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Intravascular Contrast Media in Radiography: Historical Development & Review of Risk Factors for Adverse Reactions

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Abstract

The discovery of X-ray in 1895 was promptly followed by concerted efforts in developing contrast agents for pacification of blood vessels, hollow organs and delineation of tumors from normal tissues and diagnosis of other diseases. But these efforts have been met by challenges of adverse reactions due to mismatch of the biochemical characteristics of the contrast agents and the physiological medium of the human body.

However, research efforts have yielded remarkable progress in the quality of contrast agents in current use, while improved understanding of possible risk factors have equally necessitated procedural strategies aimed at mitigating the prevalence in medical imaging practice. Presently, the qualities of contrast media in use have drastically reduced the incidence of adverse reactions; but have not eliminated them.

This paper therefore reviews the early efforts in the development of suitable contrast media for medical imaging, identified risk factors for adverse reactions and research proven considerations for reducing the incidence in Radiography practice.

Keywords: *Iodinated contrast agents, evolution, Toxicity, Radiography practice.*

Introduction

Diagnostic services rendered in Radiography departments can broadly be divided into two categories – those using ionizing radiation such as conventional x-rays and computed tomography; and those utilizing non-ionizing radiation; which may be ultrasonography or magnetic resonance imaging. There has been a marked proliferation and refinement over the years of a variety of imaging modalities and techniques[1], utilizing these radiant energies, aimed at enhancing disease diagnosis and improving overall patient care. One of the early techniques introduced in radiography for further delineation of structures was the use of contrast media. This dates back to 1919; in which gases; including room air, oxygen and nitrous oxide were used experimentally by Dandy and Jacobeus[2]. However, the use of contrast media has been challenged by the tolerability of the host body. Thus, contrast agents react with internal body milieu; producing by-products which turn out injurious to the body. These injuries manifest as adverse reactions. Adverse side effects from the administration of contrast media vary from minor physiological disturbances to rare severe life-threatening situations[3]. Contrast agents do not possess therapeutic value[4]. Their value (in case of intravascular contrast agents) lies in their ability to attenuate x-rays or radiant energies; a property imparted to them only by the constituent iodine atoms that make up a small fraction of their molecules. An ideal model intravascular contrast medium in radiography practice should be characterized by high solubility, low viscosity, low toxicity, and should be rapidly excreted from the body[5].

Although, the available marketed iodinated contrast media have undergone remarkable improvement in satisfying these qualities; some limitations still persist. Radiographic procedures involving contrast medium injection is still preceded by preparation for the investigation along with the readiness to promptly treat the potential adverse events that may arise. It is therefore recognized that there are potential risks associated with intravascular

administration of iodinated contrast aganets[6]. These risks are aggravated by certain factors posed by the patient's internal body chemistry or physiological state. These factors range from age, gender, to renal impairment and diabetes[7, 8]. Although the effects of these factors are disputed[4], a daunting challenge remains how to mitigate these factors especially where the accruing advantage of the investigation overwhelms the envisaged side effect; necessitating that the examination should be carried out.

Historical development of iodinated contrast medium

The first attempt to outline blood vessel with an enhancing contrast agent was recorded as early as 1stJanuary, 1896[9]. This was by the duo of Haschek and Lindenthal (a physicist and physician) respectively who injected calcium carbonate emulsion into the brachial artery of a severed arm of a cadaver in Vienna. An excellent post mortem arteriogram of this arm was produced following 57minutes exposure to x-ray. This fit enjoyed wide acclaim, including a publication on 23 January, 1896 in the *Klinische Wochenschrift*[10].

The first successful visceral angiogram was probably achieved by Hicks – a physics professor on 6th February 1896[11]. This was a post-mortem renal arteriogram in which a red lead mass (then used in dissection rooms) was injected as an intravascular contrast agent. This was well received by his peers and earned an immediate publication in the British Medical Journal of 22nd February 1898. These identified substances were unsuitable in life humans due to high toxicity and other associated side effects.

The use of iodine as an opacifying agent was hinted by Douglas; a young surgeon (who feared he might not return from world war) published in JAMA, 1917, from his research works that oral and intravenous sodium iodide could produce urinary cystogram, opaque to x-ray[12].

This was corroborated by a publication in JAMA of February 10, 1922 by a team of physicians from Mayo clinic on intravenous urography in which they reported the use of sodium iodide as a contrast agent[13]. The radiographs produced were adjudged of 'good quality'. The opacity of the pyelogram was related to the concentration of iodide in the solution of the contrast medium. The challenge of toxicity and the quantity of iodine required to produce good radiographs posed serious setback to these efforts. The first clinical human venogram was produced with inorganic solutions of strontium bromide in Frankfurt, Germany, while the first human arteriogram with 100% sodium iodide was at St Louis Hospital, United States of America[14].

Research efforts were in different fronts for suitable contrast agents for angiography and opacification of hollow organs. Moniz (1927) pursued development of clinical angiography for the diagnosis and localization of cerebral tumor[15]. He conducted several animal experiments in which lipoidol emulsion, bromide and iodide salt of sodium, potassium, lithium, strontium, and rubidium were tried. His successful human carotid arteriogram was obtained after injecting a 30% solution of sodium iodide into a surgically exposed carotid artery of a young man with a pituitary tumor. His brilliant effort in this direction led to the setting up of a renowned team of clinicians that established clinical arteriography, aortography, venography, pulmonary angiography and lymphography between 1927 and 1932[16].

The successful conduct of a diagnostic intravenous urography using a non-ionic, mono-iodinated pyridine molecule was carried out by Swick[17], after extensive research on iodinated organic pyridine chemicals using animals. Moses Swick worked under a famous German urologist Von Lichtenberg in Berlin. DrSwick developed and published the initial experience on water-soluble iodinated intravenous contrast media for urography procedures in 1928. [18,19.] His initial effort led to the development of a contrast agent which was marketed as 'selectan neutral'' due to its improved quality over other more toxic agents. He set a target of developing a highly soluble and stable iodinated contrast media capable of yielding high iodine content for tissue opacification, with minimal toxicity to the body. This goal has remained the target of present researchers on non-ionic, low osmolar contrast media today.

The efforts of Dr Swick in concert with Professors Lichtwitz, Binz, Rath and von Lichtenberg yielded the production of sodium iodopyrione-N-acetic acid called iopax or Uroselectan and sodium iodomethamate, called Neoiopax or Uroselectan –B (Fig 1 &2).

These compounds were N-pyridone monoiodinated and diiodinated respectively. They were developed for urography and had reasonable radiographic outcomes, but were associated with several adverse effects especially nausea and vomiting[20]. However the Uroselectan series enjoyed wide scale application in the conduct of intravenous urography examinations due to their perceived low toxicity and improved solubility, as at that time.

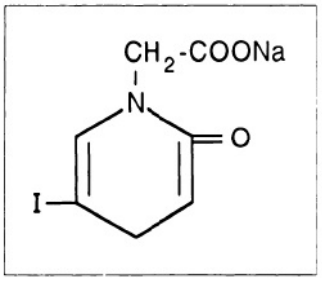

Fig 1. Iopax[Uroselectan] developed by Moses Swick.

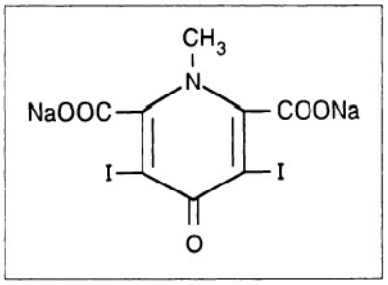

Fig 2. Neoipax[Uroselectan-B] that replaced Iopax

Dr Swick further pursued his goal and this led to the development of iodohippurate sodium; which was called Hippuran and produced by Mallinckrodt Medical Inc, St Louis. Hippuran is a monoiodinated benzoic acid derivative which application has persisted in renal scintigraphy till today. Further research efforts led to the replacement of neoiopax by Diodrast; manufactured by Winthrop Laboratories, NewYork, NY. Diodrast is a diiodinated N-pyridone compound. It's application was shortly terminated by the introduction of Urokon (sodium acetrizoate) in the early 1950s by Wallinford at Mallinckrodt Chemical Works in St Louis[21]. Urokon was developed by introducing an acetylated amide [-NHCOCH3] side chain to the benzene ring, to achieve reduced toxicity. The year 1956 heralded the introduction of diatrizoic acid , while in 1962, iothalamic acid was developed[22]. These two compounds became the mainstay of intra-arterial and intravascular contrast of choice in a variety of radiographic contrast –related procedures [18,19, 23]. They were far less toxic than the previous agents due to their benzene base and triiodination. There was equally improved diagnostic efficacy and reduced chemotoxicity and therefore universally accepted; inspite of the relative increased cost. Winthrop- Baron , New York , manufactured diatrizoic acid as hypaque, while Squib Diagnostics, New Brunswick, NJ, traded renografin. Iothalamate products were marketed as Conray but produced by Mallinckrodt Medical, St Louis, MO { Fig 3 & 4}

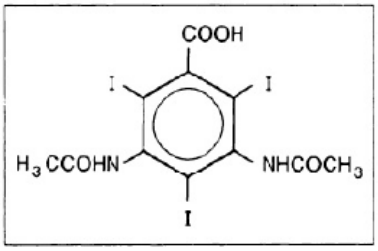

Fig 3. Diatrizoate [Hypaque, Renografin]

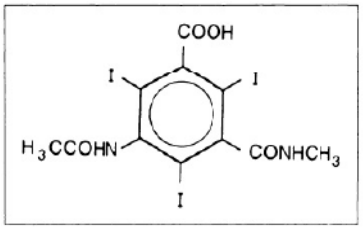

Fig 4. Iothalamate [Conray]introduced in 1962

Replaced Urokon in 1955-1956.

Non-ionic compounds

The quest for improved quality of iodinated contrast media; aimed at reducing adverse reactions, continued among researchers inspite of the wide acceptance enjoyed by diatrizoate and iothalamate products. These efforts led Dr Torsten Almen to initiate a research on the development of low osmolar compounds in 1968[23]. His research focus was on iconicity and osmolality of contrast media as key properties in the determination of the degree of adverse events due to iodinated contrast media [24]. his efforts resulted in the production of metrizamide [Amipaque] by Winthrop-Breon, New York. NY.; that marked the beginning of the era of water-soluble myelography (Fig. 5).

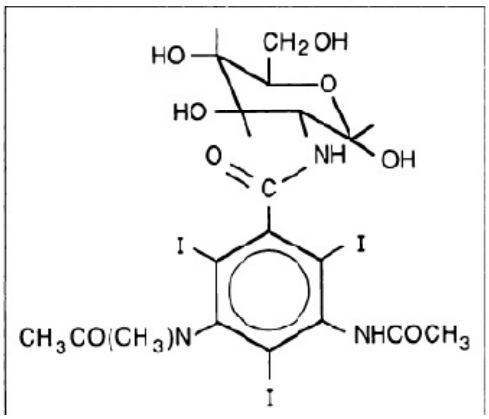

Fig 5. Metrizamide[Amipaque] developed by Torsten Almen & Nyegaard Laboratories.

Metrizamide has since been replaced by newer nonionic compounds such as iohexol and iopamidol which are of marked improvement over metrizamide for melography. Their properties are of greater diagnostic efficacy and safety. The characteristics of new non-ionic compounds are built on the concept enunciated by Almen that 'iodinated contrast media should not needlessly double it's osmolality by dissociation in solution'. This property helps to lessen virtually all the haemodynamic interactions that account for the osmotoxicity of contrast media[25] following IV administration. Current studies have established that low osmolar ionic and nonionic contrast agents elicit less adverse reactions with increased diagnostic efficacy and overall safety[26]. However, it is still argued that the present set of low

osmolar contrast media are not yet the ideal contrast agent of choice[23]. Research is still on for improved quality devoid of any significant side effect . An ideal contrast media is advocated to have optimum qualities comprising the following: water solubility, chemical and heat stability, biologically inert, low viscosity, lower or same osmolality as the human serum, selective excretion by the kidney, general safety and affordable cost. The focus on the osmolality of contrast media by Almen and co-researchers paved the way for the development of low osmolar nonionic compounds[23], which display reduced chemotoxicity. Subsequent development also led to the production of newer compounds such as ioversol [optiray by Mallinckrodt Medical, St Louis, MO] which exploits the beneficial molecular property of high hydrophilicity. These compounds possess several hydroxyl groups on the side chain and balance the distribution of the hydrophilic side chains in a three-dimensional arrangement, such that the iodine atoms are sheltered on the benzene ring (Fig. 6-8)

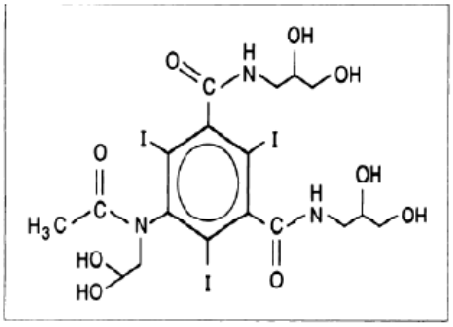

Fig 6. Iohexol [Omnipaque]

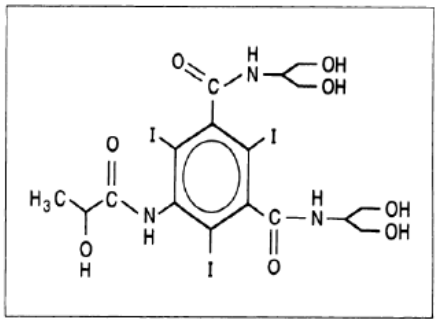

Fig 7. Iopamidol [Isovue]

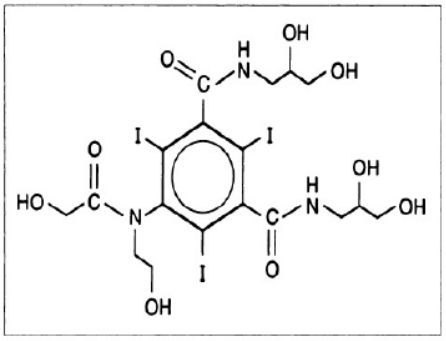

Fig 8. Ioversol [Optiray] newer nonionic contrast agent

The new nonionic contrast agents are therefore more hydrophilic and attract water when injected into the blood stream. This quality makes it more compatible with the internal body fluid and hence elicits less adverse reactions. Ionic high osmolar contrast media acts in the contrary. They are hydrophilic and form salts in solution. In evaluation of the octanol-water partion coefficient, nonionic contrast media are much more hydrophilic than conventional

high osmolar compounds [27] . The octanol–water partition coefficient also differs among individual low osmolar ionic and nonionic, and high osmolar compounds. This is suspected to be one of the reasons for the individual qualities of the different contrast media.

Risk factors to contrast media

The booking of a patient for any radiographic procedure involving the use of contrast medium requires consideration of the relevance of the investigation to the clinical indication for the study, possibility of risk of adverse reactions and departmental preparedness to address such reactions as may occur. The assessment for possible adverse reaction involves the identification of factors that may either constitute a contra- indication or increase the likelihood of adverse events; following contrast medium administration.

Risk factors for adverse reaction to intravenous contrast agents include:

The type of contrast medium

The use of conventional higher osmolality ionic contrast agents is associated with higher incidence of adverse reactions than its lower osmolality non-ionic counterpart. The relative risk of adverse reaction to these lower osmolality non-ionic media is a factor of five for mild reactions and ten for very severe reactions, less than that of the conventional higher osmolality ionic agents [27, 28 ,29]. The incidence of severe reactions with non-ionic agents is 0.04% and that of very serious reaction is 0.004%. However, fatal reactions, though rare (I: 170,000), are not totally eliminated in both, with no difference in mortality between the two types[30,31]. In spite of these remarkable improvements on safety of contrast agents since the past 30 years, an overall adverse reaction of 5-12% is cited[32]. Some authors report 5% - 8% degree of incidence[33]

Allergy

Persons with known history of allergic tendencies are at increased risk of an idiosyncratic type of reaction to a contrast medium. The relative risk of reaction to contrast medium is approximately twice that for the general population; while those with history of known allergic reaction such as asthma; the relative risk is 5 times greater[27, 33, 34].

The predictive values of specific allergies to substances such as shellfish, dairy products or sea-food are currently being disputed and are recognized to be unreliable[35, 36]. Also the use of small ‘test’ doses for prediction of radio-allergenicity is doubted, as severe, life threatening reactions have been reported at such amounts, while severe reactions to larger doses had been noted in patients who previously tolerated small doses[33]. Several studies have shown that iodine is not the cause of allergic reactions, though very common in contrast media[34.] Certain protein in seafood is reported to be the cause of allergy in patients with seafood allergies[34]. True allergic effects are by definition immunoglobulin E-related, and studies have shown that contrast media do not cause such reaction in vivo[33]. However, any history of allergy should be explored further to determine the type and severity, and possibly exclude from atopic syndrome. Most forms of atopy result in 2-3 times likelihood of contrast reaction compared with non-atopic patients[35].

Asthma

A known history of asthma has been linked with increased likelihood of reaction to contrast medium[34, 35, 36]. The incidence of a severe reaction is said to be increased by a factor of between 6 and 10[37].

Medication

Concomitant medications on patients using certain drugs can increase the risk of reactions to contrast media. It is debated that patients on β–adrenergic blocking drugs have increased risk of anaphylactoid reactions. According to Greenberger[38], anaphylactoid reactions were not more frequent in patients on cardio-selective β -blockers, non-selective β -blockers or calcium antagonists. However, a trend to more reactions was noted on patients on β – blockers. In the

contrary, a study by Lang et al[36] showed a statistically significant increase in the frequency of anaphylactoid reactions in patients taking β -adrenergic blocking drugs; including an ophthalmic preparation version. Both researchers agreed that reaction to contrast media were 'slow' and refractory. An increased prevalence of 'recall reactions' has been noted after administration of contrast medium to patients receiving interleukin–2 (IL-2); a potent stimulant of the human immune system[38, 39]. It was noted that over 10% of patients who received recombinant Inter-leukin–2 and intravenous contrast agent developed delayed reactions similar to those that occur after systemic interleukin–2 therapy. Such reactions were fever, chills, malaise, nausea and vomiting. Further reactions such as skin rashes, diarrhea, and occasionally hypotension were also observed, following a follow-up administration of intravenous contrast medium performed one month after the initial IL-2 and contrast medium administration[38]. According to Shulman etal 'recall' reaction were less prevalent with non-ionic contrast media and a longer waiting time of more than 4weeks post IL - 2 treatment and intravenous contrast administration. Some set of biguandes, phenformin and metformin that are used as monotherapy or combination therapy for patients with non-insulin-dependent diabetes mellitus are contra indicated in patients with suspected renal insufficiency and liver failure. Failure of renal excretion of metformin or failure of hepatic metabolism and excretion of phenformin leads to accumulation of these biguanides and consequent fatal lactic acidosis[40].

The use of contrast agent on patient receiving metform is debatable. Contrast media administration is not encouraged in patients with renal insuffiency abinitio and would therefore not compound the accumulation of metformin. However, the risk lies in normal renal function patients on metformin who develop contrast medium-induced nephrotoxicity following contrast administration. It is therefore advised that metformin should be stopped 2days before and 2days after the administration of contrast medium; with confirmation of normal renal function before resumption of metformin therapy. It is controversial if this regulation of metform administration should apply severally to all patients; including those with normal renal and liver function.

Cardiac status

Patients with an established cardiac disease may be at increased risk to contrast medium reaction. Symptomatic patients with agina, congestive heart failure symptoms, aortic stenosis, primary pulmonary hypertension or severe cardiomyopathy are at increased risk; especially with high osmolality contrast specie. Here, the limitation of the volume and use of non-ionic, low osmolality agents are advocated.

Anxiety

There is anecdotal evidence that severe adverse effect to contrast media can be mitigated by reducing the anxiety state of the patient[3]. In a study with reference to anxiety suspected to be generated by informed consent of risks associated with intravenous contrast procedures; a standardized anxiety index was used[37]. The result showed that majority of patients who were and were not informed had equally elevated anxiety, but their no increase in the adverse reactions in the informed group.

Age

Age per se is not a risk factor[27]. But concomitant morbidity associated with certain ages especially the elderly constitute predisposing factors to reaction to contrast medium. In infants and neonates, contrast volume is an important consideration because of the low blood volume of the patient and hypertonicity of even the non-ionic monomeric contrast agent.

Certain diseases

Some disease conditions such as phaeochromocytoma, among others, have been associated with increased serum catecholamine level after injection of high osmolality contrast

medium[41]. A subsequent study showed no elevation of catecholamine level after intravenous injection of non-ionic contrast specie. It is advised that direct injection of either type into the adrenal or renal artery should be avoided in this condition so as to avoid hypotensive crisis.

Paraproteinemias, especially multiple myeloma are known to predispose patients to irreversible renal failure following administration of high osmolality contrast medium; due to tubular protein precipitation and aggregation. However, no data is available for the case of low osmolality non-ionic contrast agents. Diseases of thyroid gland can equally predispose to increased reaction to contrast agents. Patients with hyperthyroidism or other thyroid diseases may develop iodine-provoked delayed hyperthyroidism; within 4-6weeks post administration of intravenous contrast agents. But this is noted to be self-limiting[42.]

The task of mitigating reaction to contrast media administration involves two broad stages. The first state is the assessment of the concerned patient for existing risk factors. This enquiry may involve physical examination, comprehensive review of medical history; and exclusion of predisposing concomitant medication or co-morbidity. The result of this stage informs the requirement for the second stage which is the strategic planning of practical steps to manage the identified risk factor; including total elimination of its anticipated effects if possible.

Conclusion

The use of iodinated contrast media is on the increase in medical imaging. This is due to the increase in the availability of different imaging modalities utilizing ionizing radiation and demand for advanced radiological procedures that require contrast enhancement.

Efforts had been made in alleviating adverse reactions due to these contrast media. This informed the tortuous evolutionary trend, involving different stages of contrast media development till today. The core objective has been in improving the biochemical composition of the agents. Reactions to iodinated contrast media in radiography practice have not been eliminated. However, current knowledge has enabled for wide scale application of different types with improved outcome. However, the cumulative and/or delayed effects of these enhancing agents are still subject of further research. Further studies are also required to establish other subtle predisposing factors that may arise due to such conditions like concomitant medication, co-morbidity, race and environmental factors.

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