Oral premedication in patients with a history suggesting hypersensitivity to iodinated contrast media

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Abstract

Introduction: Iodinated contrast media (ICM) are pharmaceuticals widely used in diagnostic procedures. Adverse effects associated with their administration are quite frequent and mostly mild. However, they raise concerns in patients and doctors in the context of their future use.

Aim: To determine efficacy of premedication before medical procedures with the use of iodinated contrast media in patients with a history suggesting a hypersensitivity reaction after their past use.

Material and methods: Out of 152 patients consulted due to adverse reactions after ICM (85 women and 67 men, aged 43–90), 101 were selected with the history suggesting a mild hypersensitivity reaction (urticaria, itching, skin redness, malaise etc.). All the patients had health problems requiring a procedure with ICM administration in the near future. The premedication was given with cetirizine (10 mg) and prednisone (20 mg or 50 mg, randomly assigned) 13, 7 and 1 h before the ICM administration. Presence of adverse events was compared between the subgroups with $\chi^2$ test and efficacy of premedication – with Wilcoxon test.

Results: Seventy-six patients underwent the radiologic procedure with premedication with antihistamine and a lower (40 patients) or higher dose (36 patients) of prednisone. Four of them reported a cutaneous hypersensitivity reaction (urticaria, itching, redness) and one – dyspnoea. There was no statistically significant difference in relation to the premedication protocol ($p = 0.1306$).

Conclusions: Premedication with cetirizine and prednisone before radiologic procedures proved to be efficient in patients with a history suggesting hypersensitivity to iodinated contrast media. There was no significant difference in efficacy related to the dose of prednisone (20 mg vs. 50 mg).

Key words: iodinated contrast media, contrast media allergy, drug hypersensitivity, premedication.
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**Material and methods**

Between January 2015 and January 2018, 152 patients (85 women and 67 men, aged 40–90 years) were consulted in the Department of Allergology, Medical University of Gdansk due to the past hypersensitivity reactions after ICM. Out of 152 patients, a group of 101 was selected with the history suggesting a mild hypersensitivity reaction (urticaria, itching, angioedema etc.). All the participants had health problems requiring a procedure with ICM administration in the near future (coronary angiography or computed tomography). Patients with a history of a severe drug hypersensitivity reaction, including anaphylaxis as defined by Sampson [5], unstable asthma, renal insufficiency or unstable heart insufficiency were excluded from the study. We also excluded patients with isolated subjective vasomotor symptoms (nausea, sweating, feeling of warmth etc.).

Patients were randomly assigned to one of the premedication arms: 10 mg cetirizine + 20 mg prednisone or 10 mg cetirizine + 50 mg prednisone. Characteristics of the subgroups are presented in Table 1. The premedication was given orally 13, 7 and 1 h before the ICM administration. Subjects were observed 24 h after the ICM administration. Presence of any hypersensitivity reactions was recorded.

The protocol of the study has been approved by the Independent Bioethics Committee of the Medical University of Gdansk. Subjects have given written informed consent before inclusion into the study.

**Statistical analysis**

In statistical analysis their number was compared between the groups with $\chi^2$ test. Efficacy of premedication expressed by reduction of adverse events was determined with Wilcoxon test (Statistica 13, StatSoft, USA).

**Results**

Out of 101 patients recruited into the study, 76 patients underwent radiologic procedures with premedication with antihistamine and a lower (40 patients) or higher dose (36 patients) of prednisone. Coronary angiography was performed in 67 and computed tomography – in 9 cases.

In the vast majority of cases (70 out of 76, i.e. 92%) diagnostic procedures were performed without any com-

| Parameter | Subgroup A (n = 40) | Subgroup B (n = 36) |
|-----------|---------------------|---------------------|
| Age (mean) | 53–82 years (48.9 years) | 40–90 years (46.5 years) |
| Gender (women : men) | 19 : 21 | 21 : 15 |
| Concomitant allergic diseases, n (%): | | |
| **Asthma** | 1 (2.5) | 2 (5.5) |
| **Allergic rhinitis** | 5 (12.5) | 3 (8.3) |
| **Chronic urticaria** | 0 (0) | 1 (2.7) |
| **Atopic dermatitis** | 1 (2.5) | 0 (0) |
| History of reactions to ICMs, n (%): | | |
| **Urticaria** | 26 (65) | 19 (52) |
| **Angioedema** | 8 (20) | 9 (25) |
| **Skin redness** | 29 (72.5) | 26 (72) |
| **Nausea** | 6 (15) | 4 (11) |
| **Diarrhoea** | 4 (10) | 3 (8.3) |
| **Dizziness** | 3 (7.5) | 4 (11) |
| Procedure associated with the past reaction to ICMs, n (%): | | |
| **Coronary angiography** | 20 (50) | 16 (44) |
| **Computed tomography** | 6 (15) | 6 (16) |
| **Urography** | 8 (20) | 6 (16) |
| **Other** | 2 (5) | 8 (22) |
| **Lack of data** | 4 (11) | 3 (8.3)* |

*Sum higher than 36 – some patients had more than one reaction.
In 5% of patients, a cutaneous hypersensitivity reaction was observed (urticaria, itching, redness). One patient had transient dyspnoea during the procedure with no other symptoms suggesting hypersensitivity. Finally, 1 patient had cardiac arrest during angiography, with no typical signs and symptoms of hypersensitivity, probably associated with the procedure itself. Thus, this case was excluded from the analysis. The reduction in the number of hypersensitivity symptoms between the patient’s history and current ICM administration was statistically significant ($p < 0.01$) while the difference in the rate of reactions between premedication groups was non-significant ($p = 0.1306$). The flow of patients has been shown in Figure 1.

Figure 1. Patients flow from the recruitment to assessment of premedication efficacy.

Discussion

Similarly to drug hypersensitivity, reactions to ICM are generally classified as immediate (onset of the reaction within 1 h after administration) and delayed (up to 24–48 h after administration). Immediate reactions are usually more severe with generalized symptoms (most commonly — urticaria, angioedema, dyspnoea, wheezing, fall of blood pressure) while delayed reactions are milder, usually limited to the skin [6]. For many years immediate reactions were linked to nonspecific histamine release resulting from a direct membrane effect of high-osmolality ICM, activation of complement or formation of bradykinin. However, there is a growing evidence that some of the reactions are IgE-mediated allergy [7]. Non-immediate allergic reactions are T-cell-dependent.

There are no widely accepted standards for the future use of ICM in patients with the history of adverse events. If the hypersensitivity reaction had been severe, administration of ICM is for obvious reasons strictly forbidden. On the other hand, it is believed that patients presenting mild vasomotor symptoms do not need any particular attention as they mostly well tolerate new lower-osmolality ICM. Management of mild-to-moderate hypersensitive patients has been more controversial. For many years their reactions were regarded as ‘anaphylactoid’ i.e. non-IgE-mediated. Thus, skin tests were not advised as unreliable. This approach has been changing as the increasing number of publications show that in patients demonstrating typical signs and symptoms of immediate, anaphylactic reactions, skin tests reflect sensitization [8]. As a result, the skin test, together with challenges may be applied for finding a safe ICM for future use [9]. In the vast majority of cases both immediate and non-immediate ICM-related reactions are mild. If patients’ condition requires a diagnostic or therapeutic procedure with the use of ICM and the benefit/risk ratio is clear, pretreatment is also often used. According to the current guidelines of the Polish Society of Allergology, pretreatment is particularly efficient in patients with the history of a mild reaction [10].

In order to minimize the incidence of hypersensitivity reactions in high-risk patients, several premedication protocols have been proposed, mostly based on administration of glucocorticosteroids and antihistamines. In the study of Greenberger et al., 563 patients with the history of immediate hypersensitivity reactions were given either the combination of 50 mg prednisone, 50 mg diphenhydramine and 25 mg ephedrine or 50 mg prednisone and 50 mg diphenhydramine. Both regimens were assessed to be efficient with a significantly lower number of mild reactions in the group receiving ephedrine [11]. Two years later Greenberger et al. proposed another regime for emergency administration of ICM with 200 mg hydrocortisone given intravenously repeatedly every 4 h.
until the end of the procedure and 50 mg diphenhydramine intravenously 1 h before the procedure [12]. Later introduction of lower-osmolality ICM proved to be safer in high-risk patients [13].

Although well documented, the presented regimens cannot be easily implemented. Diphenhydramine is in many counties no longer available in the oral form and the second generation of antihistamines prevail on the market due to a lower incidence of unwanted effects. Ephedrine is contraindicated in patients with hypertension and coronary artery disease. Another issue may be a relatively high dose of prednisone (150 mg/day) proposed. Although the risk of adverse events in short-term administration of systemic steroids is not high, some patients with chronic diseases, such as diabetes or hypertension, may suffer from the deterioration of their control.

Our regimens are based on oral, easily-available drugs that can be taken by patients at home and, as a result, earlier hospitalization is not required for pre-treatment. This approach proved to be efficient with only 5 patients demonstrating relatively mild hypersensitivity symptoms.

The main limitation of the study is selection of patients only with the history of mild hypersensitivity reactions. Thus, results cannot be simply extrapolated to the whole population of ICM-intolerant patients. On the other hand, regarding several patterns of reactivity and numerous clinical situations, the diagnostic approach cannot be unified. On the contrary, it should be patient-tailored with either pretreatment or allergology work-up aiming at finding safe alternative ICM [6]. For ethical reasons, no placebo group was designed, what affected the reliability of efficacy assessment. Presence of hypersensitivity reactions was compared between patients’ history and current study despite the fact that different ICMs could have been applied.

Another not investigated area is the relation between adverse events and general condition of patients as well as concomitant drugs. In this study all the procedures were elective and, as a result, performed in stable and prepared patients. That does not reflect real life where ICM are often administered in emergency situations and hypersensitivity reactions may be augmented by cardiac insufficiency, β-blockers administration etc.

Conclusions

Premedication with cetirizine and prednisone before radiologic procedures proved to be efficient in patients with a history suggesting hypersensitivity to iodinated contrast media irrespective of the dose of prednisone (20 mg vs. 50 mg).

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Conflict of interest

The authors declare no conflict of interest.

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