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Title page

Title

Adverse reactions to iodinated contrast media: safety of a study protocol that includes fast full-dose parenteral challenge-tests searching for an alternative contrast media

Short title

Fast full-dose challenge-test with iodinated contrast media

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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

To the Editor:

Iodinated contrast media (ICM) were introduced into clinical practice to improve both diagnostic imaging and therapeutic procedures. Current ICM formulations are based on tri-iodobenzoic acid ring. Incidence of adverse reactions (AR) to ICM was 15% in 1975, but nowadays it has been reduced to 3% by using low-osmolality and non-ionic ICM.

AR to ICM have been divided into three types: (i) events not suggestive of allergic reactions; (ii) toxic and dose-dependent effects related to chemical properties of ICM; and (iii) hypersensitivity reactions (HSR). These HSR to ICM are less frequent than other AR, showing an estimated incidence between 0.6%-12.66%⁽¹⁾.

Traditionally, HSR to ICM have been considered as a non-allergic but induced by non-specific releasing of mediators from mast cells and basophils after a non-immune activation. Therefore, an allergy study has not been usually performed, and then preventive rules, such as avoidance and using an alternative ICM with premedication, have been recommended⁽²⁾.

But changing to a different agent without checking its tolerance is not a safe option, due to high cross-reactivity between ICM, which is even greater in non-immediate-HSR (NI-HSR), starting from 1 hour to 1 week after ICM exposure, than in immediate-HSR (I-HSR), starting in less than 1 hour⁽³⁾. Cross-reactivity is particularly strong among iodixanol and iohexol, because the former is a dimer of the latter. On the contrary, iobitridol behaves as the least cross-reactive ICM⁽⁴⁾. Furthermore, premedication with corticosteroids and antihistamines is now questioned, because there is a 10-18% rate of repeated HSR to ICM despite premedication, namely breakthrough reactions⁽⁵⁾.

Current evidences suggest that specific immunological mechanisms are involved in HSR to ICM⁽⁶⁾, then allergy tools, such as skin- and challenge-tests, should be applied to study them. Skin-tests (ST) should be performed with a broad panel of ICM, including involved ICM when known. But ST show a low sensitivity both to predict cross-reactivity and to propose safe alternatives, since a positive drug challenge-test (DCT) has been shown in

32.3%-41.7% of patients re-exposed to a negatively skin-tested ICM, being this percentage higher in case of NI-HSR⁽⁷⁾.

Then, DCT seems to be mandatory to confirm tolerance, as it is usually done with any other drug hypersensitivity⁽⁸⁾. Unfortunately, methodology for ICM-DCT is not standardized, and both dose and administration-rate used vary among previous studies (Table 1). But ICM-DCT performed with low doses and at slow rates could not detect non-immunological reactions. And, in any case, they do not resemble the usual management of ICM during radiologic examinations, in which a bolus of 100 cc is administered in less than a minute. Then, ICM-DCT results obtained with slow infusion rates would be difficult to extrapolate to further administration.

Here we present a prospective protocol to identify a safe alternative ICM in patients with previous possible HSR to ICM, which includes an intravenous single-blind placebo-controlled DCT at a high infusion rate.

This exploratory study was conducted in the Allergy Department of Hospital Universitario de La Princesa (Madrid, Spain), from January 2014 to September 2015. Thirty adult patients with a previous history of possible HSR to ICM were included and our results are summarized in Table 2 (supplementary material). This protocol was approved by the Committee of Research and Ethics, and written informed consent was obtained from patients.

Clinical history was recorded by means of a questionnaire for drug hypersensitivity. We used the score system proposed by Ring and Messmer for assessing the severity of I-HSR: grade I included generalized cutaneous symptoms; grade II, mild systemic reactions; grade III, life-threatening systemic reactions; and grade IV, cardiac and/or respiratory arrest. Meanwhile, NI-HSR severity was graded according to the model proposed by Brockow: mild, without treatment; moderate, with good response to treatment and severe, when hospitalization, was required.

Allergy study (Fig.1) was performed with the three ICM that were available in our Hospital (iohexol, ioversol and iodixanol). Skin prick-tests (SPT) were carried out with undiluted ICM and, if negative, intradermal tests (IDT) with 10-fold dilutions.

ICM to perform DCT was selected according to ST results, HSR data and the following requirements: i) premedication was not administered in any case; (ii) involved ICM was avoided when known, even in case of negative ST; (iii) all ICM with positive ST results were avoided. DCT was performed in a 1-day hospital stay, up to 3 h after the challenge ended. An ICM dose of 100 cc was intravenously administered by an infusion pump: 30 cc at 900 cc/h during 2 min, followed by 70 cc at 420 cc/h during 10 min, to complete ICM-DCT in a total time of 12 min. If any symptoms were observed during or immediately after ICM injection, corresponding treatment and/or stopping of ICM infusion were indicated if necessary. Moreover, patients were instructed to report any AR occurring in the following 7 days.

In case of a positive ICM-CT, a new DCT was performed with one of the remaining ICM. The well-tolerated ICM was recommended as an adequate alternative without premedication. Premedication was advised only if all ST or DCT were positive. Then, a follow-up was done to verify tolerance to recommended ICM, if a subsequent radiologic exploration was performed. Statistical analysis was carried out by Minitab®17 Software, and statistical significance was set at $p < 0.05$.

Among our patients, sex distribution was 66.3% females and 33.7% males. Mean age was 58.3 years (range 23-88), being 62.1 years in I-HSR (range 36-79) and 55 years (23-78) in NI-HSR group. Patients showing concomitant morbidities with high-risk to require further ICM administration were 76.6% (95% confidence interval (CI): 60-90%); including malignancy (in 40%), as well as renal (23.3%), cardiovascular (15%), neurological (15%), and digestive (13.3%) diseases. ICM involved in HSR were iohexol in 10 cases (33.3%), iodixanol in 5 (16.7%), iopromide in 3 (10%), and unknown ICM in 12 patients (40%). Computed tomography scan (CT) was the radiological examination most involved, reaching 73.3% of patients (95% CI: 56-90%).

According to literature, I-HSR were previously more frequent and related to ionic ICM⁽⁹⁾, but at present NI-HSR prevalence is higher, due to the greater use of non-ionic ICM⁽¹⁰⁾. In our study, I-HSR was present in 18 patients (60%), and NI-HSR in the remaining 12 (40%). The kind of HSR was significantly associated to the involved ICM: when ICM was unknown, I-HSR were remarkably more frequent ($p < 0.01$), with 11 I-HRS vs 1 NI-HRS. Meanwhile, in case of known ICM, HSR were 4 I-HSR and 6 NI-HSR with iohexol; 1 I-

HSR and 4 NI-HSR with iodixanol; and 2 I-HSR and 1 NI-HSR with iopromide. Our results could be related to our high proportion of old HSR and with unknown ICM involved, probably ionic ICM. According to symptom severity, grade I was more frequent in I-HSR, and moderate symptoms in NI-HSR ($p<0.01$). None of our patients had developed severe AR. Interestingly as much as 61.1% of I-HSR and 58.3% of NI-HSR occurred in previously unexposed patients.

Mean time interval between HSR and skin testing was 79.6 months (range 2-480), with a median of 6 months. Patients studied during the first year after HSR were 63.3% (95% CI: 45-81%), with a median delay of 4 months. On the contrary, median delay was 192 months when study was performed after the first year. When we discriminate according to the kind of HSR, NI-HSR was studied with a lower delay than I-HSR (4 vs 72 months, $p<0.01$).

Regarding ST results, only two patients showed a positive IDT (6.6%), both of them studied within the first year after the AR: patient #5, with an I-HSR grade I and positive immediate reading to ioversol; and patient #9, with a moderate NI-HSR and positive delayed readings to all three ICM.

Good tolerance to an alternative ICM was confirmed by DCT in 90% of our patients (95% CI: 78.6-100%). First challenged ICM was tolerated in 25 patients (83.4%), while a second ICM-DCT was necessary in two cases (6.6%). Recommended ICM was ioversol in 12 patients (44.4%), iohexol in 9 (33.3%), and iodixanol in the remaining 6 (22.3%). An alternative ICM was not found in three cases (10%): patients #2 and #3, due to positive DCT to all checked ICM; and patient #9, who was not-challenged because of positive ST to all checked ICM.

In this prospective study, we have evaluated, in a group of patients with previous mild to moderate HSR to ICM, the tolerance and safety of a DCT using full dose administered at a high rate, approaching the normal infusion rate during radiological examinations. An alternative ICM was recommended for 27 out of 30 patients (90%). On their follow-up, 17 of them have required a radiological exploration later that has been done using the recommended ICM without premedication, showing good tolerance.

In conclusion, our results with twenty-seven negative-DCT and seven positive-DCT showing only mild reactions, despite using 100 cc of ICM at high-speed infusion, suggest a good safety of our protocol in patients with previous mild to moderate HSR to ICM

Further investigations with full-dose ICM-DCT at high rate in larger population, and including patients with severe HSR, are needed to confirm the safety of this protocol.

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HSR type	Reference	Increasing intravenous doses	Interval between doses	Full dose	Total time	Number of Days
Immediate HSR	Trcka. 2008 (56)	0.05-0.5-1-5-7.5-10-25 cc	30 min	49.05 cc	120 min	1
	Salas. 2013 (10)	5-15-30-50 cc	45 min	100 cc	180 min	1
	Sesé. 2016 (63)	10 cc	One dose	10 cc	Not reported	1
	Morales-Cabeza 2017 (68)	5-30-60 cc on day 1 120 mL on day 2	30 min	95 cc on day 1 120 cc on day 2	60 min	2
	Trautmann 2019 (69)	0.05- 0.5-1-5-7.5-10-25 cc	30 min	49.05 cc	3 hours	1
Delayed HSR	Vernassiere 2004 (17)	1/100 cc of full dose on day 1 1/10 cc of full dose on day 2	24 hours	1/100 cc on day 1 1/10 cc on day 2	One dose/day	2
	Seitz 2009 (3)	1-5-7.5-10-30 cc	1 hour	53.5 cc	4 hours	1
	Torres. 2012 (15)	5-10-15 cc on day 1 20-30-50 cc on day 2	1 hora	100 cc	2 hours on day 1 2 hours on day 2	2 (one week interval)
	Gracia-Bara 2019 (45)	5-20 cc on day 1 50-50 cc on day 2	1 hour	25 cc on day 1 100 cc on day 2	2 days	2 (one week interval)
	Trautmann 2019 (69)	1-5-7.5-10-25 cc	30 min	48.5 cc	2 hours	1
Immediate and delayed HSR	Lerondeau 2016 (43)	1/100+1/10 cc of full dose	1 hour	1.1/100 cc of full dose	1 hour	1
	Soria. 2019 (66)	5-15-30 cc	2 hours	50 cc	4 hours	1
	Our protocol	100 cc	Single dose	100 cc	12 min	1

Table 1. Challenge-tests in previous studies: ICM dose, administration rate and total time

Figure legends

Figure 1: Algorithm to identify an alternative iodinated contrast media in possible allergic patients.

\$ST (Skin Tests): Immediate readings were considered positive when a mean wheal diameter of ≥ 3 mm in skin prick tests (SPT), or an increase in the initial mean wheal diameter of at least 3 mm surrounded by erythema in intradermal tests (IDT), were observed. Delayed IDT readings were positive if an erythematous induration occurred in the ST site at 24 hours

†DCT (Drug Challenge-Test): 100 cc of alternative ICM (avoiding involved and/or positive skin-tested ICM), administered in 12 min; time interval between challenge-tests ≥ 7 days;

AR: Adverse Reaction;

ICM: Iodinated Contrast Media

Previous AR to parenteral ICM



Clinical History to characterize AR and to identify culprit



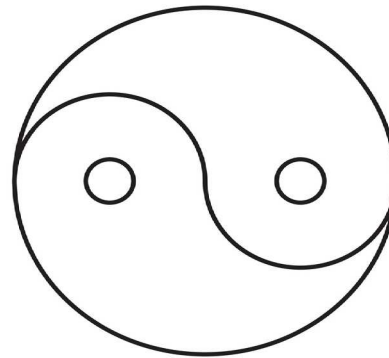
\$ST

Immediate AR: readings at 15 min (both SPT & IDT)

Non-immediate AR: additional IDT reading at 24 h

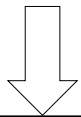


†DCT



+

**DCT with another alternative ICM
until finding a tolerated ICM**



**Only when all DCT are positive,
premedication is recommended**

-

**Tolerated ICM is
recommended**

Patient	Age (ys)	Sex	Medical History	Atopy	Examination involved in AR	Type of AR	AR severity	Previous ICM contact	Involved ICM	Time to ST (months)	ST results	DCT results	Advice
1	58	M	Diverticulosis	Yes	CT scan	I	Grade I	Yes	NK	3	Neg	Neg ID	ID
2	61	F	Nephrolithiasis	Yes	CT scan	I	Grade I	No	NK	240	Neg	Pos IO-ID-IV	PreM
3	54	F	Breast cancer, AH	No	CT scan	I	Grade II	No	NK	96	Neg	Positive IO-ID	PreM
4	75	M	Leukaemia, DM	No	Urography	I	Grade II	No	NK	480	Neg	Neg IO	IO
5	69	F	Diverticulitis, AH, Hyperthyroidism	Yes	CT scan	I	Grade I	Yes	NK	4	(I-IDR)Pos IV	Neg ID	ID
6	49	F	Ovarian cancer	Yes	CT scan	I	Grade I	No	NK	96	Neg	Pos IO, Neg IV	IV
7	67	F	Diabetes	No	CT scan	I	Grade I	Yes	IO	5	Neg	Neg ID	ID
8	23	M	Varicocele	Yes	Embolization	D	Moderate	No	ID	5	Neg	Pos IO, Neg IV	IV
9	88	M	Biliary lithiasis, AH, Ictus, IHD	No	ERCP	D	Moderate	Yes	ID	2	(D-IDR)Pos IO-ID-IV	ND	PreM
10	46	M	Hepatitis B, PT	No	AngioCT	D	Moderate	No	NK	204	(Neg	Neg ID	ID
11	25	F	Nephrolithiasis	Yes	CT scan	D	Moderate	No	IO	6	Neg	Neg IO	IO
12	76	F	Renal Cyst	No	CT scan	I	Grade I	No	NK	72	Neg	Neg IO	IO
13	79	M	Lymphoma,	Yes	Urography	I	Grade II	No	NK	372	Neg	Neg IO	IO
14	76	F	Hypothyroidism	No	CT scan	I	Grade II	No	IP	8	Neg	Neg IO	IO
15	76	F	AH, IHD	No	CA	D	Moderate	No	ID	3	Neg	Neg IO	IO
16	67	F	Aortic Disease	No	CT scan	I	Grade I	Yes	NK	192	Neg	Neg IO	IO
17	67	M	Lung Cancer,	No	CT scan	D	Moderate	Yes	IO	4	Neg	Neg ID	ID
18	53	F	Lung Cancer	Yes	PET scan	I	Grade II	Yes	IO	2	Neg	Neg ID	ID
19	49	F	Meningitis	No	CT scan	D	Moderate	Yes	IO	2	Neg	Neg IV	IV
20	51	M	Lung Cancer, IHD	No	CA	I	Grade I	No	ID	96	Neg	Neg IV	IV
21	28	F	Renal Cancer	Yes	CT scan	D	Moderate	No	IP	6	Neg	Neg IO	IO
22	62	F	Lung Cancer	No	CT scan	D	Moderate	Yes	IO	2	Neg	Neg IV	IV
23	59	F	AH, Thymoma	Yes	CT scan	D	Moderate	No	IO	5	Neg	Neg IV	IV
24	72	M	Bladder Cancer	No	CT scan	D	Moderate	Yes	IO	2	Neg	Neg IV	IV
25	36	M	Urinary Infection	No	CT scan	I	Grade II	No	IP	6	Neg	Neg IV	IV
26	58	F	Hepatitis B	No	CT scan	I	Grade II	Yes	IO	8	Neg	Neg IV	IV
27	61	M	AH	No	CT scan	I	Grade I	No	IO	8	Neg	Neg IV	IV
28	48	F	Ictus	Yes	Arteriography	D	Moderate	Yes	ID	4	Neg	Neg IV	IV
29	57	F	AH	Yes	CT scan	I	Grade I	No	NK	360	Neg	Neg IO	IO
30	76	F	Biliary Cancer	No	CT scan	D	Moderate	No	NK	96	Neg	Neg IV	IV

Table 2. Main characteristics and results of the allergic study

I: Immediate, **D:** Delayed, **PT:** Pulmonary Thromboembolism, **AH:** Arterial Hypertension, **IHD:** Ischemic Heart Disease, **DM:** Diabetes Mellitus

ERCP: Endoscopic Retrograde Cholangiopancreatography, **CA:** Coronary Angiography, **PET:** Positron Emission Tomography,

IO: Iohexol, **ID:** Iodixanol, **IV:** Ioversol, **IP:** Iopromida, **NK:** not known, **I-IDR:** Immediate Intradermal, **D-IDR:** Delayed Intradermal, **PreM:** Premedication, **ND:** Not Done

