Editorial

Acute adverse drug reactions with contrast media after cardiac catheterization: can we identify those at risk?

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Adverse reactions to contrast media are classified as acute or delayed reactions. Acute adverse drug reactions (ADRs) secondary to contrast media typically occur within 1 hour of contrast administration, as compared to within 1–7 hours for delayed reactions. ADRs have been attributed to the activation of complement and fibrinolytic systems along with the release of histamine, prostaglandins, leukotrienes, and bradykinins (1,2). These reactions range from mild symptoms such as nausea and vomiting to severe reactions including bronchospasm, vagal reactions, and various dysrhythmias. Studies have shown that these ADRs are not uncommon, with an incidence of ~1–2%, 0.2–0.4%, and 0.04–0.2% in patients with mild, moderate, and severe ADRs, respectively (1). ADRs not only negatively impact patient care but can also prolong hospital course, add additional testing or monitoring, hence accruing unnecessary healthcare costs. Pre-treatment with corticosteroids and anti-histamines have been shown to reduce the incidence of ADRs (3). However, pre-treatment in all-comers may lead to increasing costs and in fact prove to be harmful due to the side effects of corticosteroids and predisposition to hospital acquired infections (4). Although, pre-treatment is efficacious in preventing ADRs, careful selection of the appropriate patient population is necessary in whom the benefits of pre-treatment outweigh its potential side effects. To date, several investigations have evaluated and highlighted the risk factors for development of ADRs after administration of contrast media (5,6). However, there remains a lack of a clinical risk scoring system which would reliably predict the probability of developing ADRs in patients undergoing coronary angiography or percutaneous coronary intervention.

In this issue of the journal, He *et al.* examined data of 17,139 patients in TRUST (The Safety and toleRability of UltraviSt in Patients Undergoing Cardiac CaTherterization) study to develop a risk prediction scoring system for ADRs following administration of contrast media (7). Iopromide, which is an iodinated, low osmolar, non-ionic water-soluble was the only contrast agent used in this study. The cohort was divided into a development data set (67%, n=11,426) and a validation data set (33%, n=5,713). The mean contrast volume used was 124.80±72.88 cc. The overall incidence of ADRs was 0.38%. Using multivariable logistic regression, the authors identified the following predictors for ADR following contrast media administration: age <50 or >69 years (score =1), contrast dose <100 cc (score =1), lack of pre-medication with corticosteroids and/or H1/H2-receptor antagonist (score =1), and lack of pre-procedural hydration (score =2). The C-statistic was 0.694 in the validation cohort. The predicted probability for ADRs was 0.09% in the low-risk group (score 0–2), 0.36% in the moderate-risk group (score 3–4), and 1.78% in the high-risk group (score ≥5).

The predictors of ADRs identified in this study are mostly consistent with data from prior studies (7). The lack of pre-procedural hydration as a risk factor for development of ADRs has been previously alluded to by multiple other investigators (8-10). The benefits of pre-hydration in preventing ADRs may be similar to prevention of contrast induced nephropathy whereby adequate hydration decreases prolonged tubular exposure and systemic toxicity.

Studies have also examined the use of pre-treatment with medications, including anti-histamines (both H1 and H2 antagonists) and corticosteroids (3,9,11). The results of these investigations have demonstrated beneficial effects of H1 antagonists as well as corticosteroids in preventing ADRs. In terms of age, the authors found that patients < 50 or >69 years were at higher risk for ADRs secondary to contrast media administration. This finding is consistent with observations from prior retrospective data, which has shown that the risk of ADRs follows a bimodal age distribution (i.e., patients with either advanced age or young adults) (12,13). History of asthma, atopy, and other allergies are more prevalent in younger adults which might explain why younger adults are more prone to ADRs. Similarly, advanced cardiac or renal disease are associated with an increased risk of ADRs after cardiac catheterization (14). This may explain why advanced age could be linked with an elevated risk for ADRs. He *et al.* also showed that the contrast dose <100 cc is a risk factor for ADRs. Although, the dose of contrast media has been studied extensively in the context of risk for contrast induced nephropathy (14,15), the risk of developing ADRs after contrast media administration has not been clearly delineated in prior studies. The data from the current investigation (7) with regards to the association between less contrast volume and higher incidence of ADRs should be carefully interpreted and implemented in clinical practice, as the use of higher contrast volume may prove deleterious due to its negative impact on renal function. Lastly, a history of prior ADRs signifies a high risk for recurrent ADRs with exposure to contrast media (6,13), a finding which was not reported to be a significant risk factor in this study.

This study provides a novel attempt of developing a scoring system to identify patients at risk for developing ADRs following contrast media administration. The strength of study lies in its relatively large sample size and including all-comers undergoing cardiac catheterization, as well as the careful assessment of ADRs. Despite the strengths of this study, there are certain aspects which might limit its application in routine clinical practice worldwide. In this study, ~20% of the patients were pre-medicated, mostly with corticosteroids. This makes interpretation of the term "pre-medication" challenging as a vast majority of patients who were pre-medicated received corticosteroids, which is not routinely administrated prior to cardiac catheterization. Second, this study included patients receiving only one specific type of contrast media (i.e., iopromide). Thus, caution should be exercised when applying these findings to patients receiving other types of contrast media. Third, the data are driven from a single center and exclusively included patients only from Chinese descent, thereby limiting the generalizability of the findings to other geographic areas and races. Finally, the risk score would benefit from external validation in other cohorts with various ethnicities prior to having true clinical applicability.

The development of a reliable ADR risk stratification algorithm may have downstream positive implications for patients undergoing coronary angiography or percutaneous coronary intervention. Identification of patients at an elevated risk for contrast media induced ADR would allow clinicians to provide the appropriate pre-treatment to such patients. Costs associated with administration of pre-treatment medications, side effect of such medications, and potential need for increased hospitalization are not trivial (16). It would be of interest if the risk scoring system did not include pre-medication, thus allowing identification of higher risk population and allowing a more selective use of pre-medications. Although, current guidelines recommend pre-treatment with corticosteroids and anti-histamines only in high risk patients (especially those with history of prior ADRs) (17,18), there seems to be a lack of consensus regarding the routine pre-treatment with anti-histamines in patients without history of ADRs. Despite no clear commentary in society guidelines regarding pre-treatment of non-high-risk patients, most operators practice administrating pre-medication with anti-histamines for all-comers. Therefore, further investigations are needed to assess benefits of pre-treatment with corticosteroids and/or anti-histamines in non-high-risk patients.

In summary, this study provides a simple tool that could be easily implemented to identify patients of Chinese descent who are at risk of developing ADRs after cardiac catheterization. This risk scoring system can be incorporated into cardiac catheterization screening protocols to alarm clinicians when patients are deemed to be at moderate or high risk for contrast media induced ADRs. Future studies are needed to externally validate this risk score among other populations.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

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