We believe that prospective, double-blind, randomized, controlled trials comparing iodixanol with all LOCM would be necessary to confirm the results of this meta-analysis.

*Simona Detrenis, MD
Michele Meschi, MD
Giorgio Savazzi, MD
*Department of Internal Medicine and Nephrology
University of Parma
Via Gramsci, 14
I-43100 Parma
Italy
E-mail: simonadts@libero.it


REFERENCE


Contrast Nephropathy: Isosmolar and Low-Osmolar Contrast Media

We read with interest the meta-analysis by McCullough et al. (1) regarding the lower incidence of contrast-induced nephropathy (CIN) in patients who received isosmolar contrast medium (IOCM) iodixanol, as compared with those who received low-osmolar contrast media (LOCM). Nevertheless, we believe the study presents some important methodological limitations that could reduce its value.

In the meta-analysis, the greater part of the patients (789 of 1,345) included in the group receiving LOCM were given an ionic contrast medium (CM), and only 69 patients received iopamidol, the contrast agent that, according to recent data, seems to be the safest of the LOCM (2,3). Therefore, the results of the meta-analysis could derive from the small number of patients receiving iopamidol in the LOCM group, rather than to the renal safety of isosmolar iodixanol. Moreover, apart from the small meta-analysis by Claus et al. (4) comparing the nephrotoxicity of the IOCM iotrolan with different types of LOCM (iopamidol, iopromide, and iohexol), the previous major comparative studies supporting the possible safety of IOCM have been performed only between iodixanol and the monomer iohexol (5–7), which is found to be one of the CMs most responsible for CIN (2,3). Thus, at present, we do not perceive any definitive evidence of the presumed advantage derived from the use of IOCM in comparison with all of the LOCM (8).

In addition, the investigators themselves note that only 18.3% of patients included in the meta-analysis had their final creatinine (Cr) values measured on day 3 or later (1), whereas CIN is defined as an increase of serum Cr levels of 0.5 mg/dl (or 44 μmol/l) or a 25% or greater relative increase from baseline 48 to 72 h after a diagnostic or interventional procedure requiring CM administration (9). We would like to understand how the researchers completed Table 4 in their study summarizing the incidence of CIN occurring within 72 h if only 18.3% of patients have their Cr values recorded on day 3.

Finally, as underscored by the investigators (1), another important bias could be identified in the lack of data relative to the amount or type of intravenous hydration prophylactic protocol given before and after CM administration, which could influence the outcomes of each trial (10).

Dr. Detrenis and colleagues point out that only 69 patients in the low-osmolar contrast media (LOCM) group received iopamidol and suggest it may be a special case among LOCM agents. As a LOCM, iopamidol has an osmolality of 796 mOsm/kg H2O (Isovue, Bracco Diagnostics, Princeton, New Jersey; 370 mg iodine/ml, viscosity at 37°C, 9.4 Cp), which is very similar to iohexol (844 mOsm/kg H2O, Omnipaque, Amersham Health, 350 mg iodine/ml, viscosity at 37°C, 10.4 Cp) (1,2). Both of these agents are nonionic monomers. By contrast, iodixanol, an iso-osmolar contrast medium (IOCM), is a nonionic dimer with an osmolality of 290 mOsm/kg H2O (Visipaque, Bracco Diagnostics, Princeton, New Jersey; 370 mg iodine/ml, viscosity at 37°C, 11.6 Cp) and when compared to the nonionic LOCM monomers in our study had a significantly lower rise in serum creatinine (Cr) after contrast exposure (p = 0.001) (3,4). Although iopamidol and iohexol are nearly identical in their physiochemical properties as

REFERENCES


LOCM agents, we agree with Dr. Detrenis and colleagues that a large randomized trial of high-risk patients undergoing intra-arterial contrast exposure comparing iodixanol versus iopamidol would help further support the superior renal safety of IOCM compared to nonionic LOCM monomers (iohexol, iopamidol, iopromide). Such trials in lower-risk patients (<5% contrast-induced nephropathy [CIN] rate) are unlikely to show any difference between the 2 classes of agents and will not be helpful in settling this issue.

We acknowledge that we did not have complete Cr data through the entire time range of CIN, as many of these trials were not designed with CIN as an end point. When available, we used the day-3 Cr data; however, prior studies indicate the majority of serious CIN cases have a rise in Cr >0.5 mg/dl by 24 h (5). This source of incomplete ascertainment bias almost certainly biased our findings to the null hypothesis (i.e., yielding fewer CIN end points), thus strengthening our conclusions with respect to the renal safety of iodixanol. Furthermore, because many of these were not CIN trials, there was no control over hydration given before or after contrast exposure. This source of variation again would work toward biasing our results to the null hypothesis (i.e., higher-risk patients getting more aggressive hydration). Thus, iodixanol may in truth be associated with an even greater margin of renal safety than demonstrated in our analysis.

*Peter A. McCullough, MD, MPH
Michel E. Bertrand, MD
Jeffrey A. Brinker, MD
Fulvio Stacul, MD

*Divisions of Cardiology and Preventive Medicine
William Beaumont Hospital
4949 Coolidge Highway
Royal Oak, Michigan 48073
E-mail: pmccullough@beaumont.edu

doi:10.1016/j.jacc.2006.12.001

REFERENCES