Editorial Commentary

Reduced iodinated contrast media dose and injection speed for CT: how much does this decrease the risk of a hypersensitivity reactions?

Knut Brockow

Department of Dermatology and Allergy Biederstein, School of Medicine, Technical University of Munich, Munich, Germany

Correspondence to: Knut Brockow, MD. Department of Dermatology and Allergy Biederstein, Technical University of Munich, Biedersteiner Strasse 29, 80802 Munich, Germany. Email: knut.brockow@tum.de.

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Adverse reactions developing after administration of iodinated contrast media (ICM) can either constitute hypersensitivity reactions, toxic reactions, or even events unrelated to ICM exposure, such as acute spontaneous or infection-induced urticaria (1). Toxicity-related reactions (also called "physiologic" or "chemotoxic" reactions) are more common than hypersensitivity reactions and often manifest with mild unspecific symptoms, such as pruritus, heat sensation, transient erythema, dizziness, nausea, sneezing, chest tightness, arrhythmia, hypertension, and vasovagal signs (i.e., hypotension and bradycardia). Immediate hypersensitivity reactions (IHR) (acute hypersensitivity reactions) occur within 1 hour after ICM administration and either present with full anaphylaxis, involving skin, gastrointestinal, respiratory and/or cardiovascular organ systems simultaneously, sometimes with bronchospasm and/or hypotension, but may also manifest as fractions of anaphylaxis, such as urticaria, or angioedema only (2,3). Fatalities do occur (4). Among IHR, there is growing evidence that particularly severe reactions may be immunoglobulin E (IgE)-mediated and skin test-positive, whereas mild to moderate hypersensitivity reactions are mostly non-allergic (5-7). IHR have been reported in a frequency of about 0.3–3% of ICM injections (1).

The main risk factor for IHRs is a previous reaction to ICM; other reported risk factors (e.g., sex, atopy, allergy to other drugs) appear either controversial or marginal (1). For patients with past IHRs to ICM, who require future ICM exposure, it has been common practice to administer premedication including glucocorticoids, antihistamines, or both (8). This intervention appears to be effective in reducing, but not eliminating IHRs (2,9). Recently, changing the contrast medium used for future ICM exposures has been reported to be more effective in preventing recurrent IHRs than administering premedication, arguing for a possible structure-specific effect (10,11). Allergy skin testing in patients with past IHRs to ICM is evolving (5,12). In the past, it was not practiced commonly, because of a low number of skin-test-positive patients. However, in the light of multiple studies showing positive skin tests to ICM, its role in the evaluation of patients with past IHRs to ICM has now been reconsidered and its use to identify safe alternative(s) for re-exposure, at least in severe reactions, has been increasingly recommended by US and European experts (8). There is recent evidence by several studies that skin tests are particularly often positive in those patients with severe reactions and that skin testing is able to differentiate between allergic (i.e., IgE-mediated) and nonallergic IHRs (6,7,12).

Against these backgrounds, Park *et al.* reported interesting data about the relationship between dose and injection speed of ICM for CT and IHR (13). Reducing both parameters in parallel significantly decreased the number of IHRs. This Korean retrospective study has

even not been the primary aim of the authors, but came as an opportunity for additional analysis of computer tomogram (CT) data stored in electronical medical records of a quality improvement project after changing practices for CT imaging. Recent advances enabled imaging with lower tube voltage and using lower amounts of ICM. The centre changed from using CTs with 120 kVp voltage, a contrast material dose of 2 mL/kg (maximum, 150 mL), and an injection speed of 3 or 4 mL/sec (control period) to CT examinations performed with 100 kVp, a contrast material dose of 1.5 mL/kg (maximum, 130 mL), and an injection speed of 2.5 or 3 mL/sec (intervention period). In a single centre outpatient setting, they compared the per-examination rates of IHR to ICM between the control and intervention periods with use of a multivariable regression model in adults (age ≥18 years) undergoing non-ionic iodinated contrast material–enhanced abdominal CT between August 2016 and January 2017 (control period) and between August 2017 and January 2018 (intervention period). Data from more than 20,000 adults and 25,000 examinations in each group were compared. A significant reduction in the rate of acute hypersensitivity reactions was found from 1.86% (468 of 25,119 examinations; 95% CI: 1.70%, 2.04%) in the control period to 1.42% (376 of 26,491 examinations; 95% CI: 1.28%, 1.57%) in the intervention period with a multivariable-adjusted relative risk of 0.85 (95% CI: 0.74, 0.99; P=0.03).

The methods used in this retrospective single centre non-randomised study appear acceptable to indicate a significant difference related to dose and injection speed of ICM for CT, although they are not immune to potential bias through changes in the procedure, in the patient population or in the assessment. In these kinds of studies, there is always a risk for unrecognized changes in performing the intravenous administration, e.g., the contrast media used were determined according to external administrative factors and could theoretically have changed. Also, staff changes might have affected the rate of acute hypersensitivity reactions by assessing and recording differently, as this was not done blinded in the different study arms. The length of patient observation after CT examinations has been heterogeneous and rather short (30 minutes) in some patients to enable the detection of a reaction, however, it was reported to be consistent throughout both study periods.

On the other hand, the results do not come totally unexpected for two reasons:

(I) The study results are in agreement with previous two studies on this topic (14,15). Those were together interpreted as inconclusive so far, as the first study reported no significant association between dose and injection speed of ICM and the rate of hypersensitivity reactions, whereas the latter showed significantly higher IHR rates to non-ionic ICM doses of ≥100 mL as compared with doses below (61–99 mL or ≤60 mL) as well as with injection speeds of 5 mL/sec or greater as compared with lower injection speeds (4–4.9 mL/sec or ≤4 mL/sec). However, also the first study actually found a (non-significant) higher rate of IHR in 2.5% (5 of 202 patients) with injection speeds of 4–5 mL/sec to non-ionic ICM in comparison to 2% (5 of 250 patients) with injection speeds of 1–2.5 mL/sec. In comparison to that study, Park *et al.* studied data from far more patients, >20,000 adults, and more than 25,000 examinations in both the intervention group and the control group. Such a number dramatically reduces differences needed between study groups to become significant. The rate of IHR for all severities combined was only moderately lower during the intervention period than during the control period (1.42% *vs.* 1.86, respectively) with a multivariable-adjusted relative risk (RR) of 0.85 (P=0.03) and an upper limit of the confidence interval near to 1 (0.99). Thus, it can be concluded, that there appears to be a significant association between dose and injection speed of ICM and the rate of hypersensitivity reactions, however, the effect is relatively weak and high patient numbers are required to detect it. Other risk factors appear to have a stronger effect in this study, particularly previous history of IHR (RR 10.4, 95% CI: 4.5–24.2), but also premedication (RR 0.37–0.39), using the ICM Iomeprol as compared to Iohexol (RR 4.48), iodine concentration of 350 mg I/mL and ≥370 mg I/mL as compared to 300 mg I/mL (4.66 and 2.83, respectively), multiphase CT (RR 0.41 compared with single phase CT) and even female sex (RR 1.22);

(II) There is no complete dose-independency of adverse reactions, even for allergy (16). It is well known that there is a strong association between dose and rate and severity of toxic ("chemotoxic") reactions, which are thus called "predictable" and affect the majority of treated patients (17). ICM do release histamine and serotonin from blood in vitro not only in patients with prior IHR, but to a certain

extend also in normal controls (18). Furthermore, unpredictable non-allergic hypersensitivity reactions, also called pseudo-allergic reactions or idiosyncrasy are moderately dose-dependent, e.g. most patients developing urticaria or anaphylaxis to non-steroidal anti-inflammatory drugs (NSAIDs) will react after intake of 250 to 1,000 mg acetylsalicylic acid, but will normally tolerate 50 mg used for coronary artery disease therapy (19). Recently it has been suggested that ICM-induced activation of Mas-related G protein-coupled receptor X2 (MRGPRX2), a mast cell-specific receptor, might trigger mast cell degranulation in non-allergic IHRs (20). Less well known is the fact that also allergies are dose-dependent to a certain, but lesser extent. For allergies, the threshold dose for elicitation is often extremely low, so that the impression derives that allergies are not dose-dependent at all. However, it has been shown from drug provocation tests and from models of allergic cofactor-dependent anaphylaxis, that also in allergies there is a threshold dose, which might decrease when cofactors or augmentation factors (e.g., physical exercise, alcohol, NSAID intake) are present (21,22).

An unexpected and surprising finding of the study of Park *et al.* is, however, that mild IHR to ICM alone, which were predominant in this study (n>300 in both groups) were not significantly associated with the dose and injection speed of ICM for CT (P<0.39), whereas the more seldom moderate reactions (n=66 and 106, respectively) and rare severe reactions (n=3 and 9, respectively), taken together, were significantly fewer in the intervention period (P<0.004). This is surprising, because it does not follow the presumed concept that increasingly more dose-dependency can be expected for allergic hypersensitivity < non-allergic hypersensitivity < toxicity. Severe reactions have been associated with positive skin tests indicating a possible IgE-mediated allergic mechanism in ICM hypersensitivity, whereas the majority of mild to moderate IHRs are regarded as non-allergic and unspecific mild reactions may even be toxic "physiologic "reactions rather than IHRs at all (6,12). This unexpected conundrum needs further clarification.

In conclusion and in general agreement with previous studies, a reduction of ICM contrast media dose and injection speed for CT is associated with a lower number of IHR. However, as these reactions are infrequent, the effect size is limited requiring higher numbers of patients studied for reaching significance. Surprisingly and unexpectedly, the effect appears to be stronger in moderate and severe as compared to mild reactions, which has to be followed-up and clarified by further studies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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