The Effect Of Iomeprol On Platelet Aggregation And Potential Risk Of Thrombogenecity

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Citation

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Abstract

Iomeprol is a newer triiodinated nonionic low osmolar monomeric radiographic contrast agent. The physicochemical characteristics of this compound show high water solubility (aqueous solutions of higher iodine concentrations) which allows the formulation of contrast media to have lower osmolalities and viscosities. Lower viscosity values make this contrast agent flow better through catheters, allowing easier manual injection. Its formulation contains 400 mg iodine/ml, the highest concentration so far available on the market for non-ionic contrast media, resulting in better X-ray attenuation and image quality. Although Iomeprol appears to have a favorable profile because of the absence of EDTA (ethylene diamine tetra acetic acid) and the presence of trometamol, hydrochloric acid, water as buffer and stabilizer in its structure, it is still unknown whether this has a distinct advantage on thrombogenicity. In this article, we investigated the potential thrombogenicity of Iomeprol, a non-ionic, low osmolar radiocontrast medium, by measuring its effect on platelet reactivity and noted similarities with other non-ionic low osmolar agents. With the use of ADP, AYPGKF, and collagen stimulation, this contrast agent inhibited platelet aggregation at 50% contrast concentration, whereas the contrast medium did not inhibit aggregation at 10% concentrations. This behavior was similar to other non-ionic agents in its class in terms of platelet reactivity despite its unique properties.

INTRODUCTION

Contrast media plays an important role for defining coronary anatomy, vascular and other structures, in diagnostic and interventional cardiac / peripheral angiography, as well as in radiology. Iodine-containing contrast media have been shown to have radio-opaque properties that attenuate X-rays during radiographic examinations. The first organic contrast compound, Lipiodol, was discovered in 1901 but this was not used until years after in radiological studies[1]. With the introduction of water soluble compounds in later years, Dr. Seldinger was the first person who used contrast media in cardiac catheterization procedures[2]. Back then, the compound named sodium diatrizoate was the prototype of the tri-iodinated benzene ring compounds that was used in imaging.

All contrast media have the structural composition of a tri-iodinated benzene ring (monomer) or 2 bound benzene rings (dimer) mixed with buffers and stabilizers, all of which can be classified as either ionic or non-ionic monomers or dimers. They can also be classified separately as high osmolar, low osmolar or iso-osmolar agents. More recently, their viscosity has emerged as one of the most important properties since it may affect flow rate[3-4], so they can also be divided as low and high viscosity agents.

Early contrast agents were ionic, monomeric, and high in osmolality, causing multiple side effects in human body systems. In an effort to improve their safety profile, particularly in order to reduce allergic reactions, hemodynamic side effects and contrast-induced nephropathy, non-ionic and low-osmolar compounds were developed in subsequent years. Metrizamide was the first non-ionic monomeric, low osmolar agent, but since this was unstable in solution, other low osmolar agents were later produced[5]. More recently, dimeric, non-ionic, iso-osmolar agents (iodixanol, iotrolan) have been introduced in the imaging world which have the deleterious effect of increasing the serum viscosity level. Although the safety profile of these non-ionic agents has been shown to be better, there have been several reports which suggest that they may have increased thrombogenicity or less anticoagulant properties than ionic contrast agents. Increased thrombogenicity has been inferred by a variety of methodologies, including in vivo studies which measured angiographic incidence of thrombosis following administration of contrast agents[6], and in vitro tests which examined clot retraction assays[7], platelet function by

electrical impedance aggregometry and PFA-100 platelet function analysis[8], and flow cytometric analysis of platelet activation[9]. The potential for increased thrombogenicity is of particular concern given the fact that these agents are used to diagnose and treat intracoronary thrombosis following plaque rupture / erosion, the general cornerstone mechanism of acute coronary syndromes[6-15].

All of these non-ionic contrast agents have either low-osmolar or iso-osmolar properties with different viscosity levels. Among these, iodixanol and iotrolan, have been classified as iso-osmolar. It is not clear as to whether the differences in these properties may potentiate thrombosis and ultimately affect short and long-term cardiovascular outcomes, which is particularly important in cardiovascular imaging.

In this study, we sought to investigate Iomeprol, a new low osmolar, non-ionic agent manufactured by Bracco Diagnostics, Inc. (Milan, Italy) [16-18]. In particular, we investigated its effect on platelet reactivity as a surrogate marker for thrombogenicity, because of its unique features of higher iodine concentration and absence of EDTA (presence of trometamol, hydrochloric acid and water instead).

RADIOCONTRAST MEDIA USED IN IMAGING

NON-IONIC MONOMERS

NON-IONIC DIMERS

IONIC MONOMERS

IONIC DIMERS

METHODS

We studied Iomeprol (Bracco Diagnostics, Inc., Milan, Italy) at 10% and 50% concentrations in mixtures with platelets to see the differences in their aggregation curves in response to various agonist stimulations, using similar methods to those described in our previous study of non-ionic contrast media[19]. The initial 10% dilution ratio was chosen to approximate the in-vivo dilution of 500 ml of contrast media in 5 liters of circulating blood of a patient undergoing a cardiac catheterization procedure. The 50% concentration simulates the moment in time when the vessel is being injected.

Normal whole blood from subjects with no known hematological disorder, coagulopathy, systemic infection, or exposure to anticoagulant or anti-platelet agents was used. The blood samples were also tested for PT, aPTT, bleeding time, CBC, SMA, and lipid profile to assure their normality.

Iomeprol was used in this comparative in vitro study to assess platelet activation / aggregation properties, as surrogate marker for thrombogenicity.

EXPERIMENTAL PROTOCOL

Isolation of Platelets: Whole blood was drawn from healthy, normal consenting human volunteers into tubes containing one-sixth volume of ACD (2.5 g of sodium citrate, 1.5 g of citric acid, and 2g of glucose in 100 ml of deionized water) using a 14 gauge needle. Blood was centrifuged (Eppendorf 5810R centrifuge, Hamburg, Germany) at 230 x g for 20 min at room temperature to obtain platelet-rich plasma. Platelet-rich plasma (PRP) along with 1 mM acetylsalicylic acid was incubated for 45 minutes at 37 °C. The platelet-rich plasma was then centrifuged for 10 min at 980 x g at room temperature to pellet the platelets. Platelets were then resuspended in HEPES-Tyrode's buffer in the concentrations noted below (138 mM NaCl, 2.7 mM KCl, 1 mM $MgCl_2$, 3 mM NaH_2PO_4, 5 mM glucose, 10 mM Hepes, pH 7.4, 0.2% bovine serum albumin) containing 0.05 unit/ml apyrase. A 50% radiocontrast concentration was prepared using 250 µl of cells in mixture with 250 µl IV contrast agent. A 10% concentration mixture was achieved using 250 µl of cells, 200 µl Tyrode`s buffer, and 50 µl IV contrast agent. As a control, 250 µl of cells in mixture with 250 µl Tyrode`s buffer was used. The platelet pellets in mixture with Tyrode`s buffer along with 10% / 50% concentrations of IV contrast agent were then studied under a light aggregometer.

Aggregometry—Aggregation of 0.5 ml of washed platelets was analyzed using a P.I.C.A. lumiaggregometer (Chrono-Log model 440S, Chrono-Log Corp., Havertown, PA). Aggregation was measured using light transmission under stirring conditions at 37 °C. Agonists were added simultaneously for platelet stimulation (AYPGKF 500 µM, 2Mes ADP 100nM, Collagen 20 µg). Aggregometer output was recorded using Kipp & Zonen type BD 12E flatbed chart recorder (SCI-TEC, Saskatoon, Canada) set at 0.2mm/s. The aggregation curves are reported.

RESULTS

Figure 1

Figure 1: From left to right normal control, 10%, and 50% Iomeprol contrast concentration with ADP stimulation

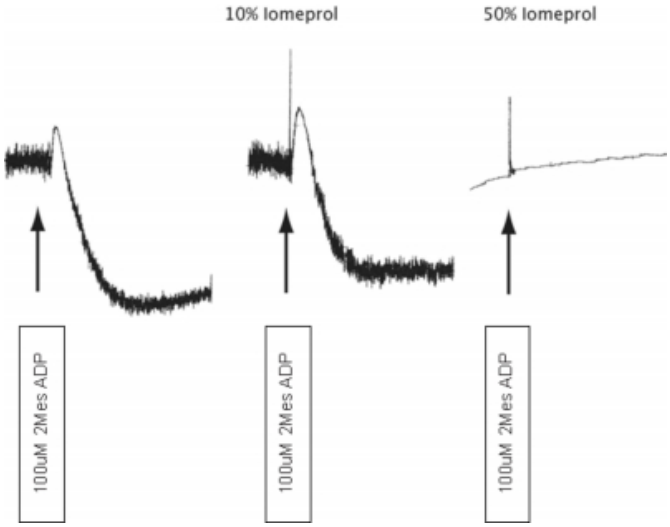


Figure 2

Figure 2: From left to right normal control, 10%, and 50% Iomeprol contrast concentration with AYPGKF stimulation

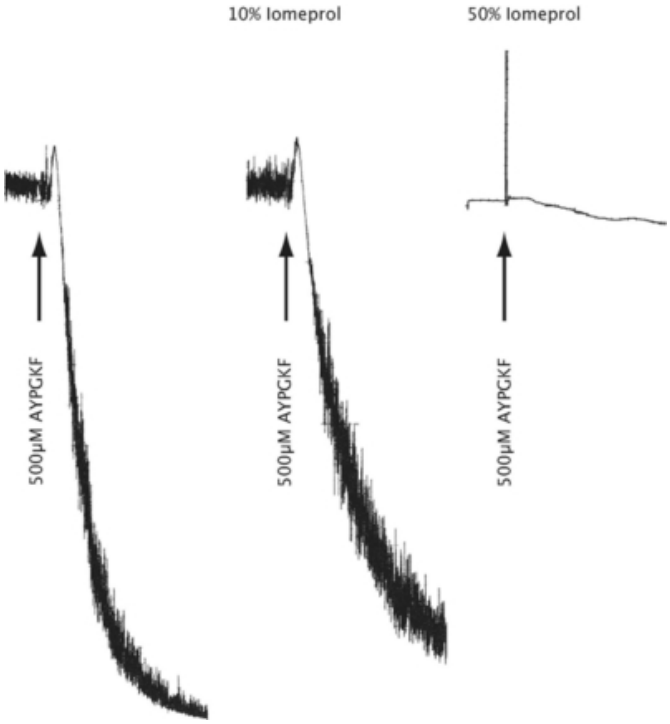
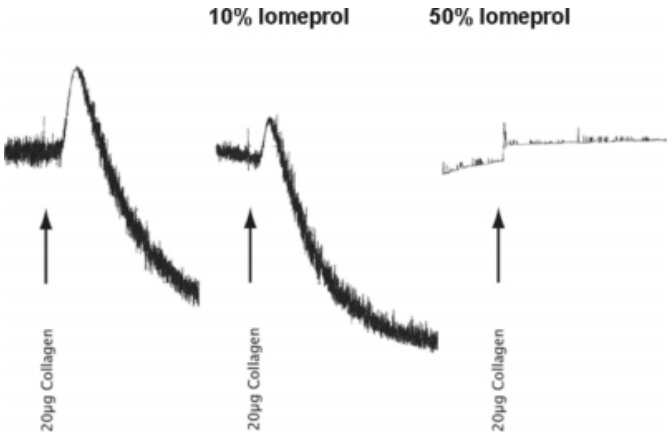


Figure 3

Figure 3: From left to right normal control, 10%, and 50% Iomeprol contrast concentration with collagen stimulation



As a result, at 10% radiocontrast media concentrations, ADP, AYPGKF and collagen stimulation essentially resulted in similar aggregation curves in comparison to the control. At 50% radiocontrast media concentration, ADP, AYPGKF, and collagen stimulation resulted in inhibited platelet aggregation in similar fashion.

DISCUSSION

Radiocontrast media is currently used widely in the radiologic imaging world. Traditionally, early studies with radiographic contrast agents showed that they may inhibit blood coagulation and activate the complement system[13-14]. Since its utilization in coronary angiography beginning in 1956 by Dr. Seldinger, multiple lessons have been learned regarding their side effect profiles. Early contrast media that was ionic and high in osmolality (even though they have a platelet inhibitory effect) have a significant side effect profile, and therefore, currently are not used in modern radiological imaging[15].

The organic chelating agent, EDTA, has been employed to block the catalytic action of metals upon deiodination for almost all of the commercial iodinated contrast agents, with the exception of iomeprol. The absence of EDTA, and the presence of trometamol , with hydrochloric acid as buffer, is an important feature of this agent. In addition, high iodine concentration with low osmolality and viscosity makes this compound a prominent one for the future in its class. It is 90% eliminated by renal glomerular filtration after 24 hours without metabolizing or binding to plasma proteins, somewhat simulating a uro-angiographic agent-like behavior[17-18]. For all of the above reasons, we chose to investigate Iomeprol's thrombogenicity in terms of its platelet reactivity.

As noted in the Methods section, we chose 10% and 50% concentrations in order to simulate the steady state condition in blood and at the moment of injection into the coronary vessel, respectively. Adenosine diphosphate (ADP), AYPGKF (a protease activated receptor 4-activating peptide of thrombin receptor), and collagen were used as stimulants.

At 50% radiocontrast media concentration, with the use of different stimulants, this agent revealed a platelet inhibitory effect, which appeared to return to near normal (similar response with control) at the 10% steady state condition. This data indicates that Iomeprol does not add additional thrombogenic risk in the millieu of acute coronary syndromes in regards to platelet activation. If anything, there is a transient reversible inhibition of aggregation, at least initially, as the vessel is being injected (at higher contrast concentration), which is potentially a desirable effect in cardiac and peripheral therapeutic interventions.

At 50% contrast concentration, it inhibited aggregation, whereas at 10% contrast concentration, this agent showed similar aggregation curves in comparison to normal controls. The mechanism by which radiographic contrast media inhibit platelet function remains to be further identified. Some of the possible postulated mechanisms include but are not limited to:

One limitation of our study is the lack of multiple controls which may affect test results as there may be some inter-individual variability. A second limitation of our article is the absence of flow cytometric evaluation as a second control. This could have been done using monoclonal antibodies directed against platelet surface receptors which would have answered the question of whether the radiocontrast media have a direct effect on platelet activation. A further limitation of this study is the inexact correlation between in vitro platelet aggregation and in vivo thrombogenicity. Future studies investigating the effects of Iomeprol and other contrast agents on a thromboelastogram may provide a more precise estimation of their thrombogenicit20[9].

In summary, Iomeprol, despite its unique properties, has a similar platelet reactivity profile in comparison to other non-ionic contrast media that we have tested previously[19]. Whether its other characteristic features may have beneficial clinical effects in different organ systems is yet to be further explored.

We dedicate this article to our fathers.

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