADH on water reabsorption is modified by the amount of osmotically active agents such as contrast medium or urea within the tubular lumen. These compounds tend to retain water within the tubule. Therefore, increasing the amount of contrast agent in the tubular lumen tends to impose a maximum on the amount of water reabsorption that occurs and therefore the concentration of contrast medium in the urine.

The steep rise in concentration in the collecting tubules may give a blush in the papillary region at urography, which is sometimes incorrectly called "backflow". The final urine diatrizoate concentration in the patient with normal renal function may be 30-50 times the plasma concentration.

In normal patients, the urinary excretion of contrast agent, expressed as a percentage of injected dose, is 12% at ten minutes, 50% at one hour, 83% at 3 hours and almost 100% at twenty-four hours. Less than 1% of the dose is excreted by other routes, mainly the liver and small bowel.

In renal impairment, the liver provides the major alternative excretory pathway, accounting for the frequent finding of opacification of the gallbladder. The small intestinal mucosa also secretes these agents, while small amounts are found in sweat, tears, saliva and gastric juice. By analysis of stool iodine content, it has been shown that 20-50% of the injected dose is eliminated in a three day period in patients with advanced renal failure.

There is no significant degree of metabolism of the contrast agent molecules in the body.

1b) NON-IONIC CONTRAST AGENTS

The search for contrast agents with good radio-opacity, low toxicity, low osmolality and suitability for intrathecal injection led to metrizamide as the first agent of this group. Metrizamide is a glucosamide derivative of metrizoic acid. It is no longer commercially available in Australia.

Non-ionic contrast agents are now available; iopamidol, iohexol, ioversol, iopromide, iodixanol and iotrolan. Like Hexabrix, the first four are RATIO 3 AGENTS but they do not dissociate in solution. Iotrolan and iodixanol are non-ionic dimers and RATIO 6 AGENTS.

These compounds are suitable for intrathecal use and have almost entirely replaced oily myelographic agents (note that ioversol and iopromide have not yet been approved for intrathecal use in Australia).

Another advantage of these compounds is that they appear to have less toxicity than RATIO 1.5 AGENTS, although it will take many years of widespread usage to confirm this. Their principal disadvantage is that they cost approximately 4-5 times as much as RATIO 1.5 AGENTS.

Some hospitals have made the decision to use non-ionic contrast agents only, because of their greater apparent safety. Other hospitals use these agents selectively and the principal indications are:

(i) Intrathecal examinations.
(ii) Examinations in which higher osmolality agents may be painful or may have a higher risk of organ damage, eg peripheral arteriography, cerebral and coronary angiography.
(iii) Patients at a high risk for adverse reactions from conventional media.

ACCORDING TO THE RANZCR, THE HIGH RISK GROUP INCLUDES:

- Patients with previous reactions to contrast media.
- Patients with asthma or significant allergic disease.
- Patients with previous episodes of anaphylaxis.
- Elderly patients or those with known significant cardiac disease.
- Renal insufficiency, particularly associated with insulin-dependent diabetes.
- Patients with sickle cell disease, polycythaemia, phaeochromocytoma or myeloma.
- Excessively anxious patients.

It should be noted that the non-ionic contrast agents have much less anticoagulant effect than the ionic agents. Thus, meticulous flushing techniques are required during angiography with non-ionic contrast media.

OSMOLALITY AND VISCOSITY

The following table indicates the osmolality of some commercially available preparations of non-ionic contrast media:

	mosm/kg water
Iopamidol 200	413
Iopamidol 300	616
Iopamidol 370	796
Iohexol 240	500
Iohexol 300	690
Iohexol 350	880
Ioversol 320	702
Iopromide 370	780
Iotrolan 300	320

The viscosity of the same preparations is as follows:

	cP @ 20 degrees C	cP @ 37 degrees C
Iopamidol 200	3.3	2.0
Iopamidol 300	8.5	4.7
Iopamidol 370	19.1	8.6
Iohexol 240	5.6	3.3
Iohexol 300	11.6	6.1
Iohexol 350	23.3	10.6
Ioversol 320		5.8
Iopromide 370	20.1	9.5
Iotrolan 300	16.4	8.1

EXCRETION

As with the ionic agents, excretion is almost entirely via the renal route in the patient with normal renal function. Because of the reduced osmolality of these agents, there is less osmotic diuresis so that there tends to be a higher urinary iodine concentration and a denser pyelogram. This is balanced to some extent by the reduction in diuresis causing less distension of the collecting systems. Because of the reduced osmotic diuretic effect, these agents produce a better pyelogram in the patient with renal impairment.

INTRATHECAL USE OF NON-IONIC CONTRAST AGENTS

Metrizamide was the first non-ionic contrast agent used for myelography. It has now largely been replaced by iopamidol and iohexol because of their reduced cost and their stability in solution. Ioversol and iopromide have not yet been approved for myelography in Australia.

DOSE

This is often dependent on the individual preference of the radiologist. Low concentration solutions are usually used such as 15ml of 180mg/ml of iodine or 12ml of 240mg/ml.

ELIMINATION FROM CSF

Within fifteen minutes of lumbar injection, the contrast agents are detectable in the blood. It seems likely that absorption into the bloodstream is via arachnoid villi related to the nerve roots rather than the villi associated with the superior sagittal sinus. Twenty four hours after injection, 60-85% of metrizamide is recoverable in the urine. Experimental evidence indicates more rapid absorption from the subarachnoid space in the sitting than in the recumbent position, showing that the lumbar subarachnoid space is a major resorptive pathway. After absorption into the blood, final excretion is renal.

Note that following intrathecal contrast agent injection, CT scans of the brain and spinal cord show penetration of the neural tissue by the agent. It is thought that this occurs because the CSF and extracellular fluid spaces in neural tissue comprise one fluid compartment.

SIDE EFFECTS AND COMPLICATIONS OF INTRATHECAL USE

(I) ARACHNOIDITIS

This may be caused by meningeal irritation due to contrast media and other forms of trauma such as surgery. The incidence of arachnoiditis is very much lower following water-soluble, non-ionic agents than with the oily contrast agent Myodil. In the patient who has not had previous surgery the incidence of arachnoiditis is close to zero.

(II) SEIZURES

The risk of grand mal seizures is low and in one series of 30,000 metrizamide examinations there were only 9 cases. It is thought that the risk of seizures increases as more contrast agent is introduced into the cranial subarachnoid space. Also, patients taking phenothiazines are more likely to fit. Seizures are controllable with I.V. diazepam.

(III) HEADACHE AND DISTURBANCES OF CEREBRAL FUNCTION

Disturbances such as hallucinations, psychotic symptoms, aphasia, hearing loss and motor paralysis have all been reported with metrizemide. Fortunately these are almost always temporary. The incidence of these problems with newer non-ionic agents seems to be lower.

To minimise the exposure of neural tissue to the contrast agent, it is recommended that patients remain in the erect or semi-erect position for up to 8 hours following water-soluble myelography. Hydration has also been shown to decrease the incidence of neurological side effects and headache.

1c) INTRAVENOUS CHOLANGIOGRAPHIC AGENTS

The only intravenous cholangiographic agent currently available in Australia is Biliscopin (meglumine iotroxate). This is a meglumine salt dimer of triiodobenzoic acid. An unsubstituted five position on the benzene ring meditates reversible binding to plasma proteins and ensures biliary excretion without conjugation. In the blood, biliary contrast agents are preferentially bound to albumin and are therefore subject to only limited renal excretion.

The degree of bile duct opacification is to a large extent determined by the plasma concerntration of the contrast medium. A slow infusion helps to optimise the biliary excretion and also reduces side effects.

The usual dose of Biliscopin is 100ml (105mg meglumine iotroxate/ml, 5.0g Iodine). This is administered slowly over a period of 30 minutes to 60 minutes via drip infusion or by infusion pump. Optimal biliary opacification occurs from 20 minutes to 90 minutes following completion of the infusion.

Patients with mildly impaired liver function may excrete sufficient contrast to opacify the bilary duct system. When the bilirubin level exceeds 1.2mg%, the opacification rate is poor.

Side effects are similar to those of other iodinated contrast media but occur with greater frequency. This is thought to be due to the protein-binding characteristics required for biliary excretion.

1d) ORAL CHOLECYSTOGRAPHIC AGENTS

These are no longer commercially available and are of historic interest only. They are derivatives of triiodobenzoic acid. The five position on the benzene ring is not substituted. This is an important structural feature determining biliary excretion. The molecules contain hydrophilic and lipiphilic groups to allow biliary absorption and hepatic excretion.

1e) OILY CONTRAST AGENTS

These agents are no longer commercially available in Australia. They include Iophendylate (Myodil, Pantopaque), a myelographic agent and Lipiodrol Ultrafluide (Ethiodol), a lymphangiographic agent.

2) BARIUM SULPHATE

Barium sulphate is derived from the mineral barytes. In aqueous suspension it has been the standard contrast agent for opacification of the gastro-intestinal tract, almost since the beginning of radiology. Barium has a K-edge at 37.4keV. Therefore, a relatively low kVp radiographic technique would seem desirable but, in many cases, barium compounds are used in quite high concentration in the alimentary tract and the need for this is doubtful. It could be of importance, however, in air contrast techniques where only a thin coating of barium is used to outline viscera.

The many proprietary preparations of barium sulphate which have appeared on the market over many years differ in their additives such as suspending agents etc.

3) MAGNETIC RESONANCE IMAGING CONTRAST AGENTS

3a) PARAMAGNETIC CONTRAST AGENTS

The magnetic dipole moments of paramagnetic substances are randomly aligned in the absence of an external magnetic field. When an external magnetic field is present, however, the magnetic moments align with the field and induce strong local magnetic fields that shorten-the Tl and T2 relaxation times of adjacent protons. When the external field is removed, the magnetic dipole moments of paramagnetic substances again become randomly aligned so that there is no retained magnetisation.

Paramagnetic substances have one or more particles (protons, neutrons or electrons) with a spin that is not cancelled by another similar particle with an opposite spin. Magnetic dipole moments of unpaired electrons are very much larger than those of protons or neutrons, so that the local magnetic fields generated by unpaired electrons are very strong. Therefore, substances that have unpaired electrons, such as the transitional elements, are very effective paramagnetic contrast enhancers. When paramagnetic ions are added to water, the relaxation of water molecules is enhanced in the vicinity of the paramagnetic substance. Both T_1 and T_2 relaxation times are reduced.

It should be noted that whereas iodine-containing contrast agents in radiography directly affect film density by photon absorption, MRI contrast agents have an indirect effect. It is not the actual contrast agent which alters the intensity of the image but the presence of the contrast agent alters the relaxation characteristics of adjacent protons, thus indirectly affecting the intensity.

There are two commercially available MRI contrast agents at present in Australia; viz, gadopentetate dimeglumine (Magnevist) and gadodiamide (Omniscan). In solution, the former substance dissociates into two methylglucamine cations and one anion, containing a gadolinium atom chelated with diethylenetriamine pentaacetate.

On the other hand, gadodiamide is a non-ionic agent which does not dissociate in solution. In this molecule, gadolinium is chelated with diethylenetriamine pentaacetic acid bismethylamide.

Gadolinium contains seven unpaired electrons, making these compounds strongly paramagnetic.

In clinical usage, T_1 weighted images are used to demonstrate the high signal caused by T_1 relaxation enhancement of tissues in which the contrast agent accumulates.

ADMINISTRATION AND DOSAGE

Magnevist and Omniscan are supplied as 0.5mmol/ml solutions. The usual dosage is 0.lmmol/kg. For example, a 70kg patient would require a 14ml intravenous dose.

At this dosage level, the effect is primarily on the T_1 relaxation time. Exceeding the dose may be counterproductive as the T_2 relaxation effect becomes more marked.

PLASMA CONCENTRATION AND DISTRIBUTION AFTER INJECTION

As with iodine-containing radiographic contrast agents, gadopentetate dimeglumine is carried free in plasma with little protein binding. It rapidly becomes dispersed in the extracelluar fluid, as well as the intravascular space. It does not penetrate the intact blood-brain barrier. There is some passage of contrast agent across the placenta. Similar remarks apply to gadodiamide.

EXCRETION

These contrast agents are eliminated by glomerular filtration and concentrated in the urine by tubular resorption of water. About 83% of the injected dose is eliminated by six hours. There is no metabolism of the molecules. About 1% of the injected dose is eliminated in the faeces.

When renal function is impaired the retention time is greatly prolonged.

TOXICITY

Adverse reactions are very uncommon (1.47%). To date, more than 20 million doses of Magnevist have been given. The most common side effects include mucosal reactions, urticaria, vomiting, local warmth and pain, headache, parathesia and dizziness.

SELECTED PHYSICAL PROPERTIES

Gadopentetate dimeglumine is markedly hypertonic with an osmolality of 1960mosm/kg H20. Gadodiamide is 789mosm/kg H20.

The viscosity of Magnevist at 20 degrees C is 4.9cP; 2.9cP at 37 degrees C. Corresponding figures for Omniscan are 2.0cP and 1.4cP.

GADOLINIUM AS AN X-RAY CONTRAST AGENT

Gadolinium complexes can be used as X-ray contrast agents in patients with a history of an adverse reaction to iodinated contrast media. The dose typically used for this application is 1.5 mmol/kg body weight.

3b) SUPERPARAMAGNETIC CONTRAST AGENTS

When placed in an external magnetic field, paramagnetic substances induce further magnetisation which is directly proportional to the strength of the applied field. Increasing the external field increases the net magnetisation in a linear fashion. When there is no external magnetic field, there is no net magnetisation.

Superparamagnetic substances, however, induce very strong magnetisation in an external magnetic field, several orders of magnitude higher than paramagnetic agents and in a non-linear fashion. There is, however, no magnetisation in the absence of an external field. It is this property which distinguishes superparamagnetic substances from ferromagnetic substances which retain magnetisation when there is no longer an external field. Particulate iron less than 300 Angstrom units in size is superparamagnetic; larger iron particles are ferromagnetic. In the latter, there is magnetic ordering of the unpaired electron spins of the iron atoms in regions which are referred to as domains.

When an external magnetic field is applied, these domains, which were previously randomly oriented, line up with the magnetic field and greatly enhance it. When the magnetic field is removed, this orientation remains. This is the property of remanence which is the cardinal feature of ferromagnetism. The particle size in superparamagnetic substances approximately equates to the size of a domain. When the external field is removed, the particles become randomly oriented again and there is no remanence.

Whereas paramagnetic substances are used diagnostically to increase proton signal, superparamagnetic or ferromagnetic materials destroy the signal, producing negative contrast. Ferrites in particulate form have been used as superparamagnetic contrast agents. Ferrites are iron oxides of the general formula Fe203.MO, where M is a divalent metal ion. Magnetite is a type of ferrite, occurring naturally, in which the metal ion is Fe++.

Particulate ferrites are taken up by the reticuloendothelial system. These contrast agents accumulate in Kupffer cells in the liver and destroy the signal from normal liver while metastatic lesions retain a signal as they do not accumulate the contrast agent.

Particulate iron contrast agents do have side effects and are not yet available for clinical use.

4) ULTRASOUND CONTRAST AGENTS

Air bubbles have been employed in echocardiography for over 30 years to transiently enhance the ventricular chambers and great vessels. Initally "hand-made" ultrasound contrast agents were created by agitating a saline solution prior to intravascular injection. More recently, a group of agents comprising stabilised microbubbles has been developed which behave as blood pool agents. These microbubbles typically have a radius of 1 - 10μm and resonate when insonated with a 1 – 10MHz ultrasound pulse as is typically used in diagnostic imaging.

Coated by a variety of substances eg. galactose microparticles (Echovist, Levovist) or albumin (Infoson, Albunex), some of the microbubbles are sufficiently small and stable to traverse the pulmonary circulation intact. The agents circulate within the blood pool and result in a 10 to 25 dB enhancement of echoes from flowing blood. The agents typically have an effect within 20 – 30 seconds following intravenous administration and the effects last for a few minutes. Side effects and toxicity are minimal with current agents.

The only agent currently available in Australia is Levovist. This is an aqueous suspension of microparticles consisting of 99.9% galactose and 0.1% palmitic acid. After injection, the microparticles dissolve rapidly, thereby releasing tiny air bubbles similar in size to red blood cells. The palmitic acid forms a protective coating around the air bubbles, permitting some of them to traverse the pulmonary circulation intact. The only contraindiction to Levovist is galactossaemia.

REFERENCES

1. Skucas J (ed). *Radiographic Contrast Agents*, 2nd Edition. Aspen Publishers, Rockville, Maryland, 1989. ASIN: 0834200066
2. Sovak M (ed). *Radiocontrast Agents*, Springer Verlag, Berlin. 1984. ISBN: 0387131078
3. Bydder G et al (eds). *Contrast Media in MRI*. International Workshop, Berlin, Medicom, Netherlands, February 1-3, 1990.
4. Cogrove D (ed). Ultrasonic echo-enhancing agents, Clinical Radiology Volume 51, Supplement 1, February 1996.
5. Biliscopin Monograph. Schering AG, Berlin, 1997.
6. Shellock FG, Kanal E. Safety of magnetic resonance imaging contrast agents. *J Magn Reson Imaging*. 1999 Sep: 10 (3): 477-484.
7. Wolf GL, Halavaara JT. Basic principles of MR contrast agents. *Magn Reason Imaging Clin N Am*. 1996 Feb; 4 (1): 1-10.