Phenotyping allergic patients and evaluating a protocol with rapid provocation tests with iodinated contrast media

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Abstract

BACKGROUND Provocation-tests with contrast media are not standardized, and our main objective was to evaluate a rapid provocation-test, including patients with a history of anaphylaxis. As secondary objectives, we phenotyping our population and proposed a predictive methodology for the outcomes of allergy tests. METHODS An allergy study using iohexol, iodixanol, ioversol, and iobitridol was conducted in patients over 18 years of age with previous hypersensitivity reactions to iodinated contrast media. A rapid provocation-test (100 cc administered in 12 minutes) was performed using a non-involved iodinated contrast medium that had tested negative on skin tests. A statistical analysis was carried out, including binary logistic regression and cluster analysis. RESULTS A total of 130 patients were enrolled. Ninety-six patients (74%) showed cutaneous symptoms exclusively, while 17 patients (13%) experienced anaphylaxis. Nine patients (7%) had positive skin-tests, and 20 of 141 provocation-tests performed were positive, all exhibiting mild cutaneous symptoms, including in those with a history of anaphylaxis. A safe alternative contrast medium was recommended to 122 patients (94%), with good tolerance in 50 patients who required a new radiological examination. We identified three patient phenotypes, each associated with a different risk of a positive drug provocation-test. A predictive model for the outcomes of allergy tests was obtained, but it exhibited a low predictive capacity. CONCLUSIONS We confirm the efficacy and safety of a protocol including rapid provocation-tests in patients with hypersensitivity reactions to iodinated contrast media of varying severity. Three patient clusters were identified, each showing a different risk level for a positive provocation-test.

Title

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Short title

Provocation test and phenotypes in contrast media allergy

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Authors' contribution

Francisco Vega conducted the prospective study, participated in all stages of the study and wrote the first draft of the article.

Azahara Lopez-Raigada, Maria Catala and M. Victoria Mugica collaborated to perform skin-tests and drug provocation-tests.

Marina Soria performed the statistical study and data analysis.

Carlos Blanco-Mota collected and reviewed the medical histories

Carlos Blanco coordinated the whole study

All authors revised the article critically and approved the final version to be published.

Abstract

BACKGROUND

Provocation-tests with contrast media are not standardized, and our main objective was to evaluate a rapid provocation-test, including patients with a history of anaphylaxis. As secondary objectives, we phenotyping our population and proposed a predictive methodology for the outcomes of allergy tests.

METHODSAn allergy study using iohexol, iodixanol, ioversol, and iobitridol was conducted in patients over 18 years of age with previous hypersensitivity reactions to iodinated contrast media. A rapid provocation-test (100 cc administered in 12 minutes) was performed using a non-involved iodinated contrast medium that had tested negative on skin tests. A statistical analysis was carried out, including binary logistic regression and cluster analysis.

RESULTSA total of 130 patients were enrolled. Ninety-six patients (74%) showed cutaneous symptoms exclusively, while 17 patients (13%) experienced anaphylaxis. Nine patients (7%) had positive skin-tests, and 20 of 141 provocation-tests performed were positive, all exhibiting mild cutaneous symptoms, including in those with a history of anaphylaxis. A safe alternative contrast medium was recommended to 122 patients (94%), with good tolerance in 50 patients who required a new radiological examination. We identified three patient phenotypes, each associated with a different risk of a positive drug provocation-test. A predictive model for the outcomes of allergy tests was obtained, but it exhibited a low predictive capacity.

CONCLUSIONSWe confirm the efficacy and safety of a protocol including rapid provocation-tests in patients with hypersensitivity reactions to iodinated contrast media of varying severity. Three patient clusters were identified, each showing a different risk level for a positive provocation-test.

Key words

Allergy, Provocation test, Cluster, Iodinated Contrast Media, Phenotype, Skin test,

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The authors declare that they have no conflicts of interest

Ethical approval

This protocol was approved by the Committee of Research and Ethics "Comité de Ética de La Investigación con Medicamentos del Hospital Universitario de la Princesa" with the approval number 3396.

MAIN TEXT

INTRODUCTION

The use of contrast media (CM) enhances the quality of radiological studies, resulting in over 75 million examinations using iodinated contrast media (ICM) annually worldwide[1]. Although the incidence of hypersensitivity reactions (HSR) to ICM is less than 3%[2,3], the high volume of ICM usage translates to more than 225,000 HSR per year[4,5]. Most reactions are mild; however, approximately 30,000 of these could be severe, with more than 70 reported fatalities[6].

Therefore, this issue is highly relevant, yet only partial solutions have been proposed. In the event of an HSR to ICM, premedication with antihistamines and corticosteroids has been usually applied[7-9], but present several limitations[10-14], particularly because HSR can still occur despite its use with an incidence exceeding 10%[15-18]. Allergy testing has been advocated to evaluate the tolerance of ICM[19-23]. Given the low sensitivity of skin test (ST)[19,24-29] and the significant and variable cross-reactivity (C-R) among different ICM[21,30-32], it is advisable to perform a controlled drug provocation test (DPT) before administering an ICM that has shown a negative ST result [21,23,33,34].

DPT with ICM is not standardized, and various protocols have been proposed, typically involving the administration of increasing doses of ICM with observation intervals in between. This results in a total administration time ranging from a minimum of 2 hours for immediate HSRs to up to 2 days for delayed-type reactions[22,30,33,35,36]. This timeline differs significantly from the use of ICM in clinical practice, where it is administered within less than 1 minute during radiological examinations.

Addressing this issue, a rapid DPT with CM has recently been developed, demonstrating both efficacy and safety confirmed[37-39].

The main objective in our study was to assess the applicability of administering ICM at rapid speed rater in a larger population, including patients with anaphylaxis. Additionally, a statistical analysis was performed to characterize our population based on diverse clinical data.

MATERIAL AND METHODS

Patients aged 18 years and older with a history of immediate or delayed HSR to ICM were included in the study. These patients were referred from both Primary Care and Specialized Medical Units. Clinical data were recorded using an adapted version of the ENDA drug allergy questionnaire[40]. Collected data included diverse demographics and co-morbidities, information about previous radiological procedures, the ICM administered, descriptions of the HSR to ICM, required treatments, and the time elapsed until initiation of the allergy study.

To differentiate between immediate and delayed reactions, we used a threshold of 1 hour, considering that intravenous administration of ICM minimized the potential bias of digestive drug absorption. Thus, a HSR was classified as immediate if onset occurred within the first hour after ICM administration, and as delayed if onset occurred more than 1 hour later.

We used the scoring system proposed by Brown[41] to assess the severity of immediate reactions and the one proposed by Brown for delayed-type reactions[19]

This prospective study was approved by the regional institutional review board under approval number 3396, and written informed consent was obtained from each patient before testing. Diagnostic procedures followed a flowchart like one previously reported[37]. ST and DPT were performed using a panel of ICM including Iohexol (Ommipaque© 300 mg/ml, GE Healthcare, Spain), Ioversol (Optiray© 300 mg/ml, Guerbet, Spain), Iodixanol (Visipaque© 270 mg/ml, GE Healthcare, Spain), and Iobitridol (Xenetix© 300 mg/ml, Guerbet, Spain).

Skin tests

Skin prick test (SPT) was performed using undiluted commercially available ICM solutions, and intradermal test (IDT) was conducted with10-fold dilutions in 0.9% sterile saline solution. When a SPT was positive after 20 minutes, and IDT was performed with immediate readings. Readings at 24 hours of IDT were also conducted to test for delayed reactions. Saline 0.9% and histamine hydrochloride 10 mg/ml (ALK-Abello©, Spain) were used as negative and positive controls, respectively.

Drug provocation tests

A DPT was conducted to evaluate tolerance to a non-CR alternative ICM, using a volumetric pump (Alaris© GW, BD©), during a 1-day hospital stay. The selection of ICM for the DPT was based on the following criteria: (i) the implicated ICM was avoided, even if ST was negative; (ii) ICM with positive ST were avoided; (iii) ioversol or iobitridol were selected if iohexol or iodixanol were implicated, due to the high C-R between the latter two, unless specifically requested otherwise by radiologists.

Blood pressure, heart rate, and oxygen saturation were monitored for up to 3 hours after the DPT. No premedication was administered. The ICM dose and infusion rate were based on a rapid DPT previously reported[37]. Specifically, an ICM dose of 100 cc was administered intravenously: 30 cc at 900 cc/h for 2 minutes, followed by 70 cc at 420 cc/h for 10 minutes, completing the DPT in a total of 12 minutes. If any symptoms were observed during or immediately after DPT, the patient's vital signs were checked, and a physical examination was performed. Cessation of ICM infusion and treatment were performed as necessary.

DPT was considered positive if any of the following occurred within 96 hours after the provocation: a decrease in oxygen saturation below 90%, a drop in blood pressure greater than 30%, or the appearance of skin, gastrointestinal or respiratory symptoms. Patients could report any adverse reactions occurring within the following 7 days.

After a positive DPT, a new DPT was conducted with one of the remaining ICMs after a washout period of at least seven days. Well-tolerated ICM was recommended as alternative for use without premedication. When all ST or DPT were positive, avoiding ICM was recommended. A nephroprotection protocol based on previous recommendations was implemented[42].

Statistical analysis was performed using the Minitab© version 18 software package for Windows (Minitab LLC, State College, Pennsylvania, USA). The mean, median, standard deviation, and minimum and maximum values were used to describe quantitative variables, while qualitative variables were represented by frequencies and percentages.

For quantitative variables, the Student's t-test was used when a parametric test was required for comparing means between independent samples. If the samples did not follow a normal distribution, two types of non-parametric tests were applied: the Kruskal-Wallis test or the Mann-Whitney test when group distributions were similar, and the Mood's median test when the distribution shapes suggested dissimilarity between

groups. In these cases, quantitative variables were expressed as medians. Results were considered statistically significant when $p<0.05$.

Group analysis and patient segmentation were conducted using unsupervised clustering techniques, utilizing algorithms and functions from the Bayes LCA© Library (Bayesian Latent Class Analysis). This technique divides the population into N groups, aiming to achieve maximum homogeneity within each group and maximum heterogeneity between the groups. The most effective variables were selected to achieve a more homogeneous distribution of patients in the clustering study.

Based on the results obtained, we proposed a mathematical model to predict the outcomes of ST and DPT, considering various variables related to both patient characteristics and the HSR to ICM . A binary logistic regression model was applied, with predictor variables selected based on their highest statistical significance and optimal variance distribution. For ST, the variables were *involved iodixanol, involved iohexol, isolated cutaneous symptomatology, previous exposition to ICM and history of atopy* . For DPT, the variables were *cardiac disease, oncologic disease, isolated cutaneous symptoms and positive ST results.*

To evaluate the predictive capacity of the proposed mathematical models, several goodness-of-fit tests were applied, including R-squared (R^2), Deviance, Pearson, and Hosmer-Lemeshow tests.

RESULTS

A total of 130 patients with a history of HSR to at least one CM were prospectively enrolled over a six-year period, from January 2014 to July 2019. The median age was 64 years (IR:23–73), with 82 women (64%). Most patients (90%) had comorbidities that likely necessitated radiological examinations involving ICM, with oncological diseases (40%) and cardiovascular diseases (15%) being the most common.

Thirty-eight patients (29%) were atopic, defined as being allergic to aeroallergens (63%), foods (19.5%), or drugs (13.4%), or as having allergic contact dermatitis (4.5%). Additionally, 18.4% of these patients had multiple types of allergies. The prevalence of atopy was higher in women ($p<0.05$;OR 3.32).

The radiological explorations associated with HSR included computed tomography (CT) in 68.5% of patients, vascular studies in 20.8%, urography in 10.8%, and endoscopic retrograde cholangiopancreatography in one patient. Vascular studies were more associated with moderate delayed reactions, CT with mild immediate HSR, and urography with the most severe episodes ($p<0.001$; Cramer's $V=0.21$). These differences are likely more related to the type of ICM used during the procedure rather than to the inherent risk of the radiological technique itself.

Immediate HSR occurred in 75 patients (58%), with 47 cases (63.5%) classified as mild, 10 cases (13.5%) as moderate, and 17 cases (23%) as severe (anaphylaxis). Among the remaining 55 patients with delayed HSR (42%), 34 cases (61.8%) were mild, and 21 cases (38.2%) were moderate in severity. There were no cases of severe delayed HSR.

Ninety-six patients (74%) exhibited exclusively cutaneous symptoms, with 43.7% presenting with immediate urticaria and 56.3% with delayed maculopapular exanthema.

The ICM involved in HSR were iohexol in 45 patients (34.6%), iodixanol in 26 patients (20%), iopromide in 3 patients (2.3%), ioversol in 2 patients (1.55%), iomeprol in 1 patient (0.7%), and unknown ICM in the remaining 53 patients (40.7%).

The type of HSR was influenced by the specific ICM used: iodixanol, iohexol, ioversol and iomeprol were predominantly associated with exclusively cutaneous symptoms, whereas iopromide was linked to a higher risk of anaphylaxis ($p<0.05$; Cramer's $V=0.22$). The use of unknown ICM was significantly associated with an increased risk of immediate HSR ($p<0.05$) and a greater severity ($p<0.001$), with 43.4% of these patients presenting with extracutaneous symptoms and 20% experiencing anaphylaxis. Moreover, iodixanol was more often linked to delayed reactions.

The median time to study initiation was 6 months (IR:2–96), with statistically significant differences depending on the type of HSR ($p<0.001$): 18 months (IR:2–180) for immediate HSR and 4 months (IR:2–12) for delayed HSR. The delay was also longer when the involved ICM was unknown. No significant differences were observed between the ST results and the delay in initiating the study.

All SPT were negative, but 9 patients (7%) showed positive IDR (4 in the immediate readings and 5 in the delayed readings). The characteristics of the patients with positive ST are described in Table 1.The likelihood of obtaining a positive ST was higher when iodixanol was involved ($p<0.05$; Cramer's $V=0.33$). The calculated negative predictive value (NPV) of ST was 87.6%.

Seventy patients (53.8%) experienced HSR upon their first exposure to ICM and 33% of the patients with positive ST had experienced the HSR during their first contact with ICM.

A total of 141 DPT with an alternative negative skin-tested iodinated ICM were performed on 129 patients, including 17 patients with a history of anaphylaxis. One patient could not undergo a DPT because they tested positive with all the ICM evaluated. The DPT was negative in 85.8% of cases (95% CI: 66.9%–95.9%). However, 20 DPT, involving 16 patients, yielded positive results despite the use of a negative skin-tested ICM. Three patients exhibited positive DPT with more than one ICM. All positive DPT were of a cutaneous type and mild in severity, resolving spontaneously or after treatment with antihistamines and corticosteroids. Two patients with a history of anaphylaxis had positive DPT, with both cases exhibiting mild symptoms (immediate urticaria). Following the DPT, the NPV of ST was calculated to be 87.6%. The characteristics of patients with positive DPT are described in Table 2.

After completing the allergy study, a safe alternative ICM, administered at a high-flow rate without premedication, was recommended for 122 patients (94%): ioversol in 55 patients (45%), iohexol in 48 patients (39.3%), iobitridol in 12 patients (9.8%), and iodixanol in the remaining 8 patients (5.9%). Fifty of these patients subsequently required additional radiological examinations, demonstrating good tolerance to the recommended ICM without premedication. Avoidance of ICM was maintained in only 8 patients: one patient due to positive ST with all tested ICM, and the other seven due to positive DPT with tested ICM.

After the statistical analysis conducted using data mining techniques, the patients were categorized into three well-differentiated clusters (Figure 1). The most common values for the various variables within each cluster, representing the significant characteristics of each, are detailed in Table 3. We compared the percentage of positive DPT in the total population of 129 patients (13.1%) with those obtained in each of our clusters. It was observed that the risk of developing a positive DPT in the allergy study was similar in cluster 3 (13.3% vs. 13.1%), higher in cluster 2 (18.3% vs. 13.1%), and lower in cluster 1 (8% vs. 13.1%)

A binary logistic regression was conducted to identify independent factors predicting the occurrence of a positive ST or a positive DPT. In the regression analysis for ST, the variables with the greatest statistical significance were the type of reaction, symptomatology, the ICM involved, previous exposure to ICM, and history of atopy. The only significant risk factor identified for a positive ST was the involvement of iopromide, with an OR of 13.79 (90% CI: 0.9–194.1). In the regression analysis of DPT, the variables considered included personal history, symptomatology, and ST results. A personal history of cancer was identified as the only risk factor for a positive DPT, with an OR of 2.53 (90% CI: 0.98–6.52).

The ROC curve and regression equation were calculated, resulting in an area under the curve (AUC) of 0.79 for ST and 0.64 for DPT. The goodness-of-fit for these regressions was evaluated using several statistics: the coefficient of determination (R^2), and the Pearson, Deviance, and Hosmer-Lemeshow tests, with results displayed in Figure 2 for the ST and Figure 3 for the DPT.

DISCUSION

The use of ICM in radiological examinations can be challenging when a patient has a history of HSR. Recommending an alternative ICM is difficult due to high CR among them[32]. Additionally, the efficacy of premedication has been debated, and there is increasing support for conducting an allergy study to identify a safe ICM for allergic patients [21,23]. Additionally, the efficacy of premedication remains controversial, and

there is growing support for considering a more effective approach, such as recommending the switch to an ICM, especially with a targeted selection based on an allergy work-up to identify a safe ICM for allergic patients[21,23].

In this study, we employed a protocol to evaluate both the safety and efficacy of rapid DPT for identifying a safe alternative ICM for 130 patients with a previous HSR to ICM. This population exhibited diverse characteristics and varying severity of symptoms, enhancing the robustness of the results. Notably, there was a significant proportion of patients with anaphylaxis (13%), which supports the safety of rapid DPT even in high-risk populations. Furthermore, a higher percentage of patients with delayed HSR was included compared to previous studies[2,13,23,27,43,44]. Enrolling such patients is challenging because their symptoms often manifest outside of healthcare settings and are frequently unrecognized[19,45–47].

In our population, the occurrence of HSR upon first contact with ICM was 53.8%, higher than previously reported[19,26,30,48–51], which reported percentages around 30%. This phenomenon has been classically attributed to the nonspecific release of mast cell mediators. However, the fact that 33% of patients demonstrated positive ST upon first contact with ICM suggests the possibility of sensitization mechanisms. These may include sensitization to the carbamoyl side chain of ICM, potentially induced by prior contact with other molecules sharing this chain, such as the antibiotic cefuroxime, or that sensitization may have occurred through inadvertent exposure to ICM via drinking water[52,53].

The results regarding the ICM involved in HSR can vary depending on the availability of ICM at each center, making direct comparisons among studies challenging. For example, some publications have reported a higher incidence of HSR, particularly immediate reactions, with iopromide and iomeprol compared to iohexol, ioversol, and iopamidol[54–56]. Conversely, other studies have identified iohexol[57] or iodixanol[58]as the most frequently implicated ICM, and a meta-analysis found no significant differences between various hypoosmolar ICM[59]. In our population, the most used ICMs were iohexol and iodixanol. Then, it is not surprising that they were also responsible for the majority of HSR that occurred.

A significant association was observed both with the type of HSR (immediate or delayed) ($p<0.001$) and with the symptoms presented ($p<0.05$) in our population. Iodixanol was more closely associated with delayed cutaneous symptoms and was not related to any episodes of anaphylaxis, which is consistent with previously reported results[60–63]. In contrast, iohexol was associated with mild symptoms, with no significant difference between immediate and delayed reactions. Unknown ICM was significantly associated with more severe symptoms, which may be related to the fact that, with such a prolonged delay, the involved ICM was of the hyperosmolar type. The ICM was unknown for a large proportion of subjects (40.7%), similar to findings in previous studies (49, 64), with a significantly longer delay in initiating the study (median of 168 months). This delay may contribute to recall bias due to the difficulty in remembering the specific ICM involved

Both the percentage of ST and the NPV in our study were comparable to those reported in previous research[26,36,47,64], underscoring the necessity of completing the allergy study with DPT. The main objective of the current study was to evaluate the safety and usefulness of rapid DPT in a large population, including patients with severe symptoms. The safety of the protocol was well-established as all positive DPT results were mild, even among patients with a history of anaphylaxis. In terms of usefulness, we were able to successfully recommend an alternative ICM to 94% of patients by the end of the study. Additionally, 50 of these patients required a new radiological examination, which could be performed using the recommended ICM without premedication, with good tolerance observed in all cases.

A previous retrospective study has reported clinical phenotyping of patients with HSR to ICM (65), based on patient characteristics, clinical history, and ST results. This study identified different risks for developing an ICM allergy, but it did not report on the risk associated with the administration of new ICM. In contrast, our study conducted a statistical analysis phenotyping patients with HSR to ICM into three distinct clusters, each associated with different risks for developing a DPT when administering an alternative ICM. According to our results, by grouping our patients into three clusters, the safety of DPT could be enhanced. An expected limitation of our approach could be that the proposed clusters may only be implemented in similar

populations and where the ICM used for the allergy study overlaps with ours. Consequently, it may be complex to apply our results to populations with different attributes.

Higher risk of a positive ST has been associated with immediate HSR, anaphylactic shock, and a shorter delay in initiating the allergy evaluation[10,64]. However, the only identified risk factor for a positive ST was the involvement of iopromide. History of oncological pathology was found to increase the risk of developing a positive DPT.

In the mathematical model designed to predict the positivity of ST and DPT, the ROC curves showed an acceptable AUC, although the predictive statistical power was limited due to a low goodness-of-fit. This suggest that the model lacked the ability to generalize to other populations. We think that the regression analysis was limited by the number of patients included, and more specifically, by an insufficient number of patients with positive ST or DPT results. This limitation may be attributed to the selected variables lacking sufficient discriminatory power.

In any case, we consider that predictive mathematical models represent a valuable tool for improving the safety of high-risk tests, such as DPT. Further research with larger sample sizes, potentially through multicentre studies, is needed to achieve more statistically significant results.

Another limitation of our study was that the median age of the patients was higher compared to previous studies, which could influence the type of comorbidities, the radiological examinations performed, and the ICM used. Therefore, our results should be cautiously extrapolated to younger populations.

Additionally, the high percentage with unknown ICM involvement increased the likelihood that the implicated ICM was not included in the panel used for the allergy study. As a result, we could not be certain whether the DPT were performed with an alternative or the implicated ICM. However, this situation reflects daily practice in Allergy Units, where DPT are often conducted without knowing the specific suspected drug.

In conclusion, we successfully evaluated the tolerability of a protocol using rapid DPT in a prospective allergy study to identify alternative ICM for patients with immediate or delayed HSR to ICM, with varying degrees of severity, ranging from mild episodes to anaphylaxis. We also characterized our population into three clusters with different risk profiles for DPT outcomes. Finally, we have developed a predictive model for allergic test results. Larger studies are needed to confirm our findings and improve the predictive accuracy of the proposed regression model.

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Patient (number)	Age	Sex	Comorbility	History of Atopy	Radiological Examination	Previous contact
5	69	F	Digestive Disease	No	CT	Yes
9	88	M	Digestive Disease	No	ERCP	Yes
14	76	F	Neurologic Disease	No	CT	No
36	79	M	Cardiovascular Disease	No	CT	Yes
39	40	F	Cardiovascular Disease	Yes	AngioCT	Yes
44	67	M	Cardiovascular Disease	No	Coronary Angiography	No
58	77	F	Neurologic Disease	No	Venticulography	Yes
72	65	F	Oncologic Disease	Yes	CT	Yes
80	67	M	Oncologic Disease	No	Arteriography	No

Patient (number)	Age	Sex	Comorbility	History of Atopy	Radiological Examination	Previous contact
2	61	F	Urologic Disease	Yes	CT	No
3	54	F	Oncologic Disease	No	CT	No
6	49	F	Oncologic Disease	Yes	CT	No
8	23	M	Vascular Disease	Yes	Phlebography	No
44	67	M	Cardiovascular Disease	No	Coronary Angiography	No
54	50	M	Digestive Disease	No	CT	No
57	72	F	Cardiovascular Disease	No	Coronary angiography	Yes
62	53	F	Oncologic Disease	No	CT	Yes
65	57	F	Oncologic Disease	No	CT	Yes
75	65	F	Oncologic Disease	Yes	CT	Yes
89	28	F	Neurologic Disease	No	CT	No
109	77	M	Cardiac Disease	No	AngioCT	Yes
110	59	F	Cardiac Disease	Yes	CT	Yes
113	72	F	Oncologic Disease	No	CT	No
116	71	M	Oncologic Disease	No	CT	Yes
130	45	M	Oncologic Disease	Yes	CT	Yes

Cluster	**Cluster 1 (50 patients)**	**Cluster 2 (49 patients)**	**Cluster 3 (30 p**
Sex	F	F	M
Age	Any age	Younger	Older
History of Atopy	Yes	Does not affect	No

Cluster	Cluster 1 (50 patients)	Cluster 2 (49 patients)	Cluster 3 (30 p
Radiological Explorations most involved	Urography	CT	Vascular Explora
Involved ICM	Uknown	Iohexol	Iodixanol
Previous Contact to ICM	No	Yes	Yes
Type of reaction	Anaphylaxis (I)	Cutaneous (I or D)	Cutaneous (D)
Delay until allergy study	Long	Short	Short
Probability of Positive ST	Low	Low	Higher
Renal Risk	Low	Low	High

Table 3: main characteristics of each cluster

CT: computed tomography; **D:** delayed; **F:** female; **I:** immediate: **ICM:** iodinated contrast Media;**M:** male; **ST:** skin test

Legends

Figure 1: Clustering of our population based using data mining techniques

Figure 2 : ROC curve and regression equation in predicting the occurrence of positive skin test results

Figure 3: ROC curve and regression equation in predicting the occurrence of positive drug provocation test results

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