PAPER SYNTHESIS

STAGE I

UTILIZING NON IONIC CONTRAST SUBSTANCES IN THE RADIODIAGNOSIS OF DOGS

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INTRODUCTION

In the present, the contrast substance radiological examination is no longer a risky stage of the medical examination. An ideal substance should follow the following criteria: it has to be intensely radioopaque, inertly pharmacologically, hydrosoluble (so it can be administered in large quantities), chemically stable (cannot disperse in the organism as iodine or other metabolites), should be excreted rapidly, should have a low viscosity, lack of toxicity and irritability.

The first non contrast substance with low osmolarity that was adequate to radiological exploration was iopamidole (1979). The studies in this domain have materialized through the synthesis of very low non ionic substances, with values close to the ones of the plasma: iohexal, iotrolan, iodamid, iopromid and iodoxanol.

Schultze et al. (1984) have performed studies referring to the in vitro effects of iopamidole in coagulation, fibrinolysis and the blood complementary system in humans. The triiodated complexes in usual chemical concentrations do not modify the trombine type or trombine coagulation. Also, they do not produce an activation of the fibrinolysis process. When it comes to the C3 fraction and its immune electrophoresis degrading processes, there is no activity within the complement system (Gries, 1988). Dawson’s et al (1986) studies have shown that aggregation inhibition was greater during usage of colangiographic substances-ioglicamides, and the least one was recorded during the usage of organ iodated/non ionic substances, whereas the latter inhibited coagulation when there was a concentration of iodine of over 10 mg/dl or more.

Tirone et al. (1981) tested the acute toxicity of non ionic contrast substances by injecting it i.v., i.d. and intracerebral in mice, rats and rabbits.

The studies performed have shown that non synthetized substances that are used on a large scale have much lesser chemotoxicity compared to organic iodated conventional substances. The authors have demonstrated that iopamidole injected im does not lead to local alterations.

The most sensitive organs when it comes to the chemical reaction produced by the contrast substance, brain, the heart and the kidneys (Whitehouse, 1982)

Cardio toxicity can lead to death in a few hours from the contrast substance (Grainger, 1980), and renal toxicity can contribute to acute tubular necrosis (Bettmann, 1982, apud Grancea, 1996).

Tirone et al. (1982) have performed an experimental study regarding iopamidole effect on the nervous system, compared to other substances from the same category. The authors of the study have noticed that iopamidol and metrizamide produce moderate changes compared to iocarmate and iothalomate, which produce more severe modifications that can lead to convulsions.

Injected subarachnoidal, the contrast substance penetrates the brain through the CSF.

Non ionic latest generation substances will penetrate in a much smaller quantity.

Bongrani et al (1979) have performed an experimental study on isolated hearts, infused with iopamidol and Urografin, first substance being non ionic with low osmolarity, the second being non ionic with a high osmolarity. The authors have noticed that iopamidol will not determine any sensible alterations on the cardiac rhythm, intra coronary pressure and left ventricular pressure, compared to Urografin, which produces this type of modifications.

THE OBJECTIVES OF THE FIRST STAGE 2007 OF THE PROJECT

The general research objectiv lies in the certain establishment of the fact that non ionic contrast substances can be used in radio diagnosis of the dog in order to produce high quality images that do not jeopardize the animal’s health.

Stage I Objectives

O₁ – Organization of the experimental lots- Establishment of the groups, by age, sex, size.

O₂ – Establishment of the administration route of the contrast substances and correlation of this with the animal’s tolerance towards the non ionic contrast substance, following each patient’s individual tolerance in these non ionic contrast substances, depending on the apparatus examined.
Research activities:
A1 – Buying the necessary animals for this project. Establishment of the groups, by age, sex, size.
A2 – Establishment of the administration route of the contrast substances.
A3 – Monitoring the individual tolerance after the administration of non ionic contrast substances.

A1 - Buying the necessary animals for this project. Establishment of the groups, by age, sex, size.
The biological material was represented by 10 adult dogs of large size, both sexes and put into two lots:

- One lot formed out of 5 males between 15-50 kg;
- One lot formed out of 5 females, between 10-40 kg.

In the beginning we only worked with adult animals, in order to prevent any accidents, being known that grown animals have a higher tolerance in potentially toxic substances. Also, we chose to work on larger animals, also because their metabolism, since in small animals there is a high intensity metabolism with a higher problem risk.

Lot formation on sexes was performed by taking into account the hormonal transformations of the females and males, in normal physiological conditions.

These transformations may interfere with certain elements in the contrast substance composition, potentially inducing hematological and biochemical blood, urine and CSF transformations.

A2 – Establishment of the administration route of the contrast substances
Non ionic contrast substances are represented by Substanțele de contrast non-ionice utilizate în această etapă au fost reprezentată de:

ULTRAVIST
It is an iopromid variation, in an injectable form. Attention, the substance cannot be administered intrathecally.

Ultravist is a non ionic water soluble solution, that can be administered iv, visible by X rays. The chemical name for iopromid is: N, N'-Bis (2,3 – dihydroxypropyl) – 2,4,6 – triiodo – 5 [(methoxyacetyl)amino] – N – metyl – 1,3 – benzenedicarboxamide. Iopromide are has a molecular weight of 791,12 (iodine content of 48,12 %) and has the following molecular formula: (www.farmaline.ro)

The injectable substance is a non ionic sterile, clear, transparent with a slight yellow hue, odorless and pyrogen free substance.

It can be found in 4 injectable forms:

- injectable Ultravist – 150mgI/ml ; injectable Ultravist– 240 mgI/ml ; injectable Ultravist– 300 mgI/ml ; injectable Ultravist – 370 mgI/ml ;

Each milliliter of Ultravist 150mg/ml assures 311,70 mg iopromid, with 2,42 mg tromethamine as a buffer solution, 0,1 mg edetate calcium disodium as a stabilizer. Ultravist injectable 300 mgI/ml, contains 623,40 mg iopromid, with 2,42 mg tromethamine as a buffer and 0,1 mg edetate calcium disodium as a stabilizer.

Ultravist injectable 370 mgI/ml, assures 768,86 mg iopromid, with 2,42 mg tromethamină as a buffer substance, 0,1 mg edetate calcium disodium as a stabilizer.

The PH of the substance is of 7,4 (6,5 – 8,0) in 25 +/- 2°C, stabilized by prin autoclavation, with no conservation. The iodine concentrations (mg/ml) that are available have the following caracteristica.:
### Properties

<table>
<thead>
<tr>
<th>Properties</th>
<th>Injectable Ultravist 150mgI/ml</th>
<th>Injectable Ultravist 240mgI/ml</th>
<th>Injectable Ultravist 300mgI/ml</th>
<th>Injectable Ultravist 370mgI/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmolarity mOsmol/kg water 37°C</td>
<td>328</td>
<td>483</td>
<td>609</td>
<td>774</td>
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<tr>
<td>Osmolarity mOsmol/L in 37°C</td>
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<td>368</td>
<td>428</td>
<td>496</td>
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<tr>
<td>Viscosity 20°C CP la</td>
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<td>9,2</td>
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<tr>
<td>Density 20°C g/ml la</td>
<td>1,164</td>
<td>1,262</td>
<td>1,330</td>
<td>1,409</td>
</tr>
<tr>
<td>Density 37°C g/ml la</td>
<td>1,157</td>
<td>1,255</td>
<td>1,322</td>
<td>1,399</td>
</tr>
</tbody>
</table>

Table 1. Physical chemical properties of Ultravist ([www.farmaline.ro](http://www.farmaline.ro))

Osmolarity was measured by vapor pressure osmometry (steam pressure). Osmolarity was calculated by starting from already measured from the osmold concentration. Ultravist has an osmolarity of 150mg, 240mg, 300mg and 370mg au osmolaritate de la 1,1 la 2,7 and the small animal one is of 285 mOsmol/kg water.

Iopromide is an X ray contrast agent, which is non ionic, water soluble, tri iodinated and with an intravascular administration. The intravascular iopromide administration opacifies the vessels that are in the way of the contrast flux by allowing the Rx imaging of the internal structures, until significant hemodilution appears.

Iopromid is lightly linked to serum proteins or plasma.

This suggests that biliary and gastrointestinal excretion is not that important for Ultravist, compared to the renal pathway.

There are no metabolic data on the injectable Ultravist. ([www.farmaline.ro](http://www.farmaline.ro))

Just as in other iodinated contrast agents, the degree of contrast is directly linked to the iodine content of the dose, peak level of iodine in plasma appear immediately after administration. These plasma level drop fast, in 5-10 minutes. This is explained and justified by the dilution of the solution in the vascular and extravascular compartments.

**OPTIRAY**

Optiray 160, 240, 300, 320, 350, which is an injectable/perfusable solution, is a non ionic contrast medium, used in radiology, especially in cerebral angiographies, peripheral, visceral and renal angiographies, aortography, venography and intravenous urography. Optiray is indicated in the CT scanning of the head and body.

IV administration of Optiray opacifies the vessels where the contrast substance passes, facilitating the Rx imaging of the internal structures until the substance is significantly hemodiluted.

The pharmacokinetic profile of Optiray, its hydrophilic properties and a very low serum and plasma linking level indicates the fact that Optiray distributes itself in the extra cellular space and is rapidly eliminated through the kidneys by glomerular filtration. This product contains an entity that is new to Romania, authorized through the CEDRAC procedures for products that are allowed in the EU ([www.farmaline.ro](http://www.farmaline.ro)).
Administration of the substance
In the dogs we studied, we took two methods into consideration:

- Fast „bolus” administration;
- Slow administration

1. Fast ‘bolus administration’ of the contrast substance
The dogs we studied were on a 12-hour diet prior to our investigations, with water ad libitum. In certain situations, we administered laxatives per os.

All this preparation was necessary for the emptying of the digestive tract of the dense content and gas, because they might influence the Rx image by overlapping with the components and segments of other systems.

Patients were given a dose of 1 % Atropine 0,02 ml/kg sc to minimize secondary effects after administrating Acepromazine for general sedation, associated with Ketamine (10 mg/kg) iv to obtain neoroleptanalgesia. The administration site was the anterior cephalic vein, which was treated according to the asepsis and antisepsis standards (shaving, washing, grooming) with Betadine. The catheters were PTFE Neotech Medical Catheter.

The tranquilized animals are put in lateral recumbence and the substance needs to be extracted from the bottle at the moment of administration after the bottle has reached body temperature.

Ultravist assures 623,40 mg iopromid/ml solution, which is an almost double concentration compared to Ultravist 150.

The next stage of the study consisted in the fast administration of Ultravist 370. This substance insures 768,86 mg iopromid/ml solution with 2,42 mg tromethamine as a buffer substance and 0,1 mg calcium disodium edetate as a stabilizer.

In this stage we also used Optiray 350, which contains Ioversol 741 mg/ml, assuring a quantity of 350 mg/ml organically linked iodine.

To follow up on the objectives we enumerated before, we administered an increased dosage from 0,5 ml to 1 ml, 2,5 ml, 3 ml, 3,5 ml/kg.

The doses 2,5 and 3,5 ml / kg administered in a bolus were easily tolerated by the dogs, with moderate secondary reactions, with an anaphylactic character. The 2 ml and 2,5 ml / kg, were also well tolerated with weak secondary effects. The 0,5 ml / kg and 1 ml / kg doses were very well tolerated, with no secondary effects.

2. Slow administration of the non ionic contrast substances
Depending on the followed objective, we either administered the substance per se, but also diluted it in glucose 5% in equal parts or in saline. We administered Ultravist 300, Ultravist 370 şi Optiray 350 diluted with 5% glucose or saline. The dilution is performed out of economical reasons, since the cost of the investigation drops. AI contrast substances were diluted equally depending on the BW, and infusion duration was of about 10 mins. The animals were tranquillized and monitored during infusion.

When the substance was administered undiluted, we doubled the dose and we followed tolerability and Rx opacity. The animals tolerated the situation well with few weak secondary reactions.

A3 – Individual tolerance after adminsitration of the non ionic contrast substance
In both types of administration, the great physiological functions of the dogs were monitored before and after administration of the substance.

There were some moderate changes, which returned to normal in a short time. The 10 cases were statistically analyzed in Table 2, were the averages are presented:
Clinically speaking, we did meet some general anaphylactic and pseudo anaphylactic reactions, with a moderate intensity. Cutaneous eruptions such as spots, erythema, both are being transitory, probably due to excessive vasodilatation.

Another clinical aspect we met was transitory purpura on the skin and mucous membranes of the mouth, but it only appeared in one patient and then completely disappeared.

In three cases we noticed there was itching and light to moderate scratching, in the contrast site, especially in slow administrations in un tranquilized dogs.

In other cases we noticed retching, but only when the pre Rx diet was not performed. These reactions were not met in the stage prior to the contrast substance administration.

When the substance was administered in a bolus in a large dose, we noticed sialorrhea in a patient, accompanied by chewing motions, but those were also transitory.

Administering the substance in un tranquilized dogs triggered reactions that were slightly more intense than in tranquilized dogs..

The secondary effects we noticed, even if just mild, might be a consequence of the hyper tonicity of the contrast substances, which is higher than in biological fluids, which have values around 0,28mol/kg.H₂O, compared to the contrast substances that have 0,60 – 0,70 mol/kg.

Therefore it is noticed that Ultravist 300 does not determine sensible alterations of the cardiac rhythm, intracoronary pressure and left ventricular pressure. Since no severe alterations in the CNS were evidentiated, it appears that the effect of the substances in the encephalic barrier is weak and the quantity of substance that manages to reach to the CNS through the CSF is so small that it is not capable of endangering the nervous cell.

The preferred renal excretion leads to alterations of different intensities in the excretion organs, depending on the substance’s osmolarity.

In conclusion, we can assume that the usage of non ionic contrast substances in radiodiagnosis has a multitude of advantages determined by the increase of quality in Rx images, and the fact that the aggression towards the organism remains reduced, compared to traditional substances.

The advantages of using these substances are the following:

- Better general tolerance;
- Excellent neural tolerance
- Minimal influence on the cardiovascular system
- Very good tolerance of the endothelium
- Adminstration is not painful
- Reduced influence on coagulation, fibrinolysis, complement activation.;
- Excellent density contrast.

Secondary effects are of little to moderate intensity.

Symptoms are usually represented by chills, itching, reflex tachycardia, anxiousness, cyanosis. The rapid intervention and interruption of contrast substance administration is crucial.
For the intervention we recommend the iv administration of 6α – metil prednisolon sodium hemisuccinate, oxygen administration, antihistamines and a substance based on Ca, iv diuretic in case of a pulmonary edema, or a short acting anesthetic agent if there are any convulsions.

References
1. BONGRANI S., G. BALDI, 1979 – Influence of contrast media osmolality on isolated rabbit heart performance, Acta Radiol (Diagn), 20, 769 – 778;
7. GRANCEA, V., 1996 - Bazele radiologiei și imagisticii medicale, București Ed. Medicală Amaltea,
8. GRANCEA, V., 1996 – Bazele radiologiei și imagisticii medicale, București Ed. Medicală Amaltea,
11. TIRONE P., BOLDRINI E., 1982 – Effects of iopamidol on tje-nervous system, An experimental study, Rays 7 (Suppl 3): 61-71;
13. TIRONE P., FERRARI D., 1982 – Pharmacokinetics of iopamidol, Rays 7 (Suppl 3): 73-82;
15. WHINTEHOUSE W. M., MARTIN D., 1953 – A comparative clinical study of Priodox and Telepaque, Radiology, t.60, p.215;

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