Changes in QTc Interval Induced With Renografin-76 and Hypaque-76 During Coronary Arteriography

GERALD L. WOLF, PhD, MD, JOHN W. HIRSHFELD, Jr., MD, FACC
Philadelphia, Pennsylvania

Renografin-76 and Hypaque-76 are both recommended for coronary arteriography. Both have the same osmolality and iodine concentration, but differ in their calcium binding properties. After selective right or left coronary arteriography in patients, Renografin-76 caused significantly more prolongation of the QTc interval than did Hypaque-76. Less calcium binding in the Hypaque formulation is probably responsible for its lesser effect on the QTc interval. This study suggests, but does not prove, that Hypaque-76 is safer than Renografin-76 for coronary arteriography.

Radiographic contrast agents disturb contraction, metabolism and electrophysiology of the heart (1-17). Animal studies (18-25) have documented a prolongation of QT interval and a reduction of fibrillation threshold immediately after coronary arteriography. The chemical formulation of the contrast agent, including the radiopaque molecule (18,23,24), the added cations (20,24) and the amount of calcium chelation (21,25), all influence the fibrillatory propensity of these agents in experimental animals. Even meglumine-sodium diatrizoate formulations with virtually identical osmolality and diatrizoate concentrations differ in their arrhythmogenic potential in normal and ischemic animal hearts when their calcium-binding additives are varied (21,25). Despite a large data base suggesting that normal ionic calcium is required for optimal cardiac contraction and conduction, commercial formulations available for coronary arteriography differ significantly in their calcium chelating properties. It has not been shown that these differences in calcium binding induce significant differences in cardiac electrophysiology in human patients.

The purpose of this investigation was to compare two such commercial formulations, Renografin-76 (Squibb & Sons, Inc.) and Hypaque-76 (Winthrop Laboratories), to determine their relative adverse effects on the rate of cardiac repolarization. The QTc interval was our variable of interest because a prolonged QT interval is a risk factor for arrhythmias (26-40) and sensitive to changes in blood calcium (41,42).

Methods

Coronary arteriography. Studies were performed on four patients undergoing selective coronary arteriography by the Judkins technique. Selective coronary arteriography was performed after left ventriculography. Both coronary arteries were hand injected with both Renografin-76 and Hypaque-76. The sequence of injections was randomized, but each patient received at least two injections of each agent into the left coronary artery and at least one injection of each agent into the right coronary artery. The volume of contrast agent delivered during each injection was recorded. There was no difference in the volume injected between the two groups.

QT interval measurement. Heart rate was controlled by right atrial pacing at a rate 10 beats/min above the patient’s spontaneous heart rate. Electrocardiographic leads I, aVF and V1 were recorded simultaneously using standard electrocardiographic filters at a sensitivity of 0.5 mV/cm and a paper speed of 50 mm/s. Recordings were begun 10 seconds before the injection and continued until the maximal electrocardiographic changes had passed (typically 30 to 45 seconds). The QT interval was measured from the earliest deflection of the QRS complex in any lead to the latest completion of the T wave in any lead. Because different patients had different cardiac cycle lengths, all QT intervals were normalized using the Bazett correction (QT/[R−R]2).
We report the response measured during a total of 26 injections (17 left and 9 right coronary artery studies).

**Statistics.** Significance of the difference between the QTc prolongation after the Renografin-76 and the Hypaque-76 injections was tested using Student's t test for grouped data.

**Results**

In these paced patients, both Renografin-76 and Hypaque-76 significantly prolonged the QTc interval (Table 1). In a particular patient, the degree of prolongation was influenced by the coronary anatomy and pathology. However, in every patient, Renografin-76 increased the QTc interval more than a similar injection with Hypaque-76. Each agent caused a similar temporal change, with maximal effects at 8 to 12 seconds after injection and maximal duration of less than 45 seconds. Despite the prolonged QT intervals, no patient experienced any significant arrhythmia during the study.

**Discussion**

Interest in the cardiac effects of contrast agents is extensive, and Fischer and Thomson (17) have published an excellent review. The effects of ionic agents, such as diatrizoates, on the heart as a pump have been well characterized. The negative inotropic effects are significantly related to calcium-binding properties of the formulation (7,43-47).

**Effect of contrast agents on fibrillation threshold and QT interval.** The electrophysiologic effects of contrast agents have not been as easily studied. Although electrocardiographic changes are well known, only one study (49) has been reported utilizing direct measures of Purkinje cell action potential and conduction velocity. In animals, the fibrillatory potential of these agents is readily demonstrated (20-25). At lower doses, these agents induced changes in QT intervals (18,19). The changes in ventricular fibrillation threshold and in QT interval are consistent within reported animal studies and also parallel clinical experience in confirming the relative safety of mixed meglumine-sodium versus pure sodium or pure meglumine formulations (7,49-52). Because direct measures of fibrillation threshold during angiography in patients are not justified, clinical comparisons of commercial formulations must be inferred. We have utilized changes in QTc interval for this inference. Prolongation of the QT interval is a well known risk factor for ventricular tachycardia or fibrillation, whether due to a congenital condition (26-32), electrolyte imbalance (18,19,41) or the various actions of other drugs (33-40).

**Discussion**

Interest in the cardiac effects of contrast agents is extensive, and Fischer and Thomson (17) have published an excellent review. The effects of ionic agents, such as diatrizoates, on the heart as a pump have been well characterized. The negative inotropic effects are significantly related to calcium-binding properties of the formulation (7,43-47).

**Effect of contrast agents on fibrillation threshold and QT interval.** The electrophysiologic effects of contrast agents have not been as easily studied. Although electrocardiographic changes are well known, only one study (49) has been reported utilizing direct measures of Purkinje cell action potential and conduction velocity. In animals, the fibrillatory potential of these agents is readily demonstrated (20-25). At lower doses, these agents induced changes in QT intervals (18,19). The changes in ventricular fibrillation threshold and in QT interval are consistent within reported animal studies and also parallel clinical experience in confirming the relative safety of mixed meglumine-sodium versus pure sodium or pure meglumine formulations (7,49-52). Because direct measures of fibrillation threshold during angiography in patients are not justified, clinical comparisons of commercial formulations must be inferred. We have utilized changes in QTc interval for this inference. Prolongation of the QT interval is a well known risk factor for ventricular tachycardia or fibrillation, whether due to a congenital condition (26-32), electrolyte imbalance (18,19,41) or the various actions of other drugs (33-40).

**Discussion**

Interest in the cardiac effects of contrast agents is extensive, and Fischer and Thomson (17) have published an excellent review. The effects of ionic agents, such as diatrizoates, on the heart as a pump have been well characterized. The negative inotropic effects are significantly related to calcium-binding properties of the formulation (7,43-47).

**Effect of contrast agents on fibrillation threshold and QT interval.** The electrophysiologic effects of contrast agents have not been as easily studied. Although electrocardiographic changes are well known, only one study (49) has been reported utilizing direct measures of Purkinje cell action potential and conduction velocity. In animals, the fibrillatory potential of these agents is readily demonstrated (20-25). At lower doses, these agents induced changes in QT intervals (18,19). The changes in ventricular fibrillation threshold and in QT interval are consistent within reported animal studies and also parallel clinical experience in confirming the relative safety of mixed meglumine-sodium versus pure sodium or pure meglumine formulations (7,49-52). Because direct measures of fibrillation threshold during angiography in patients are not justified, clinical comparisons of commercial formulations must be inferred. We have utilized changes in QTc interval for this inference. Prolongation of the QT interval is a well known risk factor for ventricular tachycardia or fibrillation, whether due to a congenital condition (26-32), electrolyte imbalance (18,19,41) or the various actions of other drugs (33-40).

**Clinical implications.** The incidence of ventricular fibrillation during coronary arteriography is normally less than 0.75% in experienced hands (55) but appears to be appreciably higher in patients with acute myocardial infarction (56). Clearly, a randomized trial to prove that less ventricular fibrillation occurs with a formulation that chelates less calcium would be extremely expensive because of the requisite sample size. Because the formulations clearly

<table>
<thead>
<tr>
<th>Case: Coronary Angiographic Findings</th>
<th>QT: Left Coronary Angiograms</th>
<th>QT: Right Coronary Angiograms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>R76</td>
</tr>
<tr>
<td>1: right dominant,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD normal, LCx 100%, RCA normal</td>
<td>397</td>
<td>551</td>
</tr>
<tr>
<td>2: right dominant,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD 90%, LCx 90%, RCA 75%</td>
<td>413</td>
<td>643</td>
</tr>
<tr>
<td>3: right dominant,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD 100%, LCx normal, RCA normal</td>
<td>540</td>
<td>670</td>
</tr>
<tr>
<td>4: right dominant,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD 70%, LCx normal, RCA 50%</td>
<td>450</td>
<td>560</td>
</tr>
<tr>
<td>Mean</td>
<td>470</td>
<td>629</td>
</tr>
<tr>
<td>± SD</td>
<td>± 18.9</td>
<td>± 18.9</td>
</tr>
</tbody>
</table>

H76 = Hypaque-76; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; p = probability; RCA = right coronary artery; R76 = Renografin-76; SD = standard deviation
Table 2. Contrast Media Formulations

<table>
<thead>
<tr>
<th></th>
<th>Renografin-76</th>
<th>Hypaque-76</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meglumine</td>
<td>66%</td>
<td>66%</td>
</tr>
<tr>
<td>diatrizoate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>diatrizoate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sodium</td>
<td>190 mEq/liter</td>
<td>160 mEq/liter</td>
</tr>
<tr>
<td>Osmolality</td>
<td>1,850 mOsm</td>
<td>1,850 mOsm</td>
</tr>
<tr>
<td>Additives</td>
<td>Sodium citrate 0.32%, disodium EDTA 0.04%</td>
<td>Calcium disodium, EDTA 0.01%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

differ in their calcium-binding properties and their influence on QTc intervals, the present study suggests, but does not prove, that Hypaque-76 is less likely to cause ventricular fibrillation than is Renografin-76. This confirms, in a patient population, the enhanced adverse effects of calcium chelation that have been shown in normal or ischemic animal hearts.

References