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HISTORY OF MEDICINE – REVIEW – OPEN ACCESS

History of Contrast Media: Celebrating the Centenary of the Use of Lipiodol® in Radiology

Bruno Bonnemain

ABSTRACT

On the occasion of the centenary of the first use of an iodinated contrast agent (Lipiodol®) in 1921, this review traces the history of contrast agents that have closely accompanied the innovation of radiology equipment. Lipiodol is an iodinated oil that has made it possible to highlight the interest of the visualization of closed structures of the body (e.g., lung, subarachnoid space, bladder, and joints) and blood and lymphatic vessels. Other water-soluble products then appeared with a radical change in 1953 with the marketing of diatrizoate. The appearance of computed tomography scanners was concomitant with that of low osmolality iodinated contrast products. The arrival of magnetic resonance imaging was quickly followed by gadolinium complexes and then superparamagnetic particles based on iron oxide particles. Thus, the landscape has changed in recent years in radiology, with imaging taking the lead in the current diagnostic scheme.

Keywords: Anniversaries and special events, contrast agents, history of medicine, history of pharmacy, radiology, X-rays

INTRODUCTION

"The history of contrast media has been intertwined with that of radiology since its inception," said Jean-François Moreau (1), a professor of radiology at the Necker Hospital (Paris), in 1994. The evolution of radiology has indeed accompanied that of contrast products and vice versa. This review aims to summarize the history of contrast agents, especially during the last 40 years.

Radiology was born at the end of the 19th century and took off after the First World War when its medical value became fully apparent (2). Whereas the use of opacification agents was limited until the 1920s to the identification of the digestive tract with barium or bismuth, the use of a synthetic iodine oil to opacify the body's cavities has completely changed radiological exploration (3).

This exploration after the injection of Lipiodol® in the subarachnoid space dates back to 1921 with the work of two physicians: Jean-Athanase Sicard (1872–1929) and Jacques Forestier (1890–1978) (4). The first results and the publications that followed had a considerable impact in radiology, paving the way to the identification of multiple cavities in the body, but also in surgery because the "Lipiodol test" was to remain for a long time the essential examination to define the most appropriate therapeutic procedure in many neurological pathologies (5). In 1924, on the occasion of the publication of Laplane's thesis on this subject, a commentator wrote: "There is no need to underline the importance of this work, an excellent clarification of a question which interests all physicians, since it is one of the most considerable progresses acquired in medicine in these last years." In the future, many other anatomical territories (e.g., bronchial tree, urinary tract, and joint cavities) will be able to be examined with this product (Figs. 1, 2) (5).

From 1922 to 1930, various works were carried out on the first water-soluble products (known as uroangiographic products): first, intravenous (IV) injections of sodium iodide and bromide in dogs by Osborne and Rowntree, and then, in 1926, the work of Lenarduzzi and Volkmann with sodium iodide combined by Roseno with urea (Pyelognost®) (3, 6). In 1929, von Lichtenberg and Binz presented the first water-soluble iodinated organic contrast agent, Uroselectan A® (Schering), before Bronner presented Abrodyl® (Bayer) or sodium monoiodine sulfonate (Methiodal®) in 1930 (3, 5). A new publication by von Lichtenberg in June 1931 proposed Uroselectan B® (7). In France, Guerbet proposed Tenebryl® that same year (8). Water-soluble triiodinated compounds derived from triiodobenzoic acid were developed from 1953 onwards (3). Diatrizoate (Radioselectan®), iothalamate (Contrix® or Conray®), and ioxitalamate (Télébrix®) are among the best known. Because of their high hyperosmolality, they are grouped under the general term of "high osmolar contrast media" (9).

In parallel, various products were developed for the opacification of bile ducts. In 1924, Graham and Cole developed the opacification of the gallbladder with tetra-iodophenolphthalein derivatives (10). However, it was not until

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Correspondence
Bruno Bonnemain,
French Society of History of Pharmacy, SHP, 4, avenue de l'Observatoire, Paris, 75270 Cedex 06 France
Phone: +33 (0)608452646
e-mail:
bruno.bonnemain@wanadoo.fr

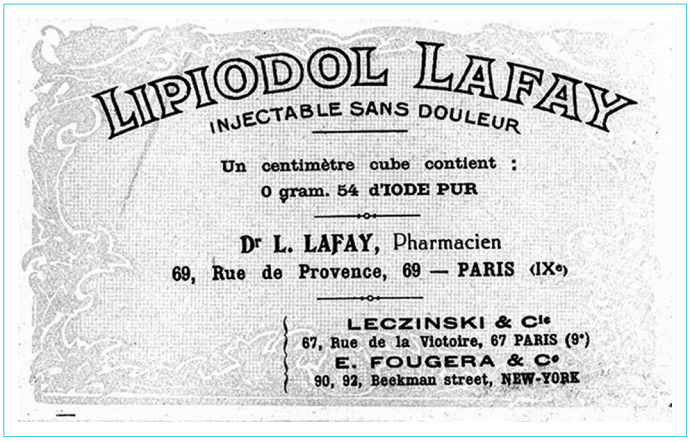

Figure 1. An early example of Lipiodol injection, the first iodinated contrast agent, 1920s
Source: Bruno Bonnemain Collection, Paris

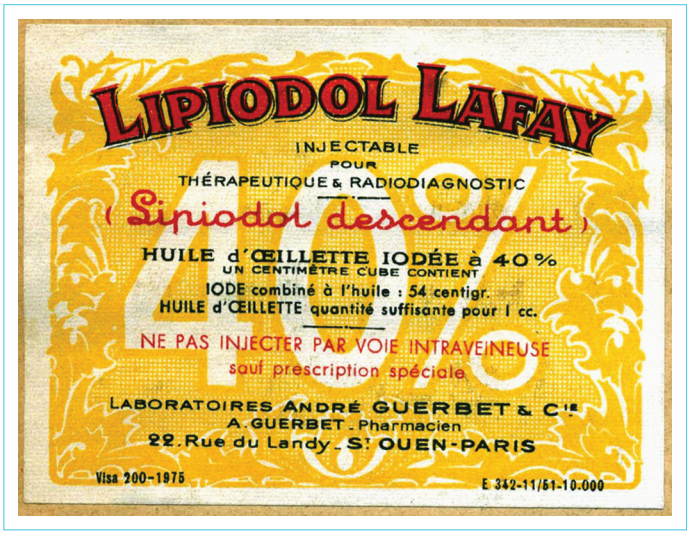

Figure 2. Label of the Lipiodol Lafay injection, 1975
Source: Bruno Bonnemain Collection, Paris

the 1950s that effective IV products appeared to highlight bile ducts [Biligrafin® (Schering) and Intrabilix® (Guerbet)]. Finally, in 1952, Winthrop discovered a product that could be used orally [iopanoic acid (Telepaque®)], and then Guerbet developed Orabilix® (11).

X-ray Contrast Media (from the 1970s to the present)

A decisive advance was made at the end of the 1970s and in the following decades by the development of low osmolality products. Conventional products, such as diatrizoate developed in 1953 and ioxithalamate developed in the 1960s, had already allowed real progress in cardiovascular and urological exploration. In the 1970s, more than 2000 tons of these products were consumed each year (12). However, their high osmolality had many disadvantages, especially the pain induced during arteriographies and the sensation of heat after IV administration. Therefore, some examinations required the use of general anesthesia, especially for peripheral arteriography.

At that time, pharmaceutical companies thought they had reached the end of possible progress, but a Scandinavian researcher, Torsten Almén, embarked on a research project that led to the development of the first nonionic product, metrizamide (marketed in several countries by Winthrop under the name Amipaque®). Although better tolerated, it had two major disadvantages: its prohibitive price and its presentation as a lyophilized powder to be reconstituted before examination. A few years later, the first studies on the side effects observed in myelography with this first nonionic agent appeared (3, 9).

However, this prototype led several companies to take an interest in this subject to find products that are stable in solution and affordable: Guerbet in France developed ioxaglate (Hexabrix®, the only low osmolality ionic product), Bracco in Italy developed iopamidol (Iopamiron®), and Nygaard (which later became Nycomed) in Norway developed iohexol (Omnipaque®). These products, which were approved in Europe in the early 1980s, were accepted in the United States and Japan in 1985. Subsequently, other nonionic products appeared on the market (iopromide, iobitridol, ioversol, iomeprol, etc.). At that time, these low osmolality products had a much higher price compared to conventional hyperosmolar products. In the United States, the price of the new products in 1986 was 13–24 times higher than that of high osmolality products, a price that did not fall substantially until the end of the 1990s (13). It was not until 2005 that Medicare in the United States began to reimburse nonionic products in general.

What the creators of these products had not initially foreseen was the evolution of the use of these new products in radiology. At that time, it was imagined that the use would be limited to myelography for nonionic products and arteriography for these same products and ioxaglate and for patients at cardiovascular risk (14, 15). However, the arrival of computed tomography (CT) scanners and digitized IV angiography, the increase in doses and injection speeds in CT scanners, and the relative decrease in product prices would upset these forecasts. The increasingly rapid IV injection of iodinated products using automatic injectors would lead to the widespread use of nonionic products by the IV route. The meeting of the latter and the new imaging techniques would ensure a considerable success of both (CT and nonionics): an unexpected synergy at the beginning.

In CT [and later in magnetic resonance imaging (MRI)], an additional element would be decisive for the rational use of contrast products: the discovery of their pharmacokinetics. Pioneers, such as Denis Gardeur in France (16) and Martti Kormano and Peter B. Dean in Finland (17), showed that, after a very brief high intravascular concentration, iodinated products diffuse into the interstitial space and allow extravascular lesions, such as tumors, particularly in the brain, to be identified 10–20 min after injection. Jean-Marie Caillé, in Bordeaux, France, wrote an article on this subject in 1977 in Journal de Radiologie to show the interest in contrast injection in neuroradiology in blood-brain barrier anomalies (18). As a result, we would gradually learn to use these two periods (vascular and parenchymal phases) depending on the pathologies to be highlighted or characterized.

This arrival of low osmolality products would stimulate research, and everyone tried to foresee tomorrow's innovation. Milos Sovak, for example, tried in 1987 to define the future in this field. As far as X-rays are concerned, he considered that research would

be directed toward products with vascular remanence (blood pool agents), which seem to him to be indispensable, probably in the form of particles. He also predicted a decrease in myelography but considered that the products used for this indication would continue to be used. He was also convinced that nothing would replace angiography, certainly not MRI or ultrasound. Other authors predicted the arrival of nonionic, isotonic dimers (19).

During this period, certain examinations, such as myelography, IV urography, lymphography with Lipiodol, biliary tract examinations, and certain barium examinations, would also decrease. Conversely, the idea of using water-soluble iodinated contrast products to characterize lesions or pathologies was gaining ground (this is known as functional imaging) (20). There was also considerable development of cardiac imaging using X-ray scanners, which necessarily involves the injection of iodinated contrast products. The most recent recommendations concern the evaluation of coronary disease, cardiac morphology, and functional evaluation of the myocardium. In addition to CT coronary angiography, new applications have emerged for calculating cardiac reserve, perfusion imaging, or the preparation of surgical interventions in this field (21).

X-ray Contrast Agents: Failures and Successes

In the field of X-rays, it is still necessary to highlight many failed attempts and some major innovations (apart from nonionics), especially in liver exploration. The visualization and characterization of liver lesions have been at the heart of the research of many radiologists for decades. In the 1980s and 1990s, with the arrival of scanners, there was renewed interest in an emulsion of iodized oil that was difficult to use in conventional radiology. However, this product would never be commercialized because of its instability. The injection of solid particles in suspension based on the ethyl ester of iodipamide was also considered. These particles, phagocytized by the reticuloendothelial system, would have facilitated the differentiation between lesions and healthy parenchyma, most lesions being devoid of Kupffer cells. Once again, this product did not lead to a commercial product (mainly related to toxicological issues), and the research was abandoned at the end of the 1990s (22).

The liver is also the focus of interest in interventional radiology, and it is worth mentioning the unique place of Lipiodol in this field since the early 1980s, thanks to Dr. Toshimitsu Konno, a surgeon and a radiologist in Japan, who introduced this technique in combination with a lipophilic anticancer agent, styrene-maleic acid neocarzinostatin (23). After Konno's work, many teams have embarked on this "chemoembolization" experiment, which was gradually recognized as one of the most effective treatment approaches for a specific population for hepatocellular carcinoma. Many countries, initially reluctant, finally gave the authorization to market this new indication, which remains very current today (24).

Contrast Agents in MRI

While some radiologists dreamed, as they did when the scanner was first discovered, that MRI would make it possible to do without contrast agents, researchers were very soon interested in developing them. However, it was necessary to find what could best modify the relaxation times of tissues without inducing unacceptable toxicity for a diagnostic product. There were then several options proposed. Stable paramagnetic radicals, such as the nitroxide radical, were considered, but the toxicity of these products did not encourage their use, especially because their effectiveness was limited. The use of oils with relaxation times different from water was also considered, but without a satisfactory technical solution (25). One quickly turned to paramagnetic metals, such as iron, manganese, or gadolinium (Gd). Schering in Germany and Guerbet in France, in parallel and without knowing the work of the others, began working on Gd in the early 1980s, leading to the marketing in Europe of DTPA Gd (Schering's Magnevist®) in 1988 and DOTA Gd (Guerbet's Dotarem®) in 1989 (25). Schering chose DTPA by analogy with what was known in nuclear medicine; Guerbet chose DOTA, a macrocycle derived from French research in macromolecular chemistry, for which Jean-Marie Lehn was awarded the Nobel Prize in Chemistry in 1987 (26).

Other similar products called "nonionic" (Gd-HP-DO3A, Gd-DTPA-BMA, Gd-DO3A-butrol, etc.) were then developed. However, over the years, scientists have shown that what differentiated these products was their stability and, even more so, their decomplexation kinetics. This realization was first made with the appearance of nephrogenic systemic fibrosis in patients with renal failure and then, more recently, the retention of Gd in tissues (bone, brain, and skin) even in patients with normal renal function. In both cases, these phenomena have been associated with linear products with the fastest decomplexation kinetics. These two problems led European authorities to ban the least stable linear products, except for Gd-BOPTA, which can still be used for its hepatic indication (27). The authorities have also recommended using the lowest possible doses of Gd. Since then, a field of research has been opened to find nonspecific macrocyclic products with high relaxivity. The first one currently under development has reached phase III clinical studies, which is gadopiclenol developed by Guerbet Laboratory. It has a relaxivity at least twice as high as the nonspecific products currently marketed. It is conceivable that such a product could also improve the diagnostic performance of MRI at the usual dose of 0.1 mmol Gd/kg (28).

The work of the last few years, apart from the tolerance concerns already mentioned, has focused on exploring the clinical applications of these products. They were first used for brain pathologies, such as acoustic neuroma, and then gradually for other brain tumors and degenerative or inflammatory diseases, such as multiple sclerosis. However, as MRI progressed, applications were extended to osteoarticular diseases (with a specific, very diluted product for intracavity injections), vascular opacification, hepatic and pelvic pathologies, cerebral vascular accidents (and, more generally, perfusion imaging), lymph node pathologies, etc. In the cardiac field, considerable progress has been made. Although coronary imaging has yet to be developed in routine to compete with X-ray scanning, myocardial perfusion imaging has become commonplace, thanks to the use of Gd chelates. The same is true for the detection and characterization of breast cancers because of the particular appearance of the enhancement curves of malignant lesions. Today, MRI with injection is a well-established technique for tumor morphology and functional characterization (29).

Various paramagnetic ion products have also been developed for liver opacification. By adding a benzene ring-containing moiety to DTPA, a more lipophilic compound was obtained that passes through hepatocytes and is excreted in the bile. Two products have

been marketed in this field: Gd-EOB-DTPA (Primovist®, not marketed in France) and Gd-BOPTA (Multihance®, marketed in 1999). A manganese-based product, Mn-DPDP (Teslascan®), was also marketed in Europe and the United States in the 1990s and withdrawn from the market in 2003 in the United States and 2010 in Europe due to its low efficacy and, above all, its contraindications in pregnant women, which considerably limited its clinical interest (30). However, university research has continued for several years in the form of small molecules but also liposomes, polymers, solid particles, etc.

Failures and Successes in MRI Contrast Agents

As in X-rays, various attempts have been made in MRI in the field of contrast agents without the expected success. The most promising approach, which did not lead to commercial success, concerns superparamagnetic particles based on iron oxide (31). Unlike Gd chelates that lower T1 relaxation time at the doses used clinically, iron oxide nanoparticles decrease the signal by acting preferentially on T2/T2* relaxation time. However, it is possible to obtain positive contrast with MRI sequences and appropriate doses.

Two types of superparamagnetic products have been developed (9): (1) Small superparamagnetic iron oxides that range in size from 80 to 600 nm. Two IV products have been marketed for the opacification of liver parenchyma (Endorem®/Feridex® and Resovist®). Another product has also received marketing authorization for the identification of the digestive tract (Lumirem®/Gastromark®). (2) Ultrasmall superparamagnetic iron oxides (USPIOs) that range in size from 20 to 30 nm. Intended for macrophage imaging, these particles have improved the characterization of metastatic lymph nodes. Unfortunately, the development of these products has not been successful for various economic, technical, and regulatory reasons.

CONCLUSION

This review of the history of contrast agents during the last 100 years shows how fruitful this work has been. It has enabled radiological practices to evolve and accompany technological innovation in imaging equipment. In all areas, patients have benefited from the knowledge acquired to improve the diagnosis and therapeutic management of their pathologies. Can we do without the new imaging examinations with contrast products developed during this recent period? No one disputes this major contribution, which has been made possible by university researchers and the pharmaceutical industry.

The question now is whether there is still a future for new contrast products in diagnostic or therapeutic imaging. The question was posed by Ulrich Speck, a former research director at Schering, back in 2002. "Considering, he says, the cost of developing a new product, one would have to imagine paying $1000 per dose to justify industrial research in this field. Only nonspecific, widely used products could be economically viable." He could have added that the regulation of clinical trials in imaging for the registration of a new product has considerably complicated the development of new products, further increasing the associated costs and the risks of failure of phase III clinical studies (32).

Gradually, most pharmaceutical companies specialized in this field are no longer bringing out new products and have stopped research to devote themselves more to other more profitable fields: interventional radiology, artificial intelligence, image processing software, medical devices, etc. Yet, the research fields remain numerous and potentially useful, as shown by the remarkable work we have seen on USPIOs in MRI.

History had shown that when we thought we were at the end of a cycle of innovation, the unexpected disrupted the deal. Therefore, we must hope that researchers will once again be present during this period of maturation and able to participate in the development for the best interests of patients and public health.

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