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Iodinated Contrast agents within Radiology

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Abstract:

Contrast media (CM) are a group of chemical substances that are used within the clinical settings in special cases in order to highlight areas of concern by standard x-rays, computed tomography (CT) and magnetic resonance imaging (MRI). These materials possess high atomic number such as barium, iodine, gadolinium and saline. Although there are number of different contrast agents available, iodine is the most frequently used one within the medical imaging field. Recently, iodinated contrast media (ICM) has been started to be used for the imaging detection techniques anywhere within the body. Even though iodinated contrast agents have a good safety profile, it is necessary to understand that some patients can have severe, life-threatening allergic reactions because of the side effects of the chemicals.

This essay is going to shed a light on the iodinated contrast media and their usage in health field. Also it is going to describe their chemical and the physical properties and their adverse reactions.

Keywords: Contrast media, iodinated contrast agents, iodinated contrast media.

1. Introduction

Within the field of the medical radiation, various forms of chemical materials such as barium, iodine, gadolinium and saline are used to enhance the visibility of the images that are taken for the internal organs in certain types of medical radiology techniques like x-rays, computed tomography (CT) and magnetic resonance (MR). These kind of substances are called radiographic contrast media and such substances have been used extensively in the practice of radiology for both diagnostic and therapeutic purposes[1]. Over the last few decades, a significant rise of using these chemicals was administered by the medical radiologists. It has been observed that these materials are generally safe to use for helping physicians to get accurate information with higher efficiency[2]. On the other hand, clinical surveys showed that the radiographic contrast media has mild side effects such as allergy, flushing, nausea or headache for small percentages of all exposed patients[3].

Among the presence of several types of contrast media, iodinated contrast agents (ICA) are the most consumptive agents in radiology because of their accessibility to diverse options, easiness to utilize and safeness for patients[4]. They are injectable and can be used intravenously in anywhere in the body. Globally, the number of patients who underwent medical examination by radiation using iodinated agent has estimated by 70 million annually[2]. Since the 1920s, sodium iodide was the first contrasting agent used in health sector although it was suspended in toxicity profile[2,5]. In the 1950s, ICA based on a tri-iodobenzoic acid ring has been introduced to clinical setting[2]. In the 1970s, modern technology started to be utilized within the radiology department accompanied by the developed ICA[2].

In spite of being generally safe and their adverse effects are ranging between simple to serious side effects, severe or life-threatening reactions can take place and may threaten the health of the patient[6]. Recent studies indicated that the percentage of adverse reactions of iodinated agents have estimated between 1 to 12% while severe reactions range from 0.01 to 0.2% of overall reactions[4].

2. Physical and chemical properties of Iodine-based contrast agent

The physical and the chemical properties of iodine-based contrast media are responsible and stating in controlling the quality of radiological pictures[5]. The main chemical composition of ICA is 2,4,6-triiodinated benzene ring (Figure 1). They are exist either as monomers which means they consist of one triiodinated benzene ring (one of benzene ring with three atoms of iodine) or dimmers of two triiodinated benzene rings connected with organic functional group (two of benzene ring with six atoms of iodine) (Figure 2).

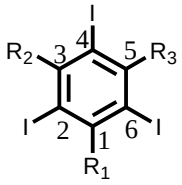


Figure 1. 2,4,6-Triiodinated benzene ring.

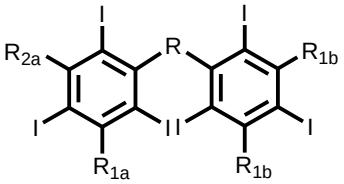


Figure 2. Dimeric form. Benzene rings are trisubstituted at the 2, 4, and 6 positions with iodine atoms[2].

Indeed, iodine atoms are essential for producing contrast agents because they are firmly bonded to the stable benzene ring with covalent bonds that lead to reduce the risk of releasing the toxic free iodide[2]. Moreover, iodine moieties provide high contrast density because their large sizes increase the effective molecular size hence attenuating longer wavelength x-rays[2].

However, to govern agents' properties, side chains are usually imposed at the positions **3** and **5**. They also modified with hydroxyl groups or other molecules to make the triiodobenzoic acid less toxic and less lipophilic (fat-soluble)[6]. On the other hand, in order to improve water solubility, ICAs' ionic tendency should be enhanced and they may be modified with

carboxylic acid (-COOH) functional group, usually on carbon **1**, to permit the formation of salts or amides[7].

2.1. Classification of iodinated contrast agents

Iodinated contrast agents (ICA) can be classified upon their physicochemical features on the bases of their ionicity, osmolality, and viscosity[8].

2.1.1. Ionicity

ICA can be found as ionic that dissociate into ions when dissolved in water or non-ionic that do not dissociate into separate particles when dissolved in water, even though they are water soluble. This is why the ionic compounds have a high osmolality, including both of the anions and the cations, while the non-ionic agents may have a lower osmolality because of the smaller amount of their particles in solution. This may explain the ionic tending to have more adverse effects compared with the non-ionic compounds. In fact, majority of studies suggest the dimers contrast agents compounds have biggest negative influence on the patient compared to the monomeric contrast agents[9].

2.1.1.1. Comparison studies of ionic and non-ionic ICAs

A comparison study has taken place from 1985 to 1989 in ten hospitals and it was held during different time periods. The study was to compare the ionic contrast agents (ionic agents combined with steroids) and non-ionic agents. The study showed that there is a relationship between the type of the agents and the risks of their adverse reactions. These researches proved that non-ionic iodine contrast media is the best for clinical usages and it is safer for patient's health than both of the ionic contrast agents and the ionic agents that combined with steroid[10].

Other comparison study between the adverse reactions of ionic and non-ionic ICAs was conducted in the largest national clinic in Japan and covered (337647) cases. The study indicated that ionic ICA has higher risk profiles with adverse reactions than non-ionic ICA. Both ionic and non-ionic ICAs have been administrated to (169283, 50.1 %) and (168363, 49.9 %) cases respectively.

As a result, the overall serious reactions were estimated by (12.66 %) with ionic agents and (3.13 %) with non-ionic agents. This means that the percentages of the normal risk cases and the adverse reactions were (0.2 %, 0.04 %) for ionic ICA and (0.04 %, 0.004 %) with non-ionic ICA[11].

Other survey involved (11306) pediatric who are younger than 19 years. They were administrated by non-ionic iodinated radiology contrast to determine the relationship between the acute allergic-like reactions and non-ionic low-osmolar iodine agents. The study started in 1st of January, 1999, to 30th June, 2006. The objective of the survey was evaluating the severity of acute allergic-like reactions that associated with non-ionic iodinated contrast among pediatric less than 19 years old who received intravenous contrast media. The results showed that (0.18 %) of the pediatric had acute allergic-like reactions to the contrast agents. For the affected children, (80 %) of the reactions were classed as mild, (5 %) were classed as moderate, and (15 %) were classed as serious. However, there were no deaths in the children apart than patients having medical history especially those who suffer from previous iodine allergy and asthma[12].

2.1.2. Osmolality

Osmolality is defined as the number of moles of osmotically active particles present in solution per kilogram of solvent[8]. There are three types of contrast agents; the first one is the high-osmolar agents containing the ionic monomers and the low-osmolar agents containing the non-ionic monomers and finally the iso-osmolar agents containing the nonionic dimmers (Figure 6).

High-osmolar contrast media of iodinated agent (Figure 3) is described as the oldest agent. They are ionic monomer molecules that dissolve in water with a valence of -1. Cations are either sodium or meglumine .[13]

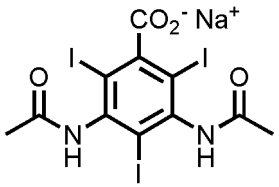


Figure 3. High-osmolar contrast media of iodinated agent[13]

Low-osmolar contrast media of iodinated agent (Figure 4) are non-ionic monomers agents. These are advanced class of ICAs that do not dissociate when dissolve in water[13].

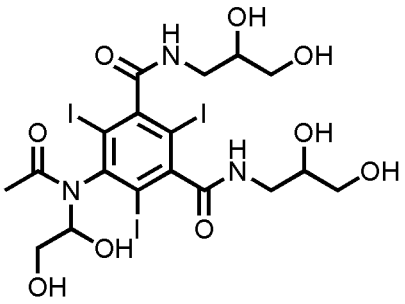


Figure 4. Low-osmolar contrast media of iodinated agent[13]

Iso-osmolar contrast media of iodinated agent (Figure 5) are the recent class of ICA. This category contains non-ionic dimers agents that do not dissolve in water[13].

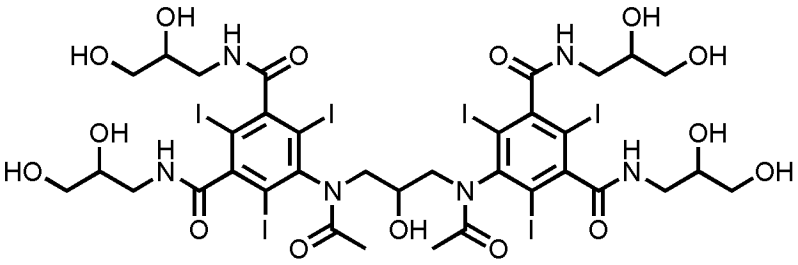


Figure 5. Iso-osmolar contrast media of iodinated agent[13]

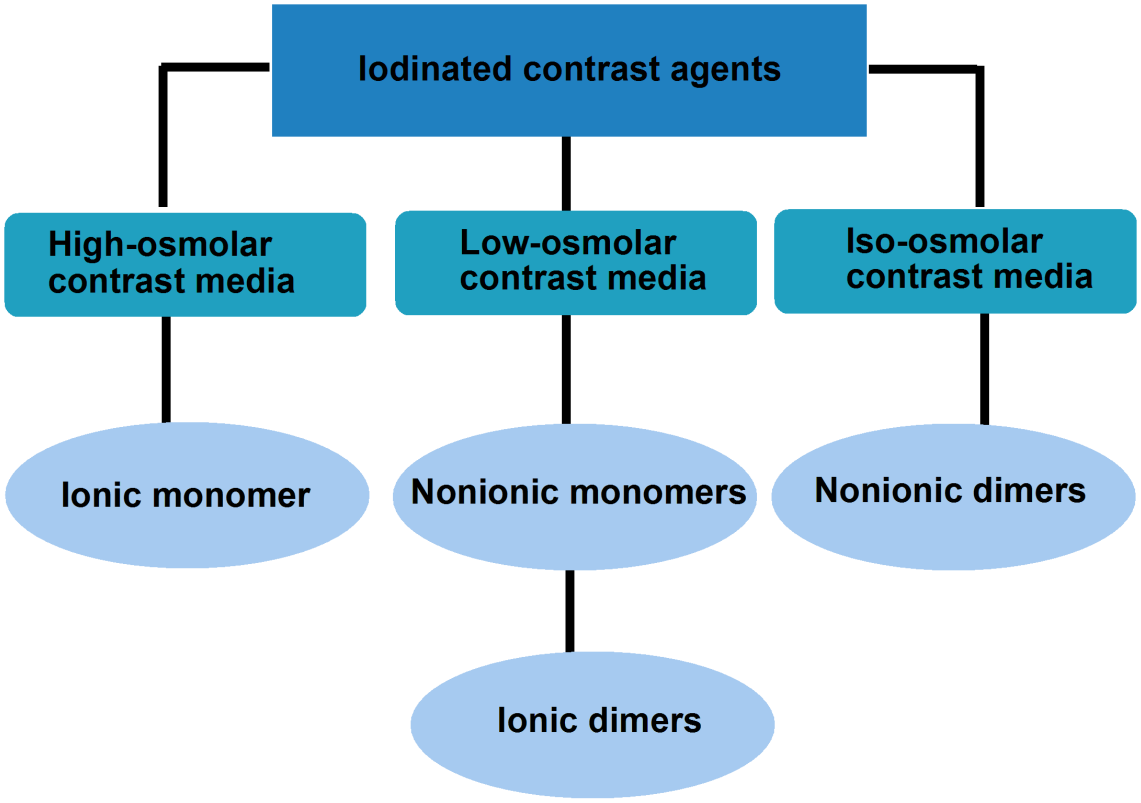


Figure 6. Diagram of ICAs classification depending on osmolality

Harmful effects of pain or warmth sensations have been noticed by using higher-osmolar contrast agents. This is because water can be drawn into the vascular system leading to blood volume expansion. These side effects are considerably reduced when using iso-osmotic agents. Accordingly, most studies pointed out that the nonionic low-osmolar ICA profiles are considered safer than the ionic high-osmolar media. However, researches showed that both low-osmotic and iso-osmotic agents have safe medical history and more convenient for patients compared with high-osmolar despite their high price that may lead to limit their usage[14].

2.1.3. Viscosity

The viscosity of contrast agents has a major consideration since viscosity influences the rate of intravascular injection. Hence, the high viscosity may recognise as a limiting factor that can limit superior scanning prospects. On the other hand,

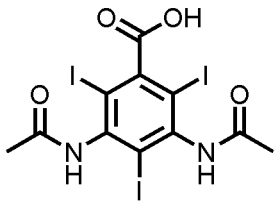
less viscose agents could increase the rate of injection and so increase the physiochemotoxic reactions and the adverse reactions. Low viscosity can be results from raising the agent's temperature to body temperature when injected[15].

Accordingly, ICAs present in four different forms; ionic monomers, non-ionic monomers, ionic dimmers and non-ionic dimmers (Figure 7). The ionic ICA is represented by the anion of triiodobenzoic acid and the cation (usually Na^{+}, Ca^{2+} or methylglucamine (meglumine)) with two organic side chains (diatrizoate or iothalamate). Therefore they are water soluble with high osmolality agents[7]. The anions triiodobenzoic acids are strong acids due to direct bonding of -COOH group with the benzene ring producing water soluble salts while the cations are important for enhancing the solubility of the acids and for achieving the physiological pH. Both cation and anion particles are responsible of the toxicity of ICA as they interrupt the electrical potential of the cell membrane. The main used ionic monomer agents are iothalamate ion (Conray) and diatrizole ion (Hypaque)[7].

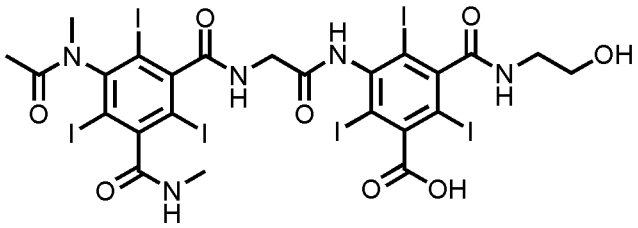
However, non-ionic monomer does not ionise in water because they does not have carboxylic acid side chain since the carboxyl group convert to amide keeping the molecule remaining as single species in solution. Also, the hydrophilic side chains on carbons 1, 3 and 5, that are holding hydroxyl (-OH) or amide (-CONH) groups, are improving the solubility of the non-ionic ICA. Furthermore, at normal concentrations, non-ionic monomers have about half the osmolality of ionic monomers in solution and a higher viscosity so they are harder to inject. Furthermore, because of the absence of the electrical charge, cell membrane would be less disrupted of electrical potential and so less toxic. Most non-ionic monomers in use are iohexol (Omnipaque), iopromide (Ultravist), iopamidol (Isovue) and ioversol (Optiray)[7].

The ionic dimers are synthesis by connecting two ionic monomers and removing one carboxyl group while the non-ionic dimers are iso-osmolar compounds and they are synthesis from connecting two non-ionic monomers. However, dimers' high viscosity limits their clinical usefulness. The only ionic dimer that used clinically is ioxaglate (Hexabrix) and is used for peripheral arteriography and the commonly non-ionic dimers that used are iotrol and iodixanol[7].

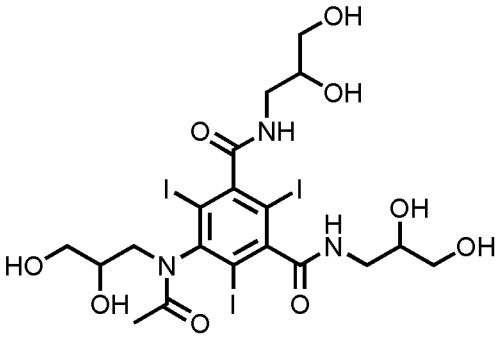
Ionic monomers
as
diatrizole ion (Hypaque)



Ionic dimers
as
ioxaglate (Hexabrix)



Non-ionic monomers
as
iohexol (Omnipaque)



Non-ionic dimers
as
iodixanol (Visipaque)

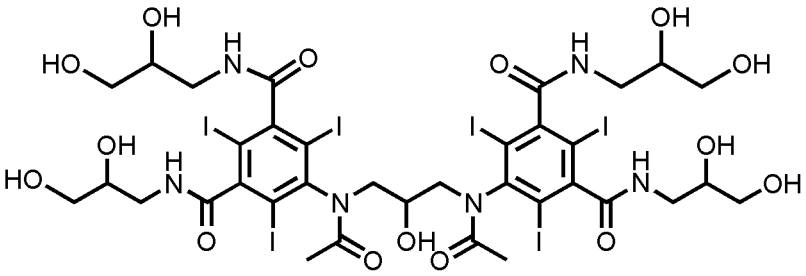


Figure 7. The four classes of iodinated contrast agents[2].

3. Some examples of the iodinated contrast media

3.1. Iopamidol

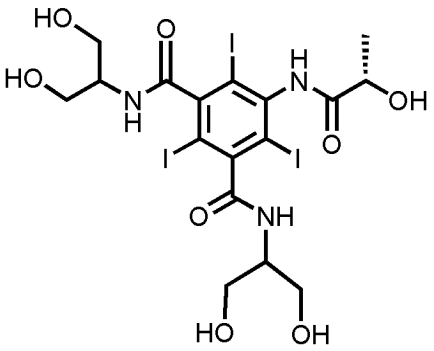
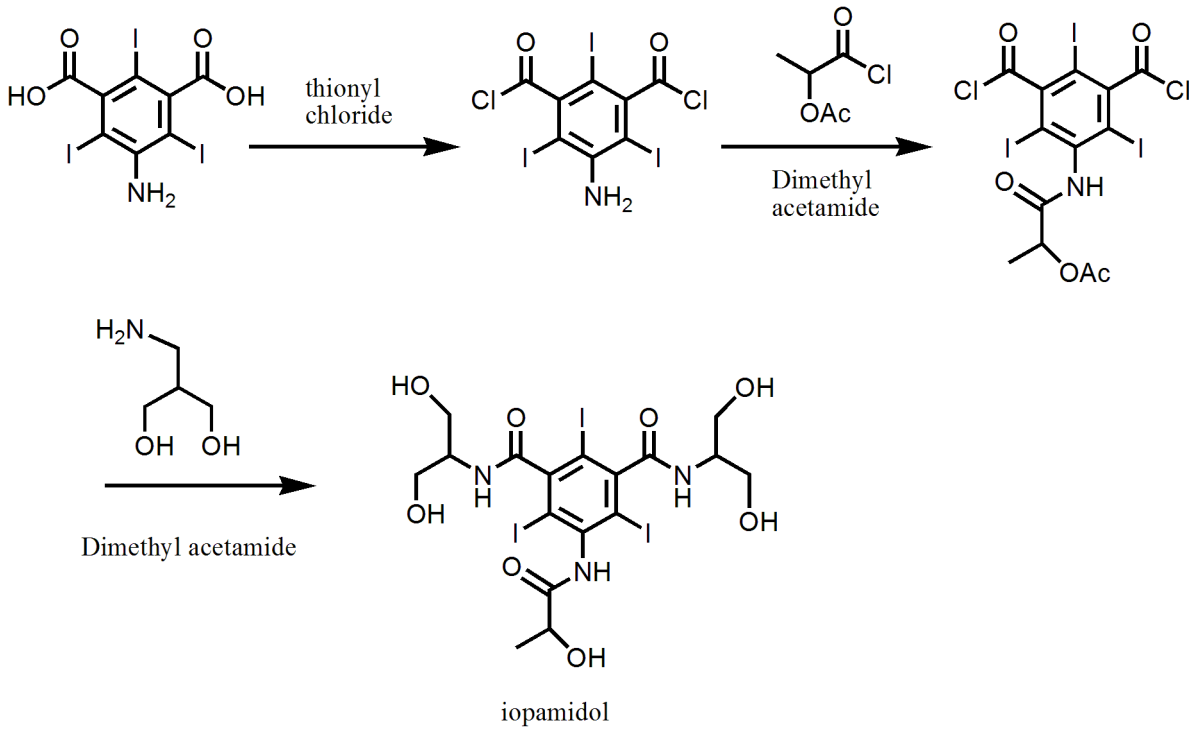


Figure 8. Iopamidol[16].

Iopamidol is a drug contains iodine that absorbs X-rays and so it is used to allow blood vessels, organs, and other non-bony tissues to be visualised more clearly on a CT scan or other radiologic examination such as x-ray. Iopamidiol is classified as non-ionic, water-soluble and low-osmolar iodinated contrast agent. It is a collection of drug and injections that available in a different concentrations ranging, from 200 to 370 mg/mL (Figure 8)[16]. It can be synthesised as illustrated in Scheme 1.



Scheme 1. Synthesis of iopamidol from commercially available starting materials on an industrial scale[16]

3.2. Diatrizoate

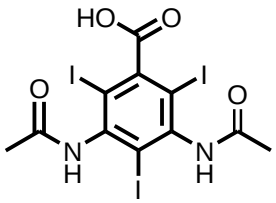
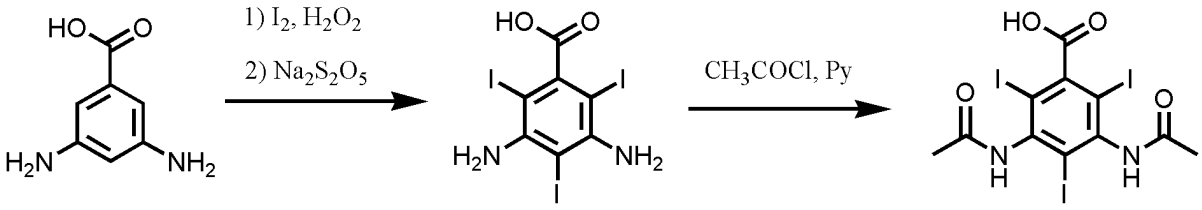


Figure 9. Diatrizoate

Diatizoate**,** also known as amidotrizoic acid, diatrizoic acid, or 3,5-diacetamido-2,4,6-triiodobenzoic acid is a contrast agent used during X-ray and CT scan during the medical examination to visualise veins, urinary system and joints. It is a set of pills that are taken by mouth or injected into the intravenous or rectally. Diatizoate belongs to ionic iodinated contrast agent with higher osmolality (Figure 9)[17]. It can be synthesised as illustrated in Scheme 2.



Scheme 2. Synthesis of Diatizoate[17]

3.3. Iodixanol

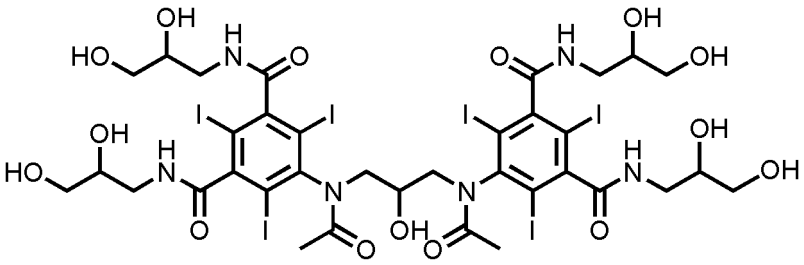
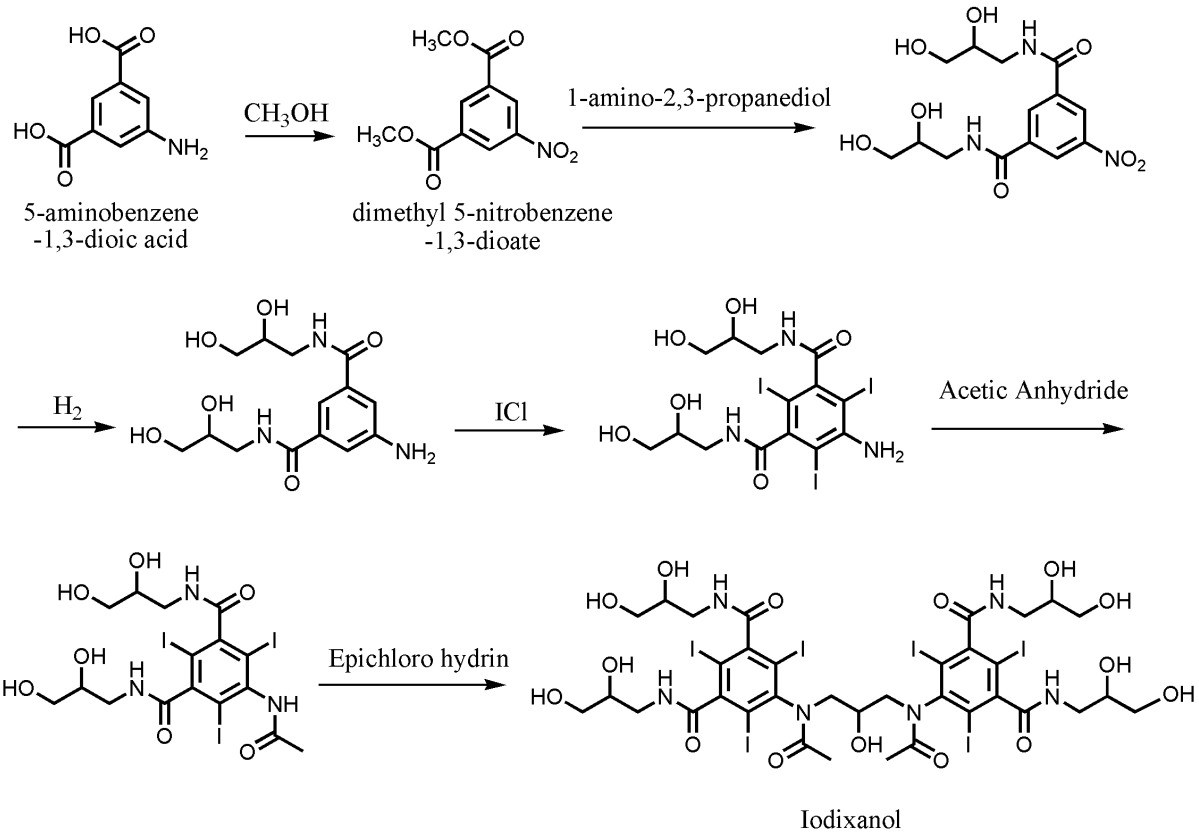


Figure 10. Iodixanol[18]

Iodixanol or Visipaque (Figure 8) is a dimeric, isosmolar, nonionic, water soluble, and iodinated X-ray contrast agent with a molecular weight of 1550.20 (iodine content 49.1%). This contrast agent is generally used as a contrast agent during coronary angiography and it is available for intravascular administration with two different concentrations 270 mg/ml and 320 mg/ml[19]. It is the only iso-osmolar contrast agent that has osmolality similar to blood (290 mOsm/kg H_2O). It can be synthesised as illustrated in Scheme 3[18-19].



Scheme 3. Synthesis of Iodixanol[18].

4. Iodinated contrast agents work within medical imaging radiology

X-rays is an invisible short wavelength electromagnetic radiation (0.01 – 10) nm. It can be generated by accelerating the electrons in vacuum tube by applying high voltage. When the accelerated electrons hit the positive electrode they emit electromagnetic radiation in the form of X-rays[20]. X-ray was discovered in 1895 by the German physicist Wilhelm Conrad Röntgen. This was the main step in the health sciences that made the organs inside the body able to be seen without the body being cut opened[21].

Computed tomography (CT) is an advanced type of X-ray that can be used as a clinical diagnostic tool. In 1972, the first successful X-ray (CT) imaging device was built by G. N. Hounsfield[20]. CT scan is used for 3D visual reconstruction and segmentation of tissues of interest or organ systems, such as the gastrointestinal tract, cardiovascular system, renal tract,

liver, lungs, bone, cartilage, tumorous tissue, etc. However, CT offers a cross-sectional image of the X-ray attenuation properties of tissues inside the body and it records projection measurements of the transmission of X-ray photons throughout the object from different angles[22].

4.1. Iodine-based X-ray contrast agents

Iodine has the main roll in attenuating of the X-rays because iodine's atomic radius is falling in the range of x-rays' wavelengths. In addition, the three large iodine atoms are connected covalently to the phenyl group in a close proximity. This leads to increase the molecular size, and so attenuating longer-wavelength x-rays. Also these covalent bonds are stabilising the phenyl group and leading to decrease the risk of toxic effects from free iodide[2].

One of the most significant factors in predicting the success of medical radiology applications is the relationship between the atomic number and the amount of absorption. It is understood that the elements that have a high density (ρ) or large atomic number (Z) give outstanding results and high-performance in the absorption of X-rays compared to the elements, which owns a small atomic number[20].

The following equation is showing the absorption coefficient (μ)[20]

$PZ^4/AE^3 = \mu$

Where:

A is the atomic mass

E is X-ray energy

Z^4 is a factor response on level of contrast within body.

As the energy of the incident X-ray is equal or little higher than the binding energy of the electron to the atom, the absorption coefficient would increase. This energy value would rise by increasing the atomic number of the element[20].

4.2. Iodine-based CT contrast agents

There is a direct relationship between the strength of absorption of the radiation and the atomic number. This means that the absorption strength increases by increasing the atomic number. Elements having higher atomic number (Z), such as iodine (Z = 53), are utilized as contrast agent molecule in the CT imaging applications to achieve better X-ray attenuation. These agents are used with CT scene to define patient's health problem via examining the internal organs and to distinguish between the natural blood vessels and the non-normal[23]. Nevertheless, iodinated contrast agents are not appropriate for most of the clinical applications because of the toxicity associated to the iodine concentration levels that required for imaging. Thus, covalently bound iodine provides a better option in contrast media design. Furthermore, the major difficulty associated with the iodine-based compounds as CT contrast agents are the short imaging times because of the fast renal clearance, renal toxicity, and vascular permeation.[24]

Compared to non-ionic contrast media, ionic iodinated contrast agents have some intrinsic difficulties even though they are extensively used in the clinic because of their tendency to interact with biological structures like peptides and cell membranes. High osmolality from the aqueous formulations of ionic contrast agent species leads to renal toxicity and other physiological problems in addition to increasing the pain and sensation of heat at the site of the injection plus decreasing radio-density because of osmotic dilution[20].

4.3. Iodine-based MRI contrast agents

Magnetic resonance imaging (MRI) is magnetism and radio waves that pass through the human body to create a digital image depending on hydrogen atoms. The use of MRI increased dramatically to examine and give more accurate information particularly in the anatomy and metabolism than the computed tomography. Not all forms of magnetic resonance imaging require contrast agents. Most publisher referred that contrast agent based on gadolinium is the most using agent with MRI hence iodine contrast media is used rarely with magnetic resonance image[25].

5. Symptoms of side effects of ICA

Symptoms of the patient's exposure to iodinated contrast agents are ranging from rapid symptoms that appear simultaneously to the one that is shown after one hour or the one that appear during seven days. Their symptoms can be classified as minor, moderate or serious symptoms[6]. Symptoms like headache, vomiting, nausea, itching, and mild urticaria are presenting mild ICA reactions. These symptoms have been observed on up to 1% of the individuals after demonstrating by non-ionic low-osmolality contrast media. The moderate symptoms of contrast agent reactions are severe vomiting, urticaria, different respiratory symptoms, and vasovagal attacks. The severe adverse reactions are rare, and they may happen less than 1 in 100,000 include hypovolemic shock, respiratory arrest, cardiac arrest and convulsions[6,8].

A study done on 160 patients to measure the immediate adverse reactions of ionic iodinated contrast showed that 25 % of the reactions were anaphylactic, 20 patients were responding to a frequency of 12.5 % and the main features were pruritic papules mainly face redness and sneezing. While other observed reactions of chemo toxic paper was only with vomiting[26].

Another study used the non-ionic medium on a group of 191 patients. The outcomes were two patients about 1.0% have developed immediate adverse reactions shown by vomiting. It was clear that the rate was positively significant lower than the uses of ionic contrast agent clarifying that the non-ionic medium within lower osmolality will decrease the risk of developing adverse reactions. However, other research done in 2003 ignored the signs and symptoms such as hotness and vomiting and declared that ionic reactions had a great effect .[26]

In addition, experiments done by Katyama et.al, 1990, Cochran et.al, 2001 and Jacobs et.al, 1998 discussed the injection method or the contrast direction speed on the adverse reaction. The results were controversial and the researchers found an important increase in the adverse reaction for the automatic injection of the contrast to the manual injection by about 3.6 %. On the other hand, the bomb injection adverse reaction was at 17 %. [26]

5.1 Risk reactions of iodine contrast media

Free iodide ions that associated with iodinated contrast media leads to developing of either hyperthyroidism or hypothyroidism. These free iodides may generate from photolytic degradation of contrast agents that becomes from the long term storage or the exposure to light. The recommended daily intake of iodide is 150 μg while the dose of contrast media contains about 13500 μg of free iodide plus 15 to 60 g of bounded iodine that may liberate as free iodide in the body. This is about 90 to several hundred thousand times more than the recommended quantity[1]. The high iodine load causes acute Wolff-Chaikoff effect and a rapid inhibition of thyroid hormone synthesis. Acute Wolff-Chaikoff effect leads to iodine-induced hyperthyroidism and so to iodine-induced hypothyroidism[1].

Patients with cirrhosis have a reduced ability to promote contrast agent after the intravenous injections because of the weakness of the liver performance. Many studies referred that hepatic disease is related with the delay and the decrease of the enhancement manner of ICA plus it causes adverse reactions.[27]

The biggest issues with iodine contrast media is the renal function because it has a higher risk accompanied by the high dose concentration of iodine agents. Many previous studies indicated that for protecting patients it is necessary to use a small amount of doses and concentrations of iodine media to avoid any side effects may affect kidney function.

Iodine agents are available with various types and various concentrations that make them suitable for the most cases and enabling them to be used in minimum amount with CT scan and X-ray.

Moreover, even small quantities of ICA are not safe for patients because they may harm the kidneys like Nephropathy and may cause other side effects. Appropriate doses should be coordinate with the patient's body mass, although it is preferd to use lower concentrations and doses.[27]

6. Contrast medium pharmacokinetics and patient

6.1. Factors influence enhancement of iodine contrast agents:

Studies on the imaging-related medications proved that there are similarities in the iodinated contrast agents and their medical images results particularly when they used similar volumes, similar concentrations and similar rates of administration. However, the significantly differences between them is their profiles of adverse-reaction[8]. On the other hand, the choice of contrast media is effected by some factors such as the type of the contrast media that is available in the hospital, the sort of examination, the radiology configuration, the reason of using it, the patient's medical history and the cost[27]. In addition, it has been found that there are some factors that may effect on the contrast's developing and on the medical screening time. These factors are patients' cases, contrast agents and radiology classes and their timing[27].

Patient's age and body size have primary impact on enhancing iodine-based CT contrast agent's adverse reactions risk. People's body size plays a key role in influencing the efficiency of the contrast agents within medical images examination. Studies have shown that the weight and height of patients have an impact on the promotion of contract medium. Overweight patients have proportionally decreased enhancement of the iodine contrast media. This means that there is an inverse relationship between patient's weight and the promoted contrast media inside body. Consequently, overweight patients need higher doses of iodine contrast agents compared with patients who have smaller size to obtain the same outcomes. These differences in the doses are owing to the differences in the size of patients' heart, body masses and blood volumes. Humans with high body mass generally have a high volume of blood that leads to reduce the contrast's enhancement via decreasing iodine's concentration in the blood. Furthermore, obese individuals have fats beneath their skins that would restrict the strengthen x-ray and CT scan.

However, it is well-known that the body size is usually associated with the gender. Due to the physiological and the biological differences between men and women,

There are differences in blood volumes that lead to inconsiderable differences in the proportion and the time that the enhancement contract need. The study has explained that there is no mention difference between them in the promotion of contrast although other researches pointed that females are more likely to negative impacts of ICA injection than males[27]. Most of the women who had exposed to iodine agents had suffered from iodine adverse reactions more than men. The survey proved that by comparing the percentages of the side effects of iodine agents between genders, women with skin reaction, digestive system and general delayed responses reaction had 41 (65%), 90 (59%), and 50 (66%), while men with the same reactions obtained 22 (35%), 63 (41%), and 26 (34%) respectively[28].

Age is one of the aspects that influence the equality of medical images. Numerous studies have indicated that the ages of patients who underwent an iodine contrast agent based radiological examination have impacts on enhancing the medical image. Therefore some studies reported that the appropriate age ranges between 40 to 60 years can be given greater outcome then younger while other studies showed that ageing could affect the heart. Hence, it is necessary to reduce iodine dose by 10% , especially with oldest people who are aged over 60[6,27].

Patient's medical history has a considerably effect on increasing the adverse reactions. Accordingly, many studies have shown that people with chronic diseases might be exposed to side reactions particular those classified as moderated and severe reactions exponentially more than others. Thus people who are suffering from asthma or they are receiving beta-adrenergic blocker therapy are more related with complication adverse reactions than general population. Therefore, patients with asthma are suffering from iodine allergic four times than others and those with previous reactions of medications or contrast agents are more likely for increasing risk of adverse reaction 4 to 6 times[6].

It has been recommended not to hold pre-injection test because this will not be a considerable standard for measuring the predicted adverse reaction that may appear on the patient after exposing to high does plus this may develop side effects due to the high quantity of contrast agents from the pre-injection test.

It has been concluded that the main reason for the adverse reaction is the differences of the doses' amounts and concentrations in addition to the intravenous route of iodine contrast media.

7. Conclusion

In conclusion, each year many of intravascular contrast media examination are performed widespread as a plan treatment with radiology technology. Iodine contract media is the one of the most frequently used agents in today's world due to its optimized methods to increase the quality of radiography images. Physical and chemical properties of iodine-based contrast agent play key roles for improvement the images equality. Utilizing iodine agents in radiology is still the subject of a debate. According to most studies that mentioned here the mortality rate due to intravenous of iodine still unknown. Adverse reactions of ICA effects are infrequent. Side effects are associated with some types of iodine agents that developed risk adverse reactions. There are many factors that affect the promotion of the images and the methodology of selecting the iodine agents.

6. References

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