Safety assessment of gadobenate dimeglumine (MultiHance®): extended clinical experience from phase II studies to post-marketing surveillance

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Introduction
Gadobenate dimeglumine (MultiHance®; Bracco SpA, Milano, Italy) is a gadolinium-based contrast agent approved in Europe for magnetic resonance (MR) imaging of the central nervous system (CNS) and liver and which is currently under investigation for MR imaging of the breast and MR angiography. To date, gadobenate dimeglumine has been administered to 2890 patients in completed clinical trials in Europe and the United States of America (USA). As yet, however, there has not been a consensus analysis of the safety profile of this novel gadolinium chelate. The present review summarizes the safety data on gadobenate dimeglumine deriving from 65 completed Phase II and III clinical trials that comprise the clinical program conducted to date in the USA and Europe in MR imaging of the CNS, liver, heart, breast and in MR Angiography (MRA). Data are also presented on the safety profile of gadobenate dimglumine in patients with kidney or liver failure and after almost 90,000 post-marketing administrations.

Methods
A total of 2367 adult patient volunteers and 110 pediatric subjects received gadobenate dimeglumine in 65 clinical trials completed by September 2000. About 75% of the adult population was recruited in clinical studies in Europe while the remaining 25% was enrolled in studies conducted in the USA. Doses up to 0.3 mmol/kg body weight were administered either as a bolus (2 ml/s) or as an infusion (10 ml/min). The safety and tolerability of gadobenate dimeglumine were generally evaluated by means of: complete physical examination on screening and at 24 hours after study agent injection; continuous patient monitoring for adverse events (AEs) for at least 24 hours following study agent administration; measurement and recording of vital signs just prior to the first administration of study agent, and at periodic intervals up to 72 hours post-dose; 12-lead electrocardiographic (ECG) controls on screening and at different time-points up to 24 hours post-dose; and clinical laboratory investigations (hematology, blood chemistry, and urinalysis) conducted pre-dose and at least 24 hours post-dose. Non-serious adverse events were graded for intensity (mild, moderate, or severe) and for relationship to the study agent (definite, probable, possible, doubtful, unknown or unrelated). All serious or unexpected adverse events occurring within 7 days of contrast administration were recorded.

Results
A total of 468 (19.8%) of the 2367 adult patient volunteers who received gadobenate dimeglumine in 63 clinical trials completed before September 2000 experienced 831 AEs. Of these patients, 357 (15.1%) reported 599 AEs that were considered of definite, probable, possible, doubtful or unknown relationship to gadobenate dimeglumine. Whereas no marked differences in the incidences of AEs were noted between the sexes, a greater incidence of both total and study-agent related events were noted in younger (18-40 years old) compared to older (65 years old) patients and in studies conducted in the USA compared to Europe. No noteworthy trends in the overall incidences of AEs were apparent on the basis of weight, race, dose received or method of injection. The most frequently reported AEs which were considered to potentially have some relationship to gadobenate dimeglumine were headache (45 subjects; 1.9%), injection site reaction (34 subjects; 1.4%), nausea (31 subjects; 1.3%), taste perversion (25 subjects; 1.1%) and vasodilation (24 subjects; 1.0%). All other AEs were reported with an incidence of <1.0% with no indication-related differences apparent. In controlled studies the overall incidence and type of adverse events were similar for gadobenate dimeglumine and comparator (28.6% [79/276] for gadobenate dimeglumine vs. 32.1% [43/134] for gadodiamide in controlled CNS studies; 44.1% [79/179] for gadobenate dimeglumine vs. 44.2% [19/43] for placebo in controlled liver studies; and 12.7% [18/142] for gadobenate dimeglumine vs. 14.9% [7/47] for gadopentetate dimeglumine in controlled breast studies. Changes from baseline in terms of vital signs parameters, ECG changes and laboratory values were minimal and not unexpected; no clinically meaningful trends were apparent. The findings for pediatric studies were similar to those in adult subjects in all respects; the overall incidence of adverse events was 12.7% [14/110] for pediatric subjects administered gadobenate dimeglumine and 14.6% [13/89] for subjects administered gadopentetate dimeglumine. Overall only 15 AEs were reported as being serious and of these only five were considered to be potentially related to gadobenate dimeglumine; two of these were of unknown relationship. Finally, post-marketing surveillance of almost 90,000 doses revealed an overall AE incidence of <0.03% with serious AEs reported for <0.005% of patients.

Discussion
Gadobenate dimeglumine possesses a safety profile that is similar to those of other MR contrast agents that are either commercially available or under development. Phase II and III clinical trials conducted in Europe and the USA, and post-marketing surveillance of almost 90,000 doses, have not revealed any evidence of untoward effects with this agent. Accumulated experience over a 7-year period indicates that gadobenate dimeglumine is safe for use in MR imaging of the CNS, liver, heart and breast and in MR angiography. Furthermore, this agent is also safe for use in pediatric subjects and subjects with renal or liver insufficiency.