

RESEARCH LETTER

WILEY

Protocol to prevent contrast-induced nephropathy in parenteral challenge tests for allergy evaluation of hypersensitivity reactions to iodinated contrast media

To the Editor,

Acute renal damage is the most frequent toxic reaction induced by parenteral administration of iodinated contrast media (ICM), leading to a condition named contrast-induced nephropathy (CIN). This pathology was described by Bartels et al in 1954, and, in most cases, it is transient and does not imply any relevant modifications of renal function. However, it is related to an increase in morbidity and mortality, being considered the third cause of acute renal failure in hospitalized patients.

Contrast-induced nephropathy is defined as a reduction in renal function within 2 or 3 days following ICM administration, with an increase in serum creatinine of ≥ 0.3 mg/dL, or of ≥ 1.5 – 1.9 times baseline, and ruling out other possible causes.¹

Contrast-induced nephropathy incidence is variable according to diverse studies, $<2\%$ in patients with normal renal function, but up to 50% in those with pre-existing renal dysfunction.² It is more frequent in case of hyperosmolar agents (15%) than in those of low osmolarity (3%)³ and higher with ionic agents (33.8% – 12.7%) than with non-ionic ones (0.7% – 3.1%).⁴

There is no specific treatment for CIN, and the most effective strategy remains an adequate prevention, evaluating the individual patient renal risk and applying appropriate measures to reduce the possibility of kidney damage. Since the greatest risk of CIN is related

to a previous renal failure,¹ it is advisable to assess the serum creatinine level before ICM administration and, if necessary, to apply appropriate preventive measures. Diverse protective actions have been tried, but, so far, both to maintain euvoemia and to decrease ICM viscosity through an appropriate hydration remain the most effective procedure. Isotonic saline solution (0.9% NaCl) seems an adequate method to provide a good hydration.⁵ Administration of sodium bicarbonate solution is more controversial,⁶ and it could be considered in patients with chronic renal failure, in whom an abnormal pH or an electrolyte alteration is present.

To date, adding specific drugs seems not to be useful as preventive measure.⁵ Ascorbic acid, statins or renal vasodilators have been some of the evaluated drugs, but they seem to be ineffective to improve CIN prevention. Only N-acetylcysteine is still recommended,⁷ especially in case of pre-existing renal dysfunction, although its use is increasingly questioned.

In recent years, position papers have recommended to include challenge tests in any allergic study of hypersensitivity reactions to ICM,⁸ in which it is not uncommon to perform several challenges to complete the study in some patients. Renal risk would be increased in these circumstances but, remarkably, published studies including challenge tests have neither mentioned that renal function or other

TABLE 1 Modified Mehran's renal risk score for administration of iodinated contrast media

Risk factor	Score
Age > 75 y	4
Anaemia	3
Diabetes mellitus	3
Congestive heart failure	5
Systolic blood pressure < 80 mm Hg	5
Intra-aortic balloon pump	5
40–60 mL/min	2
Glomerular filtration rate 20–40 mL/min	4
< 20 mL/min	6
Contrast media volume	1 for each 100 cc

Note: Modified score: Adding an extra point for each taken and not discontinued nephrotoxic drug (NSAID, diuretic, aminoglycoside antibiotic, metformin).

TABLE 2 Measures of nephroprotection according to renal risk score

Risk	Score	Treatment
Low (as general population)	≤ 5	A
Moderate ^a	6–10	A + B
High ^a	11–15	A + B + C
Very high ^{a,b}	≥ 16	A + B + C

Note: A, 0.9% saline solution, taking into account that liquid overload should be avoided. No predisposing cardiac condition and ≤ 75 y: 500 cc during 2 h after ICM administration. Predisposing cardiac condition and/or > 75 y: 100 cc during 1 h before, and 250 cc during 2 h after ICM administration. B, N-acetylcysteine 1200 mg by oral route every 12 h (both the previous and the challenge day). C, To obtain venous blood gas analysis before CT and ask for nephrologist advice regarding: (a) volume of saline to be administered, and (b) whether sodium bicarbonate 1.4% solution is needed.

^aRenal biochemistry is performed 24–48 h after drug PCT in case of moderate or greater renal risk.

^bCheck the need to use ICM.

Patient N°.	Sex	Age	Modified Mehran's score	sCr pre-ICM mg/dL	sCr post-ICM mg/dL	Change in sCr mg/dL (%)
1	M	85	14	1.53	1.49	-0.04 (-2.6%)
2	F	84	14	1.11	1.19	0.08 (7.2%)
3	M	67	13	1.24	1.04	0.2 (-16.1%)
4	M	75	11	0.95	0.83	-0.12 (12.6%)
5	F	82	11	0.68	0.92	0.24 (35.2%)
6	M	67	10	0.87	1.03	0.14 (16.1%)
7	F	81	10	0.6	0.7	0.1 (16.6%)
8	M	51	9	1.31	1.29	-0.02 (-1.5%)
9	M	79	9	0.96	0.9	-0.06 (-6.2%)
10	F	40	9	0.7	0.76	0.06 (8.5%)
11	F	82	9	0.74	0.7	-0.04 (-5.4%)
12	F	76	7	0.7	0.96	0.26 (37.1%)
13	M	72	7	0.88	0.83	-0.05 (-5.6%)
14	F	76	7	0.69	0.79	0.1 (14.5%)
15	M	70	7	1.05	1.02	-0.03 (-2.8%)
16	F	77	7	1.11	0.99	-0.12 (-10.8%)
17	F	83	7	1.01	1.07	0.06 (5.9%)
18	M	77	7	0.66	0.75	0.09 (13.6%)
19	M	88	6	0.99	0.78	-0.21 (21.2%)
20	F	81	6	0.62	0.58	-0.04 (-6.4%)
21	F	67	6	0.93	0.95	0.02 (2%-1%)
22	M	77	6	0.7	0.77	0.07 (10%)
23	M	72	6	0.98	0.95	-0.03 (3%)

Abbreviations: F, female; ICM, iodinated contrast media; M, male; post-ICM, after ICM challenge test; pre-ICM, before ICM challenge test; sCr, serum creatinine.

^aA contrast-induced nephropathy is defined as an increase in serum creatinine of ≥ 0.3 mg/dL, or of $\geq 50\%$ baseline.

TABLE 3 Changes in serum creatinine pre- and post-ICM challenge test in patients with a moderate or higher nephrotoxic risk, in order to discard a contrast-induced nephropathy^a

risk parameters had been assessed, nor nephroprotective measures had been applied.

In this line, an allergic study was started in the Allergy Unit of Hospital Universitario de la Princesa, Madrid, in 2014, including patients who had presented hypersensitivity reactions to ICM. In this study I, we performed parenteral challenge tests (PCT) with a full ICM dose of 100 cc, administered at fast speed in a total time of 12 minutes, and its first results have been recently published.⁹ To minimize nephrotoxicity risk related to these PCT, we included a protocol of nephroprotection using both an assessment of each patient renal risk according to a stratification score previously validated¹⁰⁻¹¹ and the application of the corresponding

most appropriate prevention strategies recommended by different guidelines.^{12,13}

Score scales including risk factors have been usually recommended to stratify renal risk. In our study, we have applied the score previously described by Mehran,¹⁴ which is the most used and has been validated. In this scale, eight independent predictive factors are assessed and, according to their presence or absence, a weighted integer score is assigned. Assessed variables include both patient-related (age, diabetes mellitus, anaemia, previous severe cardiac pathology, and renal disease, evaluated as an estimated glomerular filtration rate) and procedure-related characteristics (total volume of administered ICM).

In addition, and to improve renal security, we have modified this score adding an extra point for each potentially nephrotoxic drug taken by the patient and not discontinued, including aminoglycoside antibiotics, NSAIDs, diuretics and metformin. Modified risk scale used is described in Table 1. Total score shows the renal risk obtained for each patient, who were allocated in one of these four groups: low, moderate, high or very high renal risk. According to the assigned risk group, the corresponding nephroprotective measures were applied (see Table 2). In case of patients on dialysis, challenge test was performed the same day that the dialysis was scheduled.

Serum renal biochemistry was obtained 24 hours after the challenge tests to discard a renal dysfunction needing treatment after ICM administration, in our patients with a moderate or higher renal risk (Mehran's score > 5). But this request has not been carried out in our low-risk patients (with a Mehran's score ≤ 5), because their risk has been demonstrated to be similar to the general population, and then, a renal control is not needed when an ICM is administrated in regular practice to such patients.

One hundred and thirty patients (85 women and 45 men) were included in our study during the 2014-2019 period, with a mean age of 64 years (range 23-88 years). Related to renal risk factors, 40 patients presented high blood pressure, 13 diabetes mellitus, 4 a previous history of heart failure and 4 patients with chronic renal insufficiency (three of them requiring dialysis). Twenty-six patients were taking drugs potentially nephrotoxic, simultaneously in some cases: 17 of them NSAID, 15 diuretics and 9 metformin.

A total of 141 fast challenge tests with ICM were performed to 129 patients (challenge test was not performed in one patient who showed positive skin tests to all ICM). Regarding renal risk stratification by the modified Mehran scale, low renal risk, which is the general population one, was present in most our patients, with a score ≤ 5 in 104 of them (80%): sixty-six patients scored 1 point; twenty-two, 2 points; three, 3 points; two, 4 points; and eleven, 5 points. Moderate or greater renal risk was detected in 23 patients: moderate in 18 (five with 6 points, seven with 7 points, four with 9 points and two with 10 points); and, finally, high renal risk in 5 patients (two with 11 points, one with 13 points and two with 14 points). Patients with a very high renal risk were no identified. Interestingly, three patients undergoing dialysis were also included in our study.

Nephroprotective proceedings were carried out in all patients according to our protocol, with no incidences. Regarding the three dialysed patients, only the 100 cc of ICM, and no extra-dose of fluids, was administered, avoiding risk of cardiac overload. No incidences were shown during challenges, and dialysis session was carried out once the observation period in the Allergy Unit had finished. Further analysis control during dialysis session was within the expected parameters.

Isotonic saline solution was administered to 126 patients, adjusting both dose and infusion speed to age and cardiac risk. Expected dose of N-acetylcysteine was administered to 22 patients with moderate or high risk to whom challenge test was performed (one patient was not challenged due to positive skintest results to all ICM tested). Administration of saline solution was not modified in 5 patients with

high renal risk, and they did not require sodium bicarbonate serum, because alterations in venous blood gas analysis obtained previous to challenge test were ruled out. Serum renal biochemistry checked 24 hours after challenge tests in 23 patients with moderate to high risk did not show significant changes (see Table 3).

In conclusion, our protocol aimed both to stratify renal risk through validated scales and to implement measures of nephroprotection, before challenge tests with ICM was associated with no episodes of CIN in a group of 130 patients studied for ICM hypersensitivity. Its usefulness seems to be verified since unaltered renal biochemical parameters were shown after challenge in patients with a renal risk higher than the general population. In our opinion, protocols of nephroprotection should be always applied in any allergy study that includes challenge tests with ICM, and our protocol could be a safe, easy and efficient model to avoid CIN.

CONFLICT OF INTEREST

The authors declare no conflict 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.

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