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TOLERANCE TO IOPAMIDOL IN PATIENTS WITH CONFIRMED ALLERGIC IMMEDIATE HYPERSENSITIVITY TO IOMEPROL

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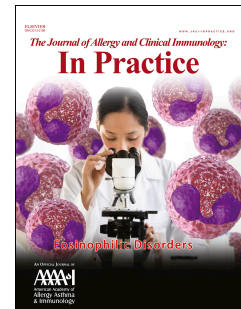
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1 REPOSITORY

2 TABLE E1. Demographic and clinical data of the 216 patients

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Sex (%)	Female 136 (63) Male 80 (37)
Age median (IQR)	61 (53-69) years
Causal ICM (%)	166 lomeprol (76.9) 40 Unknown (18.5) 6 Iopromide (2.8) 2 Iopamidol (0.8) 1 Iohexol (0.5) 1 Ioversol (0.5)
Months after reaction Median (IQR)	4 (2-24.5) months
Severity of reaction (Ring and Messmer) (%)	I - 172 (79.6) II - 28 (13) III - 13 (6) IV - 3 (1.4)
Skin tests (%)	36 Positive (16.7) 180 Negative (83.3)

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HYPERSENSITIVITY TO IOMEPROL

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TOLERANCE TO IOPAMIDOL IN PATIENTS WITH CONFIRMED**ALLERGIC IMMEDIATE HYPERSENSITIVITY TO IOMEPROL****CLINICAL IMPLICATIONS BOX**

The cross-reactivity of iomeprol with iopamidol, iopromide or iobitridol is low in immediate hypersensitivity reactions. Skin tests with iodinated contrast media are likely more effective as less time elapses from the date of the reaction.

The actual prevalence of allergic reactions to iodinated contrast media (ICM) remains unknown. Immediate, life-threatening allergic reactions to ICM can occur within minutes after administration. Subsequent allergologic evaluation helps to identify the underlying mechanism and culprit drug, and identify safe alternatives when IgE-mediated allergy is proven. For this reason, we analyze both the cross-reactivity among subjects with immediate allergic reactions to iomeprol, and the tolerance to iopamidol in these patients.

A prospective study was carried out with 216 patients referred to our Allergology Service for suspected immediate hypersensitivity reactions (less than one hour) after intravascular administration of ICM from January 2018 to June 2020. The study protocol was approved by the institutional review board of the Cruces University Hospital.

All of them underwent skin tests with undiluted ICM for skin prick-tests and, if negative, diluted at 1:10 for intradermal tests [1,2,3]. The following RCM were tested: iomeprol (Iomeron®, Rovi, Spain), iopamidol (Iopamiro®, Rovi, Spain), iopromide (Ultravist®, Bayer, Spain), and iobitridol (Xenetix®, Guerbet, Spain). For reasons of public tender for centralized supply, only two RCMs have been routinely used in our health area in the last years: iomeprol (used as first choice) and iopamidol. The severity of the reactions was classified according to the Ring and Messmer scale [4].

56 After written informed consent, we performed challenge tests with intravenous ICM (100 ml)
57 administered over 30 minutes. No premedication was administered before the challenge tests.

58 Out of the 216 patients referred, 40 subjects were excluded given their causal ICM was
59 unknown. Demographic and clinical data of these patients are included in table E1 of online
60 repository.

61 The skin tests were positive to one or more of the ICM in 36 patients (20.4%) (Figure 1): 32
62 displayed positive skin tests only to iomeprol, one patient with iomeprol and iopamidol, and
63 three patients with iomeprol and iopromide. 35 iomeprol-allergic patients tolerated the
64 challenge test to iopamidol. In the patient with a positive skin test to iomeprol and iopamidol,
65 challenge test was made with iopromide, with tolerance.

66 Cross reactivity in immediate allergic reactions with ICM is low [2,3]. In our series, only 4
67 (11.1%) out of 36 patients with positive skin tests to iomeprol showed cross-reactivity with
68 other ICMs. In our series only 20.4% of patients with immediate reactions displayed positive
69 skin tests to ICM. This proportion is within the range of other European series: 13-26% [2,3,5];
70 but higher than other Spanish series (5.5%) [5], probably due in this case to our shorter time
71 interval between reaction and study (720 vs 124 days).

72 Among the 140 patients with negative skin tests, 130 had suffered from reactions caused by
73 iomeprol and 10 by different ICM. Of these, 71 patients were challenged with iomeprol, with
74 tolerance in 60. The remaining 59 patients were challenged with iopamidol as an alternative,
75 with good tolerance in all cases. We did not challenge with iomeprol itself because of a history
76 of severe reactions (grades III-IV) in six patients; the remaining 53 did not consent the
77 challenge with the causal ICM.

78 A final diagnosis of allergic immediate hypersensitivity to iomeprol was done in 47 patients: 36
79 with positive skin test (PST group) and 11 with negative skin tests (NST group) (Table 1). The
80 median time elapsed between the reactions and the completion of the study was lower in PST

vs NST subgroup (Medians 2 vs 4 months) ($U = 2.28$; $p < 0.05$). In iomeprol-allergic patients, the reaction was more severe in PST than in NST subgroup (Kendall's Tau $b = -0.25$; $p < 0.05$). In fact, all reactions grades-III-IV severity in the 176 patients occurred in the PST group. Six patients (4 in PST, and 2 in NST subgroups) had suffered from a total number of 16 previous immediate hypersensitivity reactions to iomeprol, despite premedication with corticosteroids and antihistamines.

Afterwards, 20 of iomeprol-allergic patients underwent CT scans with iopamidol and one patient with iopromide, with a total number of 49 different CT scans tolerated without premedication (46 of them with iopamidol) in all examinations. CT scans continued to be done without ICM in three patients, despite an accomplished allergologic study; and in another two patients, CT scans with and without ICM were alternated.

However, negative skin tests performed either prior to ICM administration [6] or after the ICM-induced reaction [7] do not guarantee 100% negative predictive values. In our series, 84.7% (61/72) of the patients with reactions caused by iomeprol, and negative skin tests, tolerated challenge tests with this same ICM, but still 15.3% (11/72) did not. Nevertheless, we think that this approach with skin and challenge tests will avoid adverse reactions in the future; given that the single premedication fails to prevent immediate hypersensitivity reactions, especially IgE-mediated allergic reactions, in many of these patients; as is the case in other series as well [2,3,9-8].

The first six months after the reaction is the time period recommended for skin tests in the last published guidance [9]. In our series, the gap from the date of reaction to the study is longer in patients with negative skin tests, vs. positive ones. These data are similar to those reported in other series [3, 6].

Serum tryptase undergoes elevations in 75% of allergic episodes by ICM [2], the higher the more severe the reaction, helping decidedly to differentiate allergic vs. non-allergic reactions.

Unfortunately, increased serum tryptase levels immediately after the reaction were verified only in two of our three patients with reactions IV but are lacking in the rest.

We conclude that cross-reactivity of iomeprol with iopamidol, iopromide and iobitridol is low in IgE-mediated allergic reactions. In our study, iopamidol is a valid alternative in these patients with IgE-mediated allergy to iomeprol and negative skin tests to iopamidol. The culprit ICM itself can be administered safely in patients having experienced non-allergic immediate hypersensitivity. Allergologic investigation with the causal and alternative ICMs, conducted shortly after immediate hypersensitivity reactions, contributes to the safety in subsequent radiological procedures.

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153 Practical Guidance for the Evaluation and Management of Drug Hypersensitivity:
154 Specific Drugs. J Allergy Clin Immunol Pract 2020;8:S16-S116.

155 FIGURE 1. Flow chart: 176 patients with ICM immediate hypersensitivity reactions

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TABLE I. Demographic and clinical data of the patients of three groups of study: lomeprol allergic hypersensitivity reactions (PST and NST) and lomeprol-nonallergic immediate reactions.

	IOMEPROL ALLERGIC PATIENTS (n=47)		IOMEPROL NON-ALLERGIC PATIENTS (n=61)
	PST (n=36)	NST (n=11)	
Sex (%) [*]	Female 26 (72.2%) Male 10 (27.8%)	Female 9 (81.8%) Male 2 (18.2%)	Female 40 (65.6%) Male 21 (34.4%)
Age Median (IQR) [*]	61.5 (49.5-70) years	61 (49-70) years	59 (52-69) years
Causal ICM (%)	36 lomeprol (100%)	10 lomeprol (90.9%) 1 loversol (9.1%)	61 lomeprol (100%)
Months after reaction Median (IQR) [#]	2 (1-5) months	4 (3-26) months	4 (2-11.5) months
Severity of reaction (Ring and Messmer) (%) [#]	I – 20 (55.6%) II – 6 (16.7%) III – 8 (22.2%) IV – 2 (5.6%)	I – 9 (81.8%) II – 2 (18.2%) III – 0 (0%) IV – 0 (0%)	I – 51 (83.6%) II – 10 (16.4%) III – 0 (0%) IV – 0 (0%)

IQR: Interquartile range

PST: lomeprol allergic patients with positive skin test

NST: lomeprol allergic patients with negative skin test but positive challenge test

^{*} not significant differences between PST and NST or lomeprol-allergic and non-allergic groups.

[#] p< 0,05 between PST and NST groups.

FIGURE 1. Flow chart: 176 patients with ICM immediate hypersensitivity reactions

