Safety of Gadopentetate Dimeglumine after 120 Million Administrations over 25 Years of Clinical Use

Toru Matsumura*, Masakane Hayakawa1, Fumiki Shimada1, Masahisa Yabuki1, Susan Dohanish2, Petra Palkowitsch3, and Kohki Yoshikawa4

1Bayer Yakuhin Ltd., Medical Affairs Pharmacovigilance
4–9 Umeda 2-chome, Kita-ku, Osaka 530–0001, Japan
2,3Bayer Healthcare Pharmaceuticals, 2Montville, NJ, USA, and 3Berlin, Germany
4Komazawa University, Tokyo, Japan

(Received March 1, 2013; Accepted July 17, 2013; published online October 29, 2013)

Purpose: We evaluated the safety of gadopentetate dimeglumine (Gd-DTPA), the first contrast agent for magnetic resonance imaging, using pharmacovigilance data for spontaneously reported adverse events (AEs) after 120 million cumulative administrations worldwide.

Methods: We analyzed spontaneously reported AEs for Gd-DTPA for pre-specified time periods between 1988 and 2011.

Results: Since the market introduction of Gd-DTPA in 1988, its global utilization reached 120 million cumulative administrations in 2011, more than 80% of which was by the USA, countries in the European Union (EU), and Japan. The global AE reporting rate was 21.2 in 100,000 administrations in 1988 and 14.4 in 100,000 administrations by 2011. Regional differences included higher reporting rates in the USA and Japan, and reporting rates lower than global rates in the EU. The reported rate of global serious AEs changed from 1.4 in 100,000 administrations in 1988 to 4.0 in 100,000 administrations in 2011. The highest number of reports of nephrogenic systemic fibrosis (NSF) was received from 2006 to 2008. Since 2009, no report of a current onset of NSF has been received. The reduced report rate of NSF may be due to increased awareness about the use of gadolinium-based contrast agents (GBCAs).

Conclusion: After more than 120 million cumulative administrations, Gd-DTPA is a widely used GBCA that shows a consistently low and stable incidence of AEs.

Keywords: adverse event, gadopentetate dimeglumine, magnetic resonance imaging, MR contrast media, safety

Introduction

Magnetic resonance (MR) imaging is an important clinical diagnostic tool. Advances in hardware and software that have enhanced the signal-to-noise ratio and improvements in contrast resolution with gadolinium-based contrast agents (GBCAs) make contrast-enhanced MR imaging (CE-MRI) a comparable or better diagnostic tool than computed tomography and other conventional imaging methods.2–5 Further advances in dynamic CE-MRI perfusion6 and contrast-enhanced magnetic resonance angiography (MRA)7 have improved the efficiency of clinical diagnoses, and highlight the importance of imaging techniques in diagnostic medicine.

The first MR imaging contrast agent, gadopentetate dimeglumine (Gd-DTPA), was introduced in 1988. Since its launch, Gd-DTPA remains the most used GBCA in the USA and Japan, which together with the European Union (EU) constitute the majority of the global MR imaging market.8 Of the 9 GBCAs currently approved for intravenous ad-
ministration for CE-MRI, Gd-DTPA was the first intravenous agent indicated for whole body and central nervous system (CNS) use, with a dose of 0.1 to 0.3 mmol/kg. GBCAs have a favorable overall safety and tolerability profile, with a lower overall incidence of adverse events (AEs) than iodinated X-ray contrast media, even when considering reports in 2006 of nephrogenic systemic fibrosis (NSF) associated with GBCAs. Moreover, the overall incidence of AEs is lower with MR imaging contrast media than non-ionic X-ray contrast media, probably as a result of the lower doses of contrasting agents used in CE-MRI.

The spontaneous AE reporting database contains more than 25 years of data on the safety and tolerability of Gd-DTPA. We used pharmacovigilance data from the database to evaluate its safety and tolerability in the USA, EU, and Japan after 120 million administrations worldwide. In addition, we compared new data with previously analyzed and published analyses for Gd-DTPA.

**Materials and Methods**

**Sources of data**

The aim of this study was to analyze AEs reported in the global pharmacovigilance database for Gd-DTPA from its launch in 1988 to December 31, 2011. The database consists of spontaneous, postmarketing AE reports from healthcare professionals, patients, other individuals, literature reports, data from clinical trials, and observational/postmarketing surveillance studies. Internal unit sales data from the manufacturer (Bayer Healthcare Pharmaceuticals, Berlin, Germany), in conjunction with data from Arlington Medical Resources, Inc. (AMR; Malvern, PA, USA), were used to determine the annual number of Gd-DTPA administrations.

The geographic distribution of imaging procedures by indication were analyzed using internal unit sales data from the manufacturer and AMR. Data were organized into 3 geographic categories—the USA, EU, and Japan.

Utilization data was divided into time periods and cumulative administrations: 1988 to 1993 (10 million administrations); 1994 to 1997 (20 million); 1998 to 2002 (45 million); 2003 to 2005 (69 million); 2006 to 2009 (102 million), and 2009 to 2011 (120 million to December 31, 2011). Detailed data for time periods up to 2005 have been detailed previously.

**Statistical analysis**

Reported AE rates were calculated based on prescription denominators for the observed utilization periods (10, 20, 45, 69, 102, and 120 million administrations). Longitudinal changes were described and compared with AE data of the 3 major regions—the USA, EU, and Japan. Statistical significance tests were not performed.

**Results**

**Utilization rate**

Table 1 summarizes global annual utilization for Gd-DTPA by time period. The mean global annual utilization for Gd-DTPA increased from 1.6 million doses with 10 million cumulative administrations in the first period, 1988 to 1993, to 6.9 million doses and 120 million cumulative administrations by 2009 to 2011.

Since 1988, there have been approximately 60 million administrations in the USA, 37 million in the EU, and 13 million in Japan. These 3 regions together have utilized more than 80% of the global total Gd-DTPA administrations.

In Japan, the mean annual utilization for Gd-DTPA of 0.3 million administrations in 1988 to 1993 after 1.5 million cumulative administrations

**Table 1.** Global and regional utilization for gadopentetate dimeglumine (Gd-DTPA) from 1988 to 2011

| Global administrations | 1988–1993 | 1994–1997 | 1998–2002 | 2003–2005 | 2006–2009* | 2009–2011† |
|------------------------|-----------|----------|----------|----------|-----------|-----------|
| Cumulative administrations (millions) | 10 | 20 | 45 | 69 | 102 | 120 |
| Mean annual utilization (millions) | 1.6 | 2.5 | 5.0 | 8.0 | 9.7 | 6.9 |
| Market share Gd-DTPA (%) | 93.5 | 60.6 | 53.8 | 47.2 | 40.0 | 30.0 |

| Japan administrations | 1988–1993 | 1994–1997 | 1998–2002 | 2003–2005 | 2006–2009* | 2009–2011† |
|------------------------|-----------|----------|----------|----------|-----------|-----------|
| Administrations (millions) | 1.5 | 2.5 | 2.9 | 2.1 | 2.5 | 1.6 |
| Mean annual utilization (millions) | 0.3 | 0.6 | 0.6 | 0.7 | 0.7 | 0.6 |
| Market share Gd-DTPA (%) | 100 | 87.8 | 63.0 | 49.0 | 47.0 | 41.2 |

* 2006 to May 31, 2009; † June 1, 2009 to December 31, 2011.
increased to 0.6 million administrations by 2009 to 2011, with a cumulative 13.2 million administrations (Table 1).

Approved indications
By 2006, the largest MR imaging markets were the USA, France, Germany, Italy, the UK, and Japan.16 Table 2 summarizes the approved indications and recommended doses for Gd-DTPA in these countries. Gd-DTPA is approved for both adult and pediatric indications. The most common dose is 0.1 mmol/kg bodyweight, but in some regions a double dose (0.2 mmol/kg bodyweight) is approved for MRA use, and doses of up to 0.3 mmol/kg are approved for use in imaging the CNS.

Nonserious adverse events
Table 3 summarizes adverse events (AEs) reported globally and by region. Between 1988 and 2011, a total of 17,287 nonserious AEs had been reported. The global AE report rate per 100,000 administrations was 21.2 in 1988 and 14.4 by 2011 (Table 3). There were regional differences in the AE reporting rate per 100,000 administrations from 1988 to 2011. In the USA, the AE report rate per 100,000 administrations was 29.7 in 1988 to 1993, increased to 30.2 in 1994 to 1997, gradually decreased from 1998 to 2009, and reached 8.9 in 2009 to 2011. In the EU, the AE report rate remained constant over the time periods analyzed (Table 3). In Japan, the AE report rate per 100,000 administrations was very low, 0.9, in 1988 to 1993, increased to 27.2 in 1998 to 2002, and then decreased to 8.9 in 2009 to 2011.

Table 2. Summary of approved indications of gadopentetate dimeglumine (Gd-DTPA) in the 6 largest magnetic resonance (MR) imaging markets

| Adult | USA | France | Germany | Italy | UK | Japan |
|-------|-----|--------|---------|-------|----|-------|
| Central nervous system (CNS)/spine Whole body (WB) | | | | | | |
| Lesion with abnormal vascularity (excluding heart) | Yes, and vasculature and other | Yes, for oncology, herniated disk, myocardium | Yes, for oncology | Yes, particularly for oncology | Yes, evaluation of renal function | Yes |
| Newborns | CNS, WB | CNS, WB | CNS* | CNS | CNS, WB | CNS, WB |
| Children (>2 years) | CNS, WB | CNS, WB | CNS, WB | CNS, WB | CNS, WB | CNS, WB |
| Administration | | | | | | |
| Recommended dose (maximal WB dose)† mmol/kg | | | | | | |
| CNS/spine | 0.1(0.1) | 0.1(0.3) | 0.1(0.3) | 0.1(0.3) | 0.1(0.3) | 0.1 |
| WB | 0.1(0.1) | 0.1(0.3) | 0.1(0.3) | 0.1(0.3) | 0.1(0.3) | 0.1(0.05) |
| Flow rate (mL/s) | 0.6 | NS | NS | NS | NS | BI, if required |
| Saline flush (mL) | 5.0 | NS | NS | NS | NS | NS |

Bl, bolus injection; MRA, magnetic resonance angiography; NS, not stated.
* Hand injection only; † maximal dose 0.3 mmol/kg indicated only for adult use; ‡ if target organ is the kidney.
Table 3. Spontaneously reported nonserious adverse events (AEs) for gadopentetate dimeglumine (Gd-DTPA) by time period

| Time period | 1988–1993 | 1994–1997 | 1998–2002 | 2003–2005 | 2006–2009* | 2009–2011† | Total |
|-------------|-----------|-----------|-----------|-----------|-----------|-----------|-------|
| Cumulative administrations (millions) | 10 | 20 | 45 | 69 | 102 | 120 | 120 |
| Global | Estimated administrations (millions) | 10 | 10 | 25 | 24 | 33 | 18 | 120 |
| | Total number of AEs for time period | 2,121 | 2,630 | 4,113 | 2,852 | 4,051 | 1,520 | 17,287 |
| | Report rate/100,000 administrations | 21.2 | 26.3 | 16.5 | 11.9 | 12.3 | 8.4 | 14.4 |
| USA | Estimated administrations (millions) | 5.3 | 5.3 | 11.6 | 11.3 | 15.5 | 10.4 | 59.3 |
| | Total number of AEs for time period | 1,580 | 1,596 | 2,030 | 1,258 | 1,717 | 925 | 9,106 |
| | Report rate/100,000 administrations | 29.7 | 30.2 | 17.6 | 11.1 | 11.1 | 8.9 | 15.2 |
| EU | Estimated administrations (millions) | 2.3 | 6.4 | 10.3 | 7.7 | 7.8 | 2.7 | 37.1 |
| | Total number of AEs for time period | 119 | 317 | 574 | 449 | 384 | 138 | 1,981 |
| | Report rate/100,000 administrations | 5.2 | 5.0 | 5.6 | 5.9 | 4.9 | 5.1 | 5.3 |
| Japan | Estimated administrations (millions) | 1.5 | 2.5 | 2.9 | 2.1 | 2.5 | 1.6 | 13.2 |
| | Total number of AEs for time period | 13 | 552 | 799 | 379 | 291 | 143 | 2,177 |
| | Report rate/100,000 administrations | 0.9 | 21.7 | 27.2 | 17.9 | 11.6 | 8.9 | 16.4 |

EU, European Union
* 2006 to May 31, 2009; † June 1, 2009 to December 31, 2011.

Table 4. Spontaneous reported serious adverse events (SAEs) for gadopentetate dimeglumine (Gd-DTPA) by time period

| Time period | 1988–1993 | 1994–1997 | 1998–2002 | 2003–2005 | 2006–2009* | 2009–2011† | Total |
|-------------|-----------|-----------|-----------|-----------|-----------|-----------|-------|
| Cumulative administrations (millions) | 10 | 20 | 45 | 69 | 102 | 120 | 120 |
| Global | Total number of SAEs | 144 | 188 | 522 | 500 | 1,244 | 728 | 3,326 |
| | Rate/100,000 administrations | 1.4 | 1.9 | 2.1 | 2.1 | 3.8 | 4.0 | 2.8 |
| USA | Total number of SAEs | 83 | 76 | 144 | 222 | 678 | 454 | 1,657 |
| | Rate/100,000 administrations | 1.6 | 1.4 | 1.2 | 2.0 | 4.4 | 4.4 | 2.8 |
| EU | Total number of SAEs | 25 | 53 | 221 | 181 | 245 | 101 | 826 |
| | Rate/100,000 administrations | 1.1 | 0.8 | 2.1 | 2.4 | 3.1 | 3.7 | 2.2 |
| Japan | Total number of SAEs | 4 | 52 | 141 | 47 | 86 | 57 | 387 |
| | Rate/100,000 administrations | 0.3 | 2.0 | 4.8 | 2.2 | 3.4 | 3.5 | 2.9 |

EU, European Union
* 2006 to May 31, 2009; † June 1, 2009 to December 31, 2011.

tween 2006 and 2011. No unconfounded cases of NSF related to Gd-DTPA exposure were reported in Japan between 2006 and 2011 (Table 6). Globally, no possibly related reports of NSF were received with onset after 2009 (Table 7).

Discussion
After 120 million cumulative administrations of Gd-DTPA worldwide from 1988 to 2011, the incidence of AEs has remained stable over time, in particular among those reported between 1988 and
Table 5. Commonly reported adverse events (AEs) by time period

| Time period       | 1988–1993 | 1994–1997 | 1998–2002 | 2003–2005 | 2006–2009 | 2009–2011 | Total |
|-------------------|-----------|-----------|-----------|-----------|-----------|-----------|-------|
| Cumulative administrations (millions) | 10 | 20 | 45 | 69 | 102 | 120 | 120 |
| Number of AEs (rate/100,000 administrations)* | Nausea | 596(6.0) | 725(7.3) | 1,151(4.6) | 697(2.9) | 780(2.4) | 414(2.3) | 4,363(3.6) |
| | Urticaria | 508(5.1) | 548(5.5) | 880(3.5) | 676(2.8) | 905(2.7) | 483(2.7) | 4,000(3.3) |
| | Vomiting | 386(3.9) | 675(6.8) | 939(3.8) | 537(2.2) | 675(2.1) | 337(1.9) | 3,549(3.0) |
| | Rash/erythema/exanthema | 186(1.9) | 373(3.7) | 649(2.6) | 519(2.2) | 886(2.7) | 476(2.6) | 3,089(2.6) |
| | Pruritus | 251(2.5) | 277(2.8) | 474(1.9) | 398(1.7) | 622(1.9) | 337(2.0) | 2,383(2.0) |
| Clinically relevant AEs | Syncope/unconsciousness | 29(0.3) | 64(0.6) | 96(0.4) | 87(0.4) | 109(0.3) | 32(0.2) | 417(0.4) |
| | Shock | 15(0.2) | 38(0.4) | 89(0.4) | 64(0.3) | 68(0.2) | 86(0.5) | 360(0.3) |
| | Cardiac arrest | 9(0.1) | 18(0.2) | 42(0.2) | 28(0.1) | 35(0.1) | 11(0.1) | 143(0.1) |
| | Respiratory arrest | 17(0.2) | 20(0.2) | 30(0.1) | 21(0.1) | 36(0.1) | 7(0.04) | 131(0.1) |
| | Acute renal failure/increased serum creatinine | 0(0) | 3(0.03) | 37(0.2) | 20(0.1) | 34(0.1) | 28(0.2) | 122(0.1) |
| | Coma | 12(0.1) | 12(0.01) | 22(0.1) | 8(0.01) | 13(0.04) | 2(0.01) | 69(0.1) |
| Deaths | Total number‡ | 33(0.1) | 20(0.1) | 36(0.1) | 27(0.1) | 148(0.1) | 73(0.1) | 337(0.1) |
| Drug related | 7 | 9 | 17 | 13 | 15 | 9 | 70 |

* 2006 to May 31, 2009; † June 1, 2009 to December 31, 2011; ‡ deaths possibly drug related.

Table 6. Reports of nephrogenic systemic fibrosis received by region from 2006 to 2011

| Time period | Cumulative administrations | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 |
|-------------|----------------------------|------|------|------|------|------|------|
| Global      | Total number of reports    | 12   | 96   | 179  | 163  | 74   | 18   |
|             | Possibly related*          | 2    | 19   | 20   | 23   | 6    | 1    |
|             | Rate/100,000 administrations| 0.02 | 0.20 | 0.24 | 0.30 | 0.08 | 0.01 |
| USA         | Total number of reports    | 10   | 77   | 168  | 138  | 64   | 16   |
|             | Possibly related*          | 1    | 18   | 20   | 20   | 5    | 1    |
|             | Rate/100,000 administrations| 0.02 | 0.37 | 0.46 | 0.47 | 0.12 | 0.02 |
| EU          | Total number of reports    | 2    | 17   | 9    | 20   | 6    | 2    |
|             | Possibly related*          | 1    | 1    | 0    | 3    | 1    | 0    |
|             | Rate/100,000 administrations| 0.04 | 0.04 | 0.00 | 0.22 | 0.11 | 0.00 |
| Japan       | Total number of reports    | 0    | 1    | 1    | 4    | 2    | 0    |
|             | Possibly related*          | 0    | 0    | 0    | 0    | 0    | 0    |
|             | Rate/100,000 administrations| 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |

EU, European Union
* **Possibly related** reports were for gadopentetate dimeglumine (Gd-DTPA) only; clinical presentation and histopathology were consistent with the definition of nephrogenic systemic fibrosis developed by Cowper and associates.26

2005 from clinical and post-marketing surveillance studies.13–17 In the Phase I–IV clinical trials, the overall incidence of drug-related AEs was 3.2% (Bayer, data on file). In the Phase I–IIIa studies, which included 2,154 healthy volunteers and patients in the EU and Japan, the incidence of drug-related AEs was 0.6%; in the USA, the incidence was 7.6%.17 In the Phase IIIb–IV studies, the inci-
Table 7. Global possibly related reports of nephrogenic systemic fibrosis categorized by year of onset of disease

| Onset date | Before 2006 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | Unknown date of onset | Total |
|------------|-------------|------|------|------|------|------|------|------------------------|-------|
| Total      | 245         | 115  | 68   | 40   | 6    | 2    | 0    | 66                     | 542   |
| Possibly related | 34   | 17   | 13   | 3    | 0    | 0    | 0    | 4                      | 71    |

Source: Bayer Healthcare Pharmaceuticals pharmacovigilance database for gadopentetate dimeglumine (October 2012).

dence of AEs was 1.5%.17

Analyzing spontaneously reported AEs in conjunction with data from clinical trials provides a better understanding of the safety profile of a drug.18 The advantage of using spontaneously reported AEs from pharmacovigilance databases is that, over time, data will become available for AEs from special patient populations, who may have been excluded from clinical studies and for rare AEs that may only occur after exposure of a large number of patients. In the current analysis, the reported non-SAE rates showed an initial increase after product approval and decreased over time. The latter observation is comparable with the “Weber effect,” in which the number of spontaneously reported AEs for a medication tends to increase in the initial years after product approval and, decrease in subsequent years.19,20 According to the “Weber effect,” the peak of AE reporting is within the first 2 years of use of a drug. In the case of Gd-DTPA, the peak for non-SAE reporting was observed in the first 9 years of use. This “late” peak in reporting may be attributable to the availability of Gd-DTPA as the first contrast agent for MR imaging, so that its use was based on the availability of equipment. Therefore, it might take longer to gain experience with a drug like this, which then might lead to a later peak in AE reporting compared with that for therapeutic drugs.

The analysis showed regional differences in the reported AE rates, with higher rates in the USA and Japan. The lower reported AE rates in EU than the global rates, suggests greater under-reporting for non-SAEs in the EU than other regions. In contrast to the trends observed with non-SAE rates, the reported SAE rates increased in all regions for all analyzed periods. However, since 2006, when it was first suggested that there was a link between GBCAs and the development of NSF in patients with severe kidney impairment,11 the proportion of reported SAEs has increased. Since the recognition of NSF as a potential consequence of GBCA exposure, medical practitioners may have a higher awareness of the occurrence of SAEs and, therefore, are more likely to report SAEs after Gd-DTPA administration. It has been suggested that spontaneous reports of AEs are subject to bias resulting from publicity, prevailing perceptions, and prejudices.21 Moreover, because mild AEs are less likely to be reported as time passes after product approval and physicians have become more familiar with the drug, the proportion of reported SAEs from the overall total is expected to increase, as is the case in this analysis. Because regional reporting rates for SAEs were in line with global rates, it is likely that non-SAEs may be under-reported more often than SAEs.22

The incidence of NSF in patients who have received a GBCA is of interest because the dose of GBCAs, plus multiple other factors, including, but not limited to, history of thrombosis, recent surgery, and the combination of hemodialysis and peritoneal dialysis, have been suggested as significant cofactors for the development of NSF.23 In the USA, all GBCAs now have a boxed warning in their package inserts regarding the possible association with NSF, and all countries contain warnings about the possible association of GBCAs with NSF, leads to increased awareness and appropriate usage of GBCAs by medical experts and a subsequent decline in the incidence of NSF. Interestingly, in Japan, the reason for the low incidence of NSF cases in Japan may be related to the dosing of Gd-DTPA. In a study by Prince and associates24 of 182 reported cases of NSF for which data on GBCA dose was available, 90% of patients had received a dose greater than the standard 0.1 mmol/kg. Therefore, it is possible that administration of high doses of GD-DTPA may be very rare in Japan due to the severe restrictions on dosing by reimbursement guidelines from health insurance providers.

The current analysis showed no clear differences between the USA, EU, and Japan in the types of AEs reported, except for the reports of NSF. Most cases of NSF were reported in the USA or EU, with only a few cases in Japan, despite approximately 20% of global GBCA use in Japan.25 All patients
with possibly related NSF in Japan had received other GBCAs in addition to Gd-DTPA, thus making it impossible to attribute the report to a specific agent. The low number of reports of NSF in Japan is not only true for Gd-DTPA; Tsushima and colleagues found only 14 biopsy-verified cases of NSF in Japan in reviewing the Japanese medical literature database and MedLine from January 2000 to March 2009. In the current study, we reported 2 cases of NSF, but they were not considered to be related to Gd-DTPA administration because both patients received more than one GBCA prior to diagnosis. Since the publicity regarding the possible association between NSF and GBCAs, the incidence of NSF has decreased with the introduction of label changes and other risk minimization measures for all GBCAs, including Gd-DTPA.

Although the USA accounts for approximately 50% of global patient exposure, more than 87% of all NSF reports originated from the USA. The reason for this disproportionality is probably multifactorial, including differential usage patterns and litigation-stimulated reporting. The active solicitation of clients via television commercials and letters in the litigation process in the USA has led to more than 75% of all US reports originating as legal complaints.

This pharmacovigilance study of 25 years of experience and more than 120 million administrations of Gd-DTPA, the most widely used GBCA, shows consistently low and stable rates of AEs over time. Revisions in labeling and practice guidelines, along with education and training about NSF by academic radiology societies, have led to increased awareness about the use of GBCAs, and, in turn, a rapid decline in the very rare incidence of possible drug-related cases of confirmed NSF. The effect of this increased awareness can be easily seen when looking at the onset dates of cases received. Onset of the disease peaked in 2006 and then dramatically began to decline. There has been virtually no new onset of the disease after 2009.

Limitations

Some limitations in the spontaneous reporting of AEs worldwide should be noted in this pharmacovigilance study. SAE reporting was standardized for each country, and no differences were noted among institutions and across countries. For non-SAEs reported, we observed more variability among institutions and across countries in this 25-year study.

Conclusion

The current analysis showed that after more than 120 million cumulative administrations, Gd-DTPA is the most widely used and best documented GBCA, shows a consistently low and stable incidence of AEs, and is regarded as the standard contrast medium for MR imaging. Careful monitoring and appropriate dosing of GBCAs has led to the rapid decline in the incidence of cases of NSF.

Acknowledgments

The authors wish to thank GPV Data Analysis for their contribution in data retrieval. Funding for this study was provided by Bayer Healthcare Pharmaceuticals. Editorial support for the development of this manuscript was provided by Medicus International (London, UK) and funded by Bayer Healthcare Pharmaceuticals.

Conflicts of interest

Toru Matsumura, Masakane Hayakawa, Fumiki Shimada, and Masahisa Yabuki are employees of Bayer Yakuhin Ltd. Susan Dohanish and Petra Palkowitsch are employees of Bayer Healthcare Pharmaceuticals. Kohki Yoshikawana has nothing to disclose.

References

1. DeMarco JK, Willinek WA, Finn JP, Huston J, 3rd. Current state-of-the-art 1.5T and 3T extracranial carotid contrast-enhanced magnetic resonance angiography. Neuroimaging Clin N Am 2012; 22:235–257.
2. Motosugi U, Ichikawa T, Morisaka H, et al. Detection of pancreatic carcinoma and liver metastases with gadoxetic acid-enhanced MR imaging: comparison with contrast-enhanced multi-detector row CT. Radiology 2011; 260:446–453.
3. Seo HJ, Kim MJ, Lee JD, Chung WS, Kim YE. Gadoxetate disodium-enhanced magnetic resonance imaging versus contrast-enhanced 18F-fluorodeoxyglucose positron emission tomography/computed tomography for the detection of colorectal liver metastases. Invest Radiol 2011; 46:548–555.
4. Messiou C, Orton M, Ang JE, et al. Advanced solid tumors treated with cediranib: comparison of dynamic contrast-enhanced MR imaging and CT as markers of vascular activity. Radiology 2012; 265:426–436.
5. Scardapane A, Stabile Ianora A, Sabbà C, et al. Dynamic 4D MR angiography versus multislice CT angiography in the evaluation of vascular hepatic involvement in hereditary haemorrhagic telangiectasia.
tasia. Radiol Med 2012; 117:29–45.

6. Friedman SN, Bambrough PJ, Kotsarini C, Khandanpour N, Hogard N. Semi-automated and automated glioma grading using dynamic susceptibility-weighted contrast-enhanced perfusion MRI relative cerebral blood volume measurements. Br J Radiol 2012; 85:e1204–e1211.

7. Azuma T, Kodama T, Yano T, Suzuki M, Kimura T, Tamaribuchi Y. Improved visualization of intracranial vessels by gradient moment nulling in hybrid of opposite-contrast magnetic resonance angiography (HOP MRA). Magn Reson Med Sci 2010; 9:159–165.

8. Cheng KT, Cheng HY, Leung K. Clinical use of gadobutrol for contrast-enhanced magnetic resonance imaging of neurological diseases. Reports in Medical Imaging 2012; 2012:15–22.

9. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. Radiology 1990; 175:621–628.

10. Schild HH, Kuhl CK, Häubner-Steiner U, Bäohm I, Speck U. Adverse events after unenhanced and monomeric and dimeric contrast-enhanced CT: a prospective randomized controlled trial. Radiology 2006; 240:56–64.

11. Grobner T. Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrol Dial Transplant 2006; 21:1104–1108.

12. World Health Organization. Pharmacovigilance: ensuring the safe use of medicines—WHO policy perspectives on medicines. October 2004; No. 009. Available at: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/. Accessed 28 February 2013.

13. Niendorf HP, Alhassan A, Geens VR, Clauss W. Safety review of gadopentetate dimeglumine. Extended clinical experience after more than five million applications. Invest Radiol 1994; 29 Suppl 2: S179–S182.

14. Niendorf HP, Haustein J, Cornelius I, Alhassan A, Clauss W. Safety of gadolinium-DTPA: extended clinical experience. Magn Reson Med 1991; 22:222–228.

15. Niendorf HP, Alhassan A, Balzer TH, Clauss W, Geens VR. Safety and risk of gadolinium-DTPA: extended clinical experience after more than 20 million applications. Magnevist Monograph. 3rd ed. Oxford: Blackwell Science, 1998:17–27.

16. Knopp MV, Balzer T, Esser M, Kashanian FK, Paul P, Niendorf HP. Assessment of utilization and pharmacovigilance based on spontaneous adverse event reporting of gadopentetate dimeglumine as a magnetic resonance contrast agent after 45 million administrations and 15 years of clinical use. Invest Radiol 2006; 41:491–499.

17. Niendorf HP, Michel A, Lowe A, Dohanish S, Balzer T. Safety and risk of gadolinium-DTPA: extended clinical experience after more than 69 million applications. In: Lemke A-J, Niehues SM, Felix R, et al, eds. Magnevist Monograph. 5th ed. Oxford: Blackwell, 2007; 29–37.

18. Härmark L, van Grootheest AC. Pharmacovigilance: methods, recent developments and future perspectives. Eur J Clin Pharmacol 2008; 64:743–752.

19. Weber JCP. Epidemiology of adverse reactions to nonsteroidal antiinflammatory drugs. In: Rainforest KD, Velo GP, eds. Advances in Inflammation Research. New York: Raven Press. 1984; 1–7.

20. Hartnell NR, Wilson JP. Replication of the Weber effect using postmarketing adverse event reports voluntarily submitted to the United States Food and Drug Administration. Pharmacotherapy 2004; 24:743–749.

21. Fletcher AP. Spontaneous adverse drug reaction reporting vs event monitoring: a comparison. J R Soc Med 1991; 84:341–344.

22. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf 2006; 29:385–396.

23. Heinz-Peer G, Neruda A, Watschinger B, et al. Prevalence of NSF following intravenous gadolinium-contrast media administration in dialysis patients with endstage renal disease. Eur J Radiol 2010; 76:129–134.

24. Prince MR, Zhang HL, Roditi GH, Leiner T, Kucharczyk W. Risk factors for NSF: a literature review. J Magn Reson Imaging 2009; 30:1298–1308.

25. Tsushima Y, Kanal E, Thomsen HS. Nephrogenic systemic fibrosis: risk factors suggested from Japanese published cases. Br J Radiol 2010; 83:590–595.

26. Cowper SE, Rabach M, Girardi M. Clinical and histological findings in nephrogenic systemic fibrosis. Eur J Radiol 2008; 66:191–199.