Assessment of the Adverse Reactions of Gadobenate Dimeglumine (Gd-BOPTA) from Preliminary Clinical Experience in Taiwan

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Gd-BOPTA (MultiHance®) is a gadolinium-based contrast agent that was approved in Taiwan in March, 2004. It was supplied as sterile, clear, colorless solution with the concentration of 0.5M in a ready-for-use form. We conducted this study to evaluate the safety profile of this particular gadolinium chelate in 1041 patients referred for contrast-enhanced MRI studies in our hospital between October 2004 and February 2005. Of these cases, 188 females and 214 males aged between 22-96 years (mean, 57.5 years) without fasting were injected with hand-push single bolus injection (2 mL/second) of a dosage of 0.2ml/kg body weight (0.1 mmol/kg). The other 323 females and 316 males aged between 21-94 years (mean, 58.6 years) with 4 hours fasting were injected by slow injection (10 mL/minute). A total of 16 (1.54%) cases experienced adverse reactions (ARs) considered to have definite relationship to Gd-BOPTA. All ARs were graded as mild and each of the patients recovered fully without sequelae. No definite serious Gd-BOPTA-related ARs occurred in our cases. There is no significant difference of the incidences of ARs including nausea, vomiting, skin rash, dizziness and chillness between these two groups. There were completely no ARs in all 9 cases older than 91 years. Our results confirm Gd-BOPTA (Gadobenate Dimeglumine, MultiHance) is a safe contrast agent for routine MRI studies in clinical patients. Our experiences also showed that the incidence of its ARs is not significantly influenced by the injection rate and fasting status prior to injection of the agent.

Key words: Gadobenate dimeglumine; Gd-BOPTA; MR contrast media; MR imaging; safety of MR contrast media

Gd-BOPTA (MultiHance®) is a gadolinium-based contrast agent that is currently approved in Europe for magnetic resonance imaging (MRI) of the central nervous system (CNS) and liver [1]. Unlike other available gadolinium-based agents that are excreted exclusively by glomerular filtration through the kidneys [2-6], Gd-BOPTA is eliminated through both the renal and hepatobiliary pathways [7]. Further more, a capacity for weak and transient interaction with serum albumin [8] provides Gd-BOPTA with an in vivo T1 relaxivity that is approximately twice that of the conventional “extracellular” gadolinium chelates [9].

Our hospital is the first site using Gd-BOPTA since its approval for clinical application in Taiwan in March, 2004. We conducted this study to evaluate the safety profile of this particular gadolinium chelate in the 1041 patients administered Gd-BOPTA for contrast-enhanced MRI studies in our hospital. We are also going to examine the influence of different injection and preparation methods on the adverse reaction of Gd-BOPTA.

MATERIALS AND METHODS

Studies and Cases
All the 1041 adult patients enrolled in this study...
had known or were suspected to have a lesion of the CNS (including brain and spine), the neck, the liver, abdomen or pelvis. This clinical study of the safety profile of Gd-BOPTA was carried out between October 2004 and February 2005 (Table 1). Of the 1041 cases, 402 cases were studied in initial two months and they were considered as group I. They were 188 males and 214 females. Their ages were ranged between 22-96 years (mean, 57.5 years). The other 639 cases were studied in the following three months and they were considered as group II. They were 323 females and 316 males. Their ages were also ranged between 21-94 years (mean, 58.6 years). All of them had no history of hypersensitivity to any food or drug prior to this study.

Contrast agent dosing and administration

Gd-BOPTA (Gadobenate Dimeglumine, MultiHance®, Bracco Imaging SpA, Milano, Italy) was provided as a sterile, clear, colorless, ready for injection solution of 0.5M. The contrast agent was administered through a 21-gauge indwelling venous catheter set at forearm. A hand-push single bolus injection (2 mL/second) of a dosage of 0.2ml/kg body weight (0.1 mmol/kg) was applied in 402 cases of group I. Similar dosage at slower injection rate (10mL/minute) was used in another 639 cases of group II. No fasting and 4 hours fasting prior to injection of the agent were asked for group I and group II respectively. The injection and fasting preparation methods in group I are similar to adminstration of Gd-DTPA in our hospital.

Monitoring of Safety

The safety and tolerability of Gd-BOPTA were generally evaluated by means of:

1. General inspection of the patients before injection of the agent and immediately after MR study;
2. Monitoring for any adverse reaction (AR) including discomfort at injection site, localized edema, headache, dizziness, nausea, vomiting, dry mouth, taste perversion, abdominal pain, pruritus, skin rash, chillness and tremor during injection during intra-venous administration of the agent, and continuous follow up of each AR and subjective physical discomfort up to 7 days following injection.

For each AR, the investigators were asked to record the onset time, the duration, the treatment required, if any, and the outcome. Non-serious AR was graded for intensity (mild, moderate or severe) and for relationship to the study agent (definite, probable, doubtful or unrelated). An AR was classified as serious if it met the definition established by the U.S. Food and Drug Administration (FDA), i.e., it was fatal or life-threatening, permanently or significantly disabling or incapacitating, requiring or prolonging, in-patient hospitalization, or resulting in congenital anomaly/birth defect [10]. All serious or unexpected ARs occurring during the follow-up period were recorded.

The ARs of group I and II with different injection rate and fasting preparation were analyzed with Chi square test to assess whether there is any statistically significant difference in the incidence of ARs. Such difference is not significant statistically if P > 0.05.

RESULTS

Of the 1041 cases enrolled in this study, a total of 16 (1.54%) cases experienced ARs considered to have definite relationship to Gd-BOPTA. All ARs were graded as mild and each of the patients recovered fully without sequelae. No definite serious Gd-BOPTA-related ARs occurred in our cases.

A breakdown of the incidence of ARs by age groups, sexes is given in Table 2. The incidences of ARs in each decade age groups above 21 to 90-year-old were 0.19%, 0.38%, 0.28%, 0.19%, 0.28%, 0.19% and 0.09% respectively. There were 0.98% of ARs in female and 2.08% in male respectively. There were completely no ARs in all 9 cases older than 91 years.

A summary of the ARs occurred in the 16 adult cases of our study is presented in Table 3. The most frequently occurring reactions were nausea (9 cases; 0.86%), vomiting (5 cases; 0.48%), skin rash (3 cases; 0.29%), dizziness (4 cases; 0.38%), chillness (1 case; 0.10%). The overall incidence of adverse reaction was 1.54% (16 cases). No any single case in our study experienced discomfort at injection site, localized edema, headache, dry mouth, taste perversion, abdominal pain, pruritus and tremor.

The incidences of ARs of the two groups with different ways of injection of the contrast agent and fasting period prior to injection were 1.00% versus 0.7% of nausea, 0.50% versus 0.47% of vomiting, 0.25% versus 0.31% of skin rash, 0.75% versus 0.16% of dizziness, 0% versus 0.16% of chillness and 2.24% versus 1.10% of overall ARs respectively (Table 4). There is no significant difference of the incidences of ARs between these two groups.

DISCUSSION

Gd-BOPTA combines the properties of conventional non-specific, extracellularly-distributed gadolinium-based contrast agents with those of
contrast agents targeted specifically to the liver [1]. It has a capacity for weak and transient interaction with serum albumin [8] and in consequence, an increased T1 relaxivity in blood relative to other gadolinium agents [11], Gd-BOPTA can also be considered a viable alternative to the intravascular 'blood-pool' agents currently being developed for MRA. Thus, in terms of its overall clinical usefulness, Gd-BOPTA may be potentially useful for many of the indications for which other contrast agents are currently in use or under development [12]. Our hospital is the first site using Gd-BOPTA since its approval for clinical application in Taiwan in March, 2004. Therefore, we conducted this study to assess the safety profile of Gd-

Table 1. Number of cases in each age groups and sexes in different patient grouping enrolled in the study to evaluate adverse reactions after intravenous injection of Gd-BOPTA (MultiHance) over a 5 months period in Taiwan.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Group I</th>
<th></th>
<th></th>
<th>Group II</th>
<th></th>
<th></th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female (n=188)</td>
<td>Male (n=214)</td>
<td>Total (n=402)</td>
<td>Female (n=323)</td>
<td>Male (n=316)</td>
<td>Total (n=639)</td>
<td></td>
</tr>
<tr>
<td>21–30</td>
<td>18</td>
<td>8</td>
<td>26</td>
<td>22</td>
<td>15</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>31–40</td>
<td>21</td>
<td>25</td>
<td>46</td>
<td>51</td>
<td>22</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>41–50</td>
<td>31</td>
<td>41</td>
<td>72</td>
<td>49</td>
<td>51</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>51–60</td>
<td>40</td>
<td>32</td>
<td>72</td>
<td>42</td>
<td>63</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>61–70</td>
<td>32</td>
<td>50</td>
<td>82</td>
<td>58</td>
<td>73</td>
<td>131</td>
<td></td>
</tr>
<tr>
<td>71–80</td>
<td>30</td>
<td>39</td>
<td>69</td>
<td>76</td>
<td>69</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>81–90</td>
<td>13</td>
<td>19</td>
<td>32</td>
<td>21</td>
<td>21</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>91–100</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>188</td>
<td>214</td>
<td>402</td>
<td>323</td>
<td>316</td>
<td>639</td>
<td></td>
</tr>
</tbody>
</table>

Note: Periods of data collection; injection rate, fasting preparation:
Group I = Oct, 2004-Nov, 2004; 402 cases with bolus injection by hand, no fasting.
Group II = Dec, 2004-Feb, 2005; 639 cases with slow slow injection, 4 hours fasting.

Table 2. Incidences of adverse reactions in 1041 adult cases received intravenous injection of Gd-BOPTA (MultiHance) over a 5 months period in Taiwan.

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Group I</th>
<th></th>
<th></th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female (n=188)</td>
<td>Male (n=214)</td>
<td>Total (n=402)</td>
<td>Female (n=511)</td>
</tr>
<tr>
<td>21–30</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>31–40</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>41–50</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>51–60</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>61–70</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>71–80</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>81–90</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>91–100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>5</td>
<td>9</td>
<td>5</td>
</tr>
</tbody>
</table>

Note: Please refer to note of Table 1.

Table 3. Incidences of various types of adverse reactions in 1041 adult cases received intravenous injection of Gd-BOPTA (MultiHance) over a 5 months period.

<table>
<thead>
<tr>
<th>Studied Groups</th>
<th>Types of adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nausea*</td>
</tr>
<tr>
<td>I (n=402)</td>
<td>4(1.00%)</td>
</tr>
<tr>
<td>II (n=639)</td>
<td>5(0.78%)</td>
</tr>
<tr>
<td>I + II (n=1041)</td>
<td>9(0.86%)</td>
</tr>
</tbody>
</table>

Note: Please refer to note of Table 1. *p > 0.05
BOPTA with different injection and preparation methods in our population that had not been reported before.

In recent years, a number of excellent review articles have summarized the safety profiles of the currently available MR contrast agents with an overall incidences ranging from 4.9 to 47.9% [13-18]. A great variety of the incidence of ARs following administration of Gd-BOPTA from 8.7 to 25.6% had been reported [18, 19]. In a latest cumulative report of the overall incidence of ARs for 2367 adult patient volunteers receiving Gd-BOPTA in 56 clinical trials conducted in Europe and the USA by September 2000 was 19.8% [12] The wide variation of the reported incidences might mainly be influenced by the methodology applied in different studies. However, in post-marketing surveillance by patients’ voluntary reports, the adverse drug reactions of Gd-BOPTA were recorded in just 24 patients (< 0.03%) out of a total of 99711 patients received the contrast agent in Europe between October 1998 and October 2000 [12]. There was 1.5% of non-serious self-resolved ARs occurring in our cases. Such number is relatively higher than the experiences of using Gd-BOPTA in Europe. Owing to the voluntary nature of reporting in the post-marketing surveillance, it may tend to under-estimate the number of non-serious, mild, and moderate events occurring in routine clinical practice [12]. The criteria in judging the ARs by different institutes may also influenced the results. However, the incidences of ARs is still very low in comparison with other former reports [15, 18, 19].

The incidence of ARs in our study showed that it was not affected by different age groups and genders. Surprisingly, the incidence of ARs was also not influenced by the injection rate and fasting period prior to injection of the agent. Therefore we might be able to adjust the strict routine requirement of fasting for at least four hours prior to contrast injection. We can shorten the fasting time for easier schedule arrangement and to improve patient throughput of the MRI examination.

The ARs occurred most frequently after Gd-BOPTA administration were similar to those reported after the administration of other gadolinium agents: headache, injection site reaction, nausea, taste perversion, and vasodilation [13, 14]. These events after Gd-BOPTA injection occurred in a dose- and study-independent manner with a frequency of 2.6% or less which is similar to or less than the frequencies observed in studies with other gadolinium agents [15-18, 20]. The most frequently occurring overall reactions in our cases were nausea (0.86%), vomiting (0.48%), skin rash (0.29%), dizziness (0.38%), chillness (0.1%). All of them were mild and transient, and subsided completely shortly after the examinations. No definite serious ARs in all of our patients receiving Gd-BOPTA had been found throughout this study. Moreover, there was no definite delayed ARs occurring up to one week after injection.

Regarding the unique properties of Gd-BOPTA, i.e., a capacity for weak and transient interaction with serum albumin [7] and 2-4% of the injected dose eliminated though the biliary pathway [5, 6], there was no evidence in any of the studies to dates suggested that these features might affect its overall safety profile [17, 19-21].

CONCLUSIONS

Results of the present study performed in Taiwan appear to confirm that Gd-BOPTA (Gadobenate Dimeglumine, MultiHance) is a safe contrast agent for routine MRI studies. Our experiences also showed that the incidence of its ARs is not significantly influenced by the injection rate and fasting period prior to injection of the agent.

ACKNOWLEDGEMENT

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Gadobenate Dimeglumine (Gd-BOPTA) 的不良反應：
以台灣的初步臨床經驗作評估

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Gd-BOPTA（Gadobenate Dimeglumine, MultiHance®, Bracco Imaging SpA, Milano, Italy）屬於釓類MRI顯影劑。它於2004年3月經衛生署核准在台灣使用。它以無菌清澄無色的隨時可用0.5M液體包裝供應。本文針對於2004年10月至2005年2月首先利用Gd-BOPTA在本院進行增強對比MRI檢查的1041名患者進行本劑的安全性研究。所有患者的使用劑量為0.2ml/kg（體重）（0.1 mmol/kg），其中第一組為年齡22-96歲（平均57.5歲）的188女性和214男性，本組未預先禁食並用手快速注射（2 mL/秒）第二組為年齡21-94歲（平均58.6歲）的323女性和316男性，本組預先禁食4小時及用手緩慢注射（10 mL/分）。總共有16名（1.5%）患者的不良反應確定和Gd-BOPTA有關，全部屬於輕微不良反應（ARs），而且都完全消退。在兩組的ARs包括噁心、嘔吐、皮疹、暈眩、寒顫等並無有意義的差異。在9名91歲的受檢者都未發生ARs。我們的結果確定Gd-BOPTA是一種可以在所有例行MRI檢查安全使用的顯影劑，同時顯示Gd-BOPTA的ARs並不受注射速度和注射前禁食所影響。

關鍵詞：Gadobenate dimeglumine；Gd-BOPTA；MR顯影劑；MR造影；MultiHance；MR顯影劑的安全性