Historical Perspective of Imaging Contrast Agents

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KEYWORDS

• History • Historical • Contrast media • Contrast agents • Iodine • Gadolinium

KEY POINTS

- The use of external compounds as contrast agents was introduced early in the history of medical imaging.
- Research in contrast agents has focused not only on their ability to enhance an image but also on their biological tolerances and safety.
- Development of iodinated agents with low osmolarity resulted in a significant improvement in patient tolerance.
- Gadolinium has shown to have a strong effect on proton relaxivity compared with other compounds.
- Development of ultrasonography contrast agents with small but sufficiently echogenic particles has historically been difficult.

INTRODUCTION

The use of external agents as imaging enhancers dates back to the early days after the discovery of x-rays. Because imaging has evolved to encompass a wide range of modalities based on diverse physical phenomena the nature and properties of these agents are varied. This article reviews the historical context in which the contrast agents discussed in this issue were developed.

EARLY AND ABANDONED CONTRAST AGENTS

The use of x-rays to study the human body started shortly after their discovery in November 1895. Within a couple of weeks, Roentgen had managed to obtain rudimentary images of his own hand and later that of his wife clearly showing her bones and a wedding ring. The following year, radiographs were already being used in Italy to show skeletal injuries and localize ballistic fragments in soldiers during the Abyssinian war, thus avoiding unnecessarily invasive and long surgical explorations.[1] The most extraordinary property of these new rays, that of traversing different substances and particularly the human body, sparked intense interest not only from the scientific community but also the lay public. However, despite its ability to depict dense materials like bone and metal, it was evident from the beginning that this new technique of photography provided very little contrast between soft tissues, which could be only faintly discriminated depending on their interfaces with air-filled structures and bones. Following Roentgen's observation that heavy elements cast dark shadows, attempts at overcoming such limitations and improving the visibility of anatomic structures concentrated on the use of elements with high atomic numbers, the most widely known of which are bismuth, barium, and iodine, the last 2 still widely used in radiology today.[2]

Disclosure: The authors have nothing to disclose.

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Magn Reson Imaging Clin N Am 25 (2017) 685–696
http://dx.doi.org/10.1016/j.mric.2017.06.002

The first documentation of an external medium used to enhance a radiographic image can be traced back to Haschek and Lindenthal[3] in Vienna, who just 1 month after Roentgen's discovery obtained the first in vitro angiogram of the human body by injecting an amputated hand with a mixture of cinnabar (a toxic ore of mercury), lime, and petroleum. Two months later in Berlin, Becker described a method to depict the anatomy of hollow organs by introducing lead acetate into the stomach of a dead guinea pig; however, its toxicity and corrosiveness precluded its clinical use.[4] Later that year, in June, Hemmeter[4] at the Johns Hopkins Hospital devised a different method that would allow its human use, which consisted of having patients swallow a rubber bag that would then be filled with mercury or lead acetate after it had reached the stomach. He later stopped using the bag and had patients directly ingest bismuth subnitrate, a cheap and heavy salt already widely used for the treatment of peptic disorders.[4,5] Bismuth salts became popular for gastrointestinal examinations, but they were replaced eventually by barium sulfate, in part because of their toxic effects, a transition that occurred rapidly in the United States after the European supply of bismuth (a strategic metal) was essentially halted during World War I.[5,6] Barium sulfate then became the agent of choice for gastrointestinal studies and even had a limited role in bronchography for several decades, despite some complications.[7]

What can be considered as the first cystogram was performed by Wittek in 1903, who filled the urinary bladder with air to outline a stone.[8] The following year, Wulff[9] directly injected a radiopaque mixture consisting of bismuth subnitrate and starch into the urinary bladder and showed what was probably a diverticulum. In 1905, Voelcker and von Lichtenberg[10] serendipitously succeeded in imaging the upper urinary tract while performing urograms with colloidal silver, and a year after that effectively performed a retrograde pyelogram by injecting the same substance through ureteral catheters into the renal pelvis.[10,11] The use of different silver compounds continued for several years and was fraught with adverse reactions, which were often severe. After its introduction by Burns in 1915, thorium nitrate was used for a few years but later abandoned because of its toxicity.[11,12] Cameron started successfully using sodium and potassium iodides in 1917 and sodium bromide was introduced a year later.[6]

THE EMERGENCE OF IODINATED COMPOUNDS

Although its efficacy was never proved with certainty, iodine became popular for the treatment of syphilis in the nineteenth century because of its known antibacterial properties, long before penicillin was discovered in 1928.[13] Its first use as a contrast agent marked the departure from silver-based compounds and is attributed to Cameron,[14,15] who performed cystograms and pyelograms initially in animals and later in human patients through ureteral catheterization. The first intravenous injection with an iodine compound came later with Osborne and colleagues[16] from the Mayo Clinic in Rochester, who in 1923, working in the section of Dermatology and Syphilology, performed the first intravenous excretory urography following the recognition that urine with iodine was radiopaque.

The first iodinated aqueous media were fairly toxic and it took a few years and the work of various researchers to develop a water-soluble agent. This effort was led by Binz and Rath at the Chemical Institute of the Agricultural College in Berlin during the 1920s, who developed N-methyl-5-iodo-2 pyridone (Selectan-neutral), a compound that was much less toxic than iodide salts by virtue of attaching iodine to a pyridine ring.[11] This compound was further refined in 1929 by Swick, an American research fellow studying in Germany, who proposed modifications to Selectan-neutral and developed Sodium 2-Oxo-5-Iodo-Pyridine-N-Acetate (Uroselectan), which featured higher water solubility, higher iodine content, and less toxicity in animal experiments.[17] These achievements set the stage for the continued development of water-soluble contrast media, which ultimately led to their widespread use in excretory urography, angiography, and myelography.

Despite major advances, a persisting issue with iodine-based contrast agents was the often severe pain that many patients experienced on intravenous injection. Torsten Almén, a Swedish radiologist, was the first to propose that such excruciating pain could be related to the hyperosmolarity of the contrast agent relative to plasma.[17] Although not a chemist, he engaged in the study of chemistry and advocated for the development of a contrast agent with decreased osmolarity. The general scientific consensus at the time was that, in order for a contrast agent to be water soluble, it had to be constructed as a salt that would dissociate into ions when in solution, a property that would in turn increase its osmolarity. Development of such an agent was therefore not thought to be feasible and Almén was turned away by several pharmaceutical companies. He eventually started working with Holtermann and others at Nyegaard & Co in Norway, where the first nonionic contrast medium was developed in 1968, leading to a commercially available compound in 1969,