Lessons learned from crises

Kurzfassung: Starting with a brief discussion of the fundamental safety basis for the gadolinium chelates, the history of their development and the discussions that occurred therein regarding safety are presented. The focus within this framework is on the two crises that have occurred, one historical – nephrogenic cystic fibrosis, and one current – deposition of gadolinium in the brain and body in patients with normal renal function.

Many lessons are readily evident from the observation of these crises, the circumstances that led to their advent, and the resultant changes. Basic science investigations, whether in vitro or in vivo (in animal studies), are critical to our understanding of toxicity. Fundamental principles should not be ignored, and commercial interests should not be allowed to influence decisions in regard to patient safety. Politics may play a role in the best of scientific publications, especially when pressure is brought to bear. Irrespective of these problems, the scientific literature is far less than perfect, even with the best of intentions. By carefully adhering to science, predictable crises can potentially be avoided. And when within such a crisis, science and logic can be used to advance our knowledge more rapidly.

Crises in general arise slowly, influence medical practice slowly, and take many years to thoroughly investigate. However in today’s world, they can assume a life of their own due to the media and the legal system. The changes that result from such crises take years to play out, however the increased globalization of science and medicine is speeding this process. Keeping the discussion public, making all the scientific data available, and disseminating this in a clear message worldwide are critical.

Risk assessment and pharmacovigilance of Gadolinium compounds

Referent(en): Thomsen H
Kurzfassung: The commercially available agents for MRI are for the time being based on gadolinium (Gd). Gd does not occur naturally in man. Enhanced MRI is clinically indicated in about 40% of MRI examinations. A contrast medium without adverse reactions does not exist. Due to the toxicity of Gd, the atom is bound to a chelate in order to protect the body from the toxic atoms. The chelate may be linear or macrocyclic. Both the linear and macrocyclic chelates may be either ionic or non-ionic. The macrocyclic chelate has the best grab on the Gd atom (the lowest release if any of the Gd from the chelate in blood). The non-ionic linear chelates have the poorest grab.

There is no difference in the prevalence of acute non-renal adverse reactions between the various Gd agents despite the fact that the osmolality of the various agents varies from 600 mOsm til 2000 mOsm. The viscosity is low. It is the same acute adverse reactions that are seen after all other contrast media (for CT or UL). Acute renal adverse reactions (also called CIN) occur extremely rarely, if they occur at all, due to the low number of moles used for MRI (for CT: 8 times more moles of the agent are used). Patients who undergo an unenhanced MRI examination may experience some of the mild adverse reactions, which contrast media have been blamed for. Late adverse reactions to Gd based contrast media has not been reported (yet?).

When it comes to very late adverse reactions, Gd based contrast media differ from other contrast agents, as the adverse reactions are related to the gadolinium atom as well as the prevalence is higher after exposure to the least stable agents (non-ionic linear chelates) than after exposure to the most stable agents (macrocyclic chelates). Patients with severely reduced renal function or on dialysis may develop nephrogenic systemic fibrosis (NSF) after exposure to the least stable agents (“high risk agents” according to the EMA classification). After a couple of injections of Gd based contrast media the signal intensity in some parts of the brain (mainly the basal ganglia) may increase probably due to gadolinium although it can also be due to manganese, iron, lipid and calcium. It is only been seen after exposure to linear chelates. Finally gadolinium may also accumulate in the skin and cause so-called gadolinium plaques. Again they are seen after exposure to the least stable agents. Both increased signal intensity on T1-weighted images in the brain and gadolinium plaques occur both in patients with normal and decreased renal function.

Is it time to consider not using the agents with highest risk of NSF at all? In Denmark the least stable agents (high risk of NSF agents) are no longer available. Danish radiologists voluntarily stopped using the high risk agents.
**Contrast enhanced MR Angiography** is a robust technology to depict vascular lumen by shortening the blood T1 values with intravenously administered gadolinium chelate, and reconstruct the acquired signals on T1 weighted images in a 3D fashion. Although safe in most cases, contrast enhanced MRA is sometimes unavailable in patients with allergy to contrast media or severely impaired renal function.

In such cases, non-contrast MRA is a useful adjunct to enhanced MRA. Magnetic resonance imaging (MRI) is a unique modality that allows for measurements of location and the velocities of the moving protons, which abilities are utilized for non-contrast MRA. Utilizing fast spin echo type of sequences, many vendors have released the non-contrast MRA postprocessed by subtracting images between systole and diastole, which are termed FBI, TRANCE, Native, Inhance delta, etc. Arterial spin labeling (ASL) based non-contrast MRA are also utilized as time SLIP, NATIVE true FISP, B-TRANCE, IFIR, VASC-ASL. The capability to chase flowing blood protons can also be exploited by ECG gated 3D phase contrast MRI (4D Flow). This technique used to be time consuming; however, recently innovated MR hardwares and emerging technologies have made 4D Flow performable in a reasonable period of time. Combined use of appropriate post-processing software, in-vivo assessment of the flowing blood is readily available in a 3D fashion as 3D vector fields, streamlines or pathlines. Not just depiction of the flow, the accurate velocimetry allows for quantitative assessment of the blood flow velocities and flow volume supplying to specific organs. The capability of measuring temporal changes of the velocities and locations on the whole 3D axes of the flowing protons provide us an access to new hemodynamic derivatives such as wall shear stress (WSS) or oscillatory shear index (OSI). Abnormally low WSS or significantly high OSI are known to trigger atherosclerotic changes by inappropriate stimuli to the mechanoreceptors of the vascular endothelium. MR flow visualization may not merely allow for the assessment of the current vascular pathologies, but may open a door to predict the future integrities of the vessels, and thereby, contribute to the preventative medicine for the cardiovascular pathologies.

In this talk, several unenhanced MRA technologies to depict vascular anatomies and to assess flow velocities are referred, and the potentials of those technologies in assessing vascular and other pathologies are discussed.

<table>
<thead>
<tr>
<th>RöKo INT 101.4</th>
<th>Alternative Contrast Mechanisms in clinical MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>13:00 Uhr</td>
<td>Referent(en): Duerk J</td>
</tr>
<tr>
<td>RöKo INT 101.5</td>
<td>Diskussion</td>
</tr>
<tr>
<td>13:20 Uhr</td>
<td></td>
</tr>
</tbody>
</table>