STRUCTURE AND PROPERTIES OF X-RAY CONTRAST MEDIA

Optimal use of CM in radiology requires a knowledge of the nature and relevant properties of the available substances. This chapter describes the properties of currently used and newly developed contrast-giving agents that influence their behavior in the human body, their side effects, and their practical utility.

The main X-ray contrast agents in use today are insoluble barium sulfate for the diagnostic evaluation of the GI tract and water-soluble CM for the radiological assessment of the different vascular systems, body cavities and organs. In addition, a water-soluble CM based on tri-iodobenzene is the alternative agent of choice for oral use when barium sulfate is contraindicated.

Barium Sulfate

Barium is used in the form of the insoluble sulfate for radiography of the GI tract. If perforation is suspected, however, only water-soluble, iodinated agents (Gastrografin, Ultravist-370) can be used since the body is virtually incapable of eliminating barium sulfate once it has entered the peritoneum. Barium sulfate is available either as a powder to be prepared directly before use or as a ready-to-use suspension. For double-contrast examinations (filling of the lumen with gas, coating of the wall with barium sulfate), barium sulfate is either mixed with a carbon dioxide additive, or a gas-forming agent is taken in addition.

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Common to all barium preparations is concentration of barium sulfate which may diluted according to the needs of the examination. The amount of suspension needed depends on the type of examination and the target organ to be examined [1].

Lipiodol

Lipiodol and other iodinated herbal oils have been in use for a wide range of different purposes, including myelography, ventriculography, hysterosalpingography and lymphography, since the beginning of radiology, mainly due to their low acute local toxicity. Lipiodol used to be the most popular compound made of poppyseed oil, whose unsaturated fatty acids were substituted with iodine.

The iodinated oils that are in use today are mono-, di- and tri-iodinated ethyl esters of a mixture of various saturated and unsatured fatty acids in poppyseed oil as carrier (Lipiodol UF, Ethiodol). Those highly fluid and better-tolerated substances are or were used for visualization of fine structures in direct lymphography, for hysterosalpingography and mixed with cyanoacrylate for embolization of endoleaks.

In addition, Lipiodol mixed with cytostatic agents (e.g., doxorubicin) can be used for the treatment of hepatocellular carcinoma (HCC), because iodine-lipids embolize the vasculature and to some extent accumulate in cancer cells.

Liver lesions as small as 2 mm can be made visible in a CT scan. In a study of 47 patients examined by CT after intra-arterial Lipiodol, 5-10 ml of Lipiodol mixed with chemotherapeutic agents and a water-soluble CM was infused via a catheter whose tip was advanced into a hepatic artery, either into the common hepatic artery or selectively into the right or left hepatic artery. Lipiodol-CT was statistically superior to sonography, CT and angiography in detecting small hepatocellular carcinomas [2]. The exact mechanism of this accumulation remains unclear. The selective intra-arterial injection of Lipiodol combined with a cytostatic agent (e.g., doxorubicin) into hepatic artery branches that supply a hepatic tumor is known as transarterial chemoembolization (TACE) and is used to induce tumor necrosis by slowly releasing the trapped cytostatic agent from Lipiodol-embolized tissue.

Water-soluble contrast media

The first CM on the basis of ionic tri-iodobenzene were introduced around 1950 (fig. 2) and had virtually taken over the field by the second half of the fifties. In the 1980s, the ionic forms were largely replaced by CM on the basis of non-ionic tri-iodobenzene. The reasons why such a homogeneous substance class still dominates intravascular contrast medium applications in X-ray-based radiological examinations without any recognizable competition are as follows:

- Iodine is the only chemical element which combines three properties essential for the production of a successful CM: high contrast density, chemical behavior which allows firm binding to the highly variable benzene molecule, and low toxicity.
- The iodine is optimally bound in the symmetrically substituted tri-iodobenzene; at 84 %, the iodine content of the basic molecule is extremely high.
- Positions 1, 3 and 5 in the molecule are available to the chemist for the most diverse modifications of the physicochemical and biological properties by the introduction of side chains.

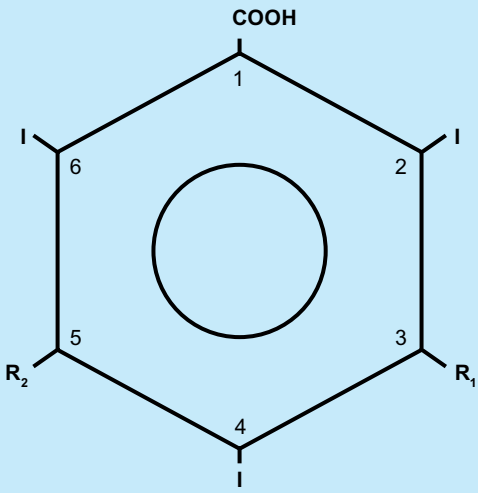


Fig. 2. Structure of tri-iodinated CM
Aromate = Parent substance
-COOH = Salt or amide binding, water solubility
-I = Contrast-giving component
-R_1 R_2 = Reduction of toxity and lipophilia
-R_2 = Elimination pathway

Chemical structure, biological behavior and use

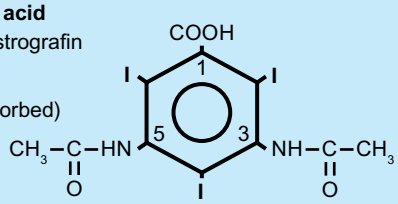
The substance classes shown in figure 3 were produced by varying the basic molecule of tri-iodobenzene. Thanks to the large variety of substances that were synthesized, the relationship between the chemical structure of the molecules and their principal biological behavior is well documented.

High-osmolar, ionic contrast media

Diatrizoic acid, which was introduced in 1953, is contained in numerous products and was the most widely used CM in the world for urography, angiography and CT for three decades. Because its COOH group is connected directly to the tri-iodobenzene ring, diatrizoic acid (Urografin, Angiografin, Urovist, Urovison) is a strong acid, forming salts which are readily soluble in water. The two side chains (-$NHCOCH_3$) further improve the solubility, reduce protein binding (thereby increasing its ability to be filtered in the glomerulus) and improve above all the tolerance. The substance is eliminated almost exclusively via the kidneys. There is a series of related compounds which are derived from diatrizoic acid; meanwhile, however, these are less important. Nowadays, the use of high-osmolar ionic contrast media decreases due to better tolerance and same efficacy of low-osmolar nonionic CM. However, ionic CM still matters as an oral CM and in radiological examinations of body cavities.

Diatrizoic acid
e.g. in Gastrografin

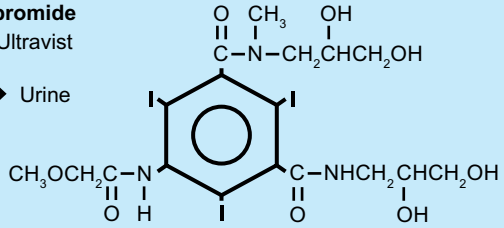
→ Urine
(if absorbed)



conventional or CT GI study

Iopromide
in Ultravist

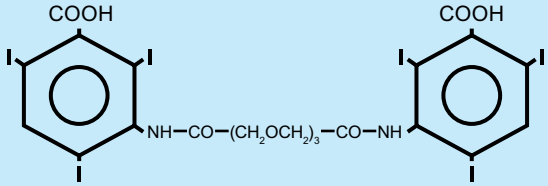
→ Urine



Angiography
arterial and venous

Cavography
CT, Urography

Iotroxic acid
in Biliscopin



→ Bile

Intravenous cholecysto-cholangiography

Fig. 3: Basic chemical structures of water-soluble CM, main elimination pathway, fields of use as exemplified by a representative of each substance class

Low-osmolar substances

In the course of the 1960s, it became increasingly clear that many of the side effects of the conventional CM − particularly of those used in angiography − were caused more by the high osmolality of the concentrated CM solutions than by their chemotoxicity. CM with less osmotic activity were synthesized following the basic work by Almén [3].

Nonionic contrast media

Above and beyond their reduced osmolality, nonionic CM have surprising advantages over ionic CM in two respects (figs. 4 and 5):

1. The neural tolerance of nonionic CM proved to be considerably better than that of ionic CM. As a result, the nonionic substances quickly replaced the ionic agents in myelography. The dimeric compound iotrolan merits particular mention. Iotrolan, which has been on the market since 1988 (Isovist), has excellent neural and tissue tolerance, which can be explained, inter alia, by its blood-isotonic character and its viscosity.

2. The incidence of both general reactions, such as nausea and vomiting, and of the sometimes life-threatening, acute allergy-like or idiosyncratic reactions, is apparently far lower when nonionic CM are given [4, 5, 6, 7, 8, 9].

As a result more than 90 % of ionic CM in angiography, urography and CT have been replaced by nonionic products today. However, the incidence of fatal reactions is too rare to allow statistical comparison. The good general tolerance of nonionic CM compared to that of ionic CM and the low-osmolar compound ioxaglate can be explained by the following main properties:

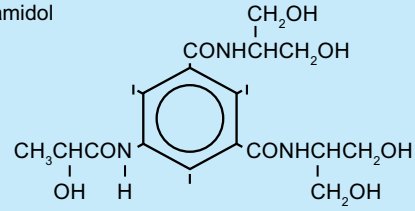
Nonionic contrast media

- contain no electrical charges,
- contain no cations, such as sodium or meglumine, and
- are considerably better shielded by hydrophilic side chains.

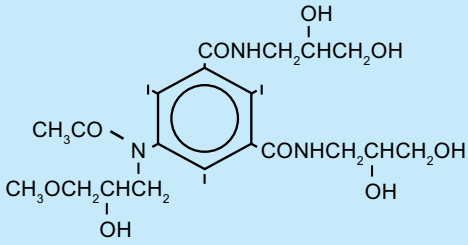
This results in minimal protein binding and enzyme inhibition and in reduced impairment of the function of biological membranes.

For the patient, this means substantially better general tolerance. Nausea and vomiting, urticaria, mucosal swelling, increased respiratory resistance and effects on the cardiovascular system are less frequently observed with nonionic CM.

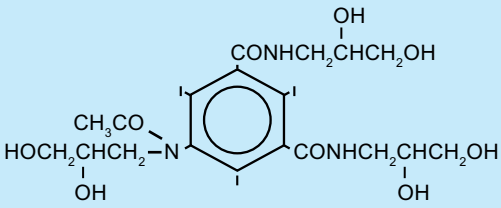
CT/uro/angiographic agents
Iopamiro(n), Solutrast
isovue, Niopam*
Iopamidol



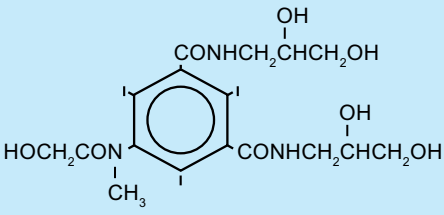
Imagopaque*
Iopentol*



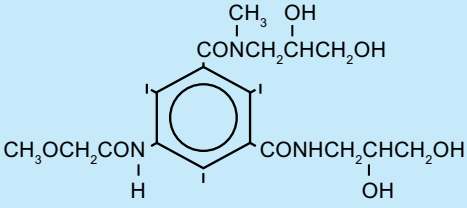
Omnipaque
Iohexol



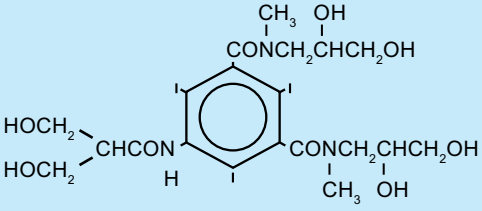
Iomeron*
Iomeprol*



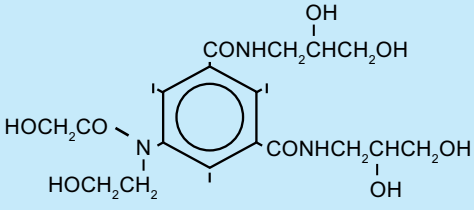
Ultravist
Iopromide



Xenetix*
Iobitridol*



Optiray
Ioversol



Oxilan
Ioxilan

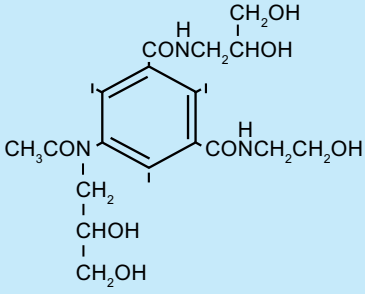


Fig. 4. Chemical structures of nonionic CM for angiography, urography and CT

Osmolality and side effects caused by hypertonicity

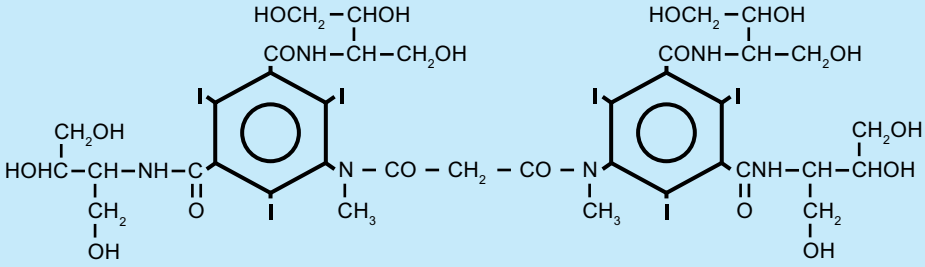
Nonionic CM all have distinctly lower osmotic activities than conventional ionic CM. With the same iodine content, osmolality at 37° C can be more than 2.5 times higher for an ionic CM than for a nonionic compound.

CM side effects mainly related to excessively high osmolality are:

- Vascular pain
- Endothelial damage
- Disturbance of the blood-brain barrier
- Thrombosis and thrombophlebitis
- Bradycardia in cardioangiography
- Increase of pressure in the pulmonary circulation, predominantly in patients with pre-existing pathological values.

Some of these side effects occur very frequently especially in angiography with conventional CM. Wherever possible, therefore, only nonionic CM should be employed in angiography.

Myelography and other body cavities: Isovist, Iotrolan



Angiography, urography, CT: Visipaque, Iodixanol

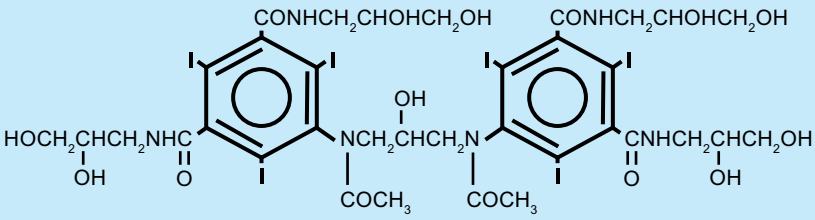


Fig. 5. Chemical structures of nonionic dimeric X-ray CM

	Osmolality 300 mg I/ml, 37° C mosm/kg H_2O mean and 95 % confidence interval	Viscosity, 37° C		Protein binding in % at 1.2 mg I/ml plasma
		300 mg I/ml m Pa • s	370 mg I/ml m Pa • s	
Iopromide	586 ± 5	4.6	9.5	0.9 ± 0.2
Iopamidol	653 ± 7	4.5	9.5	2.9 ± 0.2
Iohexol	667 ± 8	5.7	10.5*	1.5 ± 0.3
Ioversol	661 ± 3	5.5	9.0*	1.6 ± 0.9**
Iopentol	683 ± 4	6.5	12.0*	1.9 ± 0.6***
Iomeprol	538	4.3	7.0*	1.7 ± 0.4
Iobitridol	695	6.0	10.0*	-

* 350 mg Iod/ml ** more than Iopromide *** less than Iohexol

Table 2. Nonionic CM for intravascular administration

At high dosage and irrespective of the mode of administration, high-osmolality CM cause general vasodilatation and a drop in blood pressure, hypervolemia and diuresis. When nonionic CM are used, these effects are less severe or only occur at an even higher dosage.

How do nonionic CM differ from each other?

Nonionic CM differ (because of their chemical structure) in terms of their osmolality, their viscosity, and their substance-specific properties. Comparative measurements were performed. The results are presented in tables 2 and 3 [10]. When an individual nonionic CM for a given purpose is chosen taking into account its specific properties, radiodiagnosis can be optimized and the risk for the patient reduced.

	Osmolality mosm/kg H_2O	Viscosity m Pa · s, 37° C
Iotrolan		
Isovist-240	270	3.9
Isovist-300	291	8.1
Iopamidol-200	413	2.0
Iopamidol-250	580	3.0
Iohexol-180	390	2.0
Iohexol-240	520	3.3

Table 3. Nonionic CM for myelography and other body cavities (Isovist)

Ionic contrast media

It is also possible to produce low-osmolar ionic CM. The only one of these CM to have achieved any importance in angiography is meglumine sodium ioxaglate (Hexabrix [11]). Its use is confined to angiography because it has neither the neural nor the general tolerance of nonionic CM [12, 13].

Ioxaglate (Hexabrix, only one acid function) consists of two tri-iodobenzene rings (dimers) which are connected via a chain (fig. 6).

The resulting doubling of the molecular weight has no influence on the basic properties of the molecules: Good solubility, renal elimination and a lack of enteral absorption suggest the same uses as for diatrizoate. The distinctly lower osmotic pressure of sodium meglumine ioxaglate solutions is why patients experience virtually no pain after administration for peripheral angiography. High viscosity and a higher rate of general reactions are disadvantages of ioxaglate.

Ioxaglate

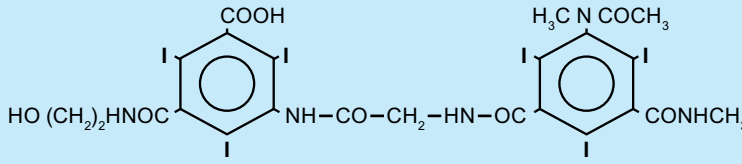


Fig. 6. Monocarbonic acid dimer

Contrast media for intravenous cholegraphy

As for urography, CM with very similar chemical properties are available for i.v. cholegraphy. Unlike the urographic agents, however, not every i.v. cholegraphic agent has its specific advantages and disadvantages, since it was possible to improve the first i.v. cholegraphic agent, iodipamide, in terms of both opacification and tolerance.

Iodipamide (Biligrafin) is the prototypical i.v. biliary CM. It is a dimeric diacid which contains no further side chains. It is eliminated for the greater part with the bile without the molecules undergoing any chemical changes (metabolism).

The modern i.v. biliary CM Biliscopin is bound somewhat less firmly to albumin. The rate of elimination and the contrast density are increased; tolerance is very much improved, especially when the CM is administered by infusion. Since a constant infusion rate is decisive for tolerance the use of an automatic infusion pump is recommended.

Cations

The ionic CM for angiography, urography, CT, i.v. cholegraphy and oral cholegraphy are sufficiently soluble in water only as salts. While, for most oral biliary CM, the formation of salt is left to the organism, a few oral cholegraphic agents and all the other compounds mentioned are offered as finished salts. Iodine-free bases (usually sodium or meglumine) are used to dissolve the iodinated CM acid.

At present, diatrizoate is also available as a lysine salt only in Germany and ioxithalamate as an ethanolamine (mixed) salt only in France. Numerous other cations can be used as counterions for CM acids but, so far, no cations have been found which are better suited than or even as well as meglumine or sodium.

The cations introduced into the body with the CM are freely mobile independently of the CM acids and are eliminated independently of the acids.

As far as is known at present, the pharmacokinetics of the acids are not affected by the cations [14, 15]. Similar to the CM anion, the meglumine cation diffuses into the extracellular space with only little uptake into cells and is eliminated almost exclusively via the kidneys. Sodium behaves the same as endogenous sodium. Meglumine, which was originally introduced because of the solubility of its salts, has, in general, proved to be a well tolerated cation.

Disadvantages of meglumine are the higher viscosity and the somewhat stronger diuretic effect. A certain proportion of sodium in the salt mixture is essential in cardioangiography (Urografin), in which pure sodium or meglumine salts were contraindicated already before the introduction of nonionic CM.

Synthesis of water-soluble contrast media

The parent substances for the synthesis of water-soluble CM are iodine and nitrobenzoic acid derivatives. Iodine is a valuable raw material which is obtained partly from marine algae and partly from salt deposits. A significant part of the annual world production of iodine is used for the manufacture of CM.

The complexity of CM synthesis largely depends on the chemical structure of the compound concerned. While ionic CM can be produced from the parent substances in just a few steps, the new nonionic products require a large number of steps (fig. 7). Apart from the expenditure for materials and labor involved in each individual step, some of the material employed − including some of the usually already iodinated precursors − is lost at each step in the synthesis. As an example, even when the yield at each individual step is 90 %, the total yield of an 8-step synthesis is only 43 % of the materials originally employed.

The purification of nonionic CM, which are readily soluble in water, is yet another problem. Ionic CM can be precipitated from water by acid. Nonionic agents cannot be precipitated from water but at most to a limited extent from the customary organic solvents.

Consequently, the extremely high demands made on the quality of CM make the purification of nonionic substances an expensive production step because of the complicated procedures required and the high losses involved.

The number of steps in CM synthesis

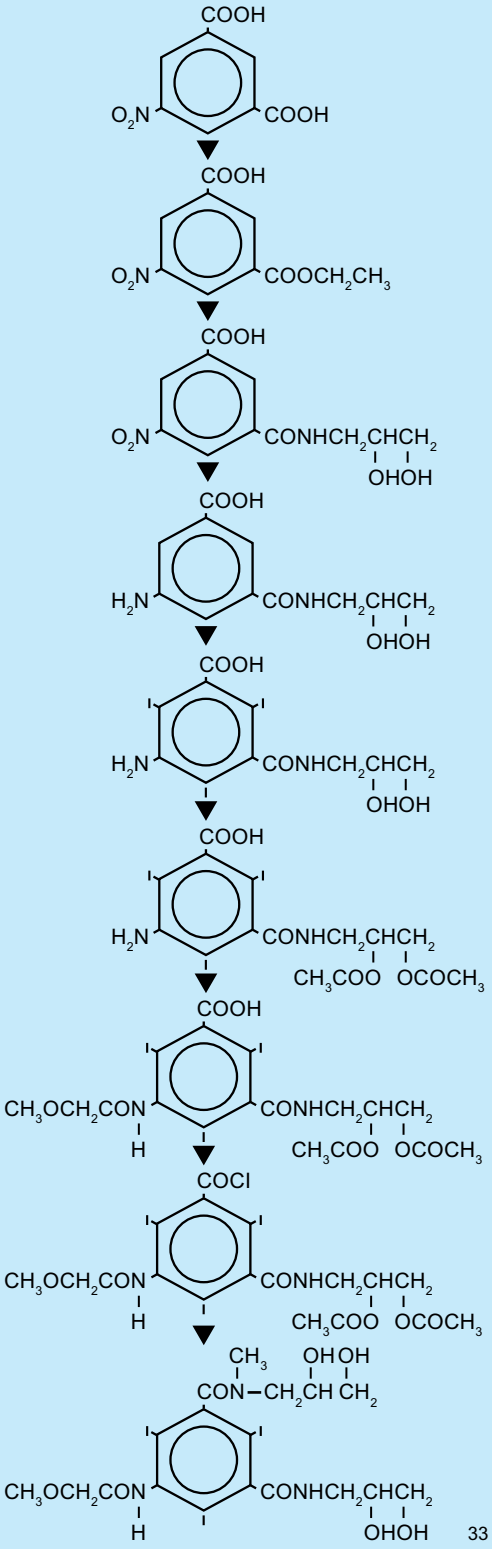


Fig. 7. Example of synthesis scheme for water-soluble CM (nonionic)