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Paradigm and element shift in MR contrast agent applications

Peter A. Rinck

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The Gadolinium Story is the permanent talk of the town: In certain people the injection of some gadolinium contrast agents can either lead to deposits of gadolinium in tissues or to severe, partly deadly side effects. I have been in the scientific gadolinium contrast agent business for more than 35 years and have summarized the history as I have witnessed it in a number of columns. The last and most factual report appeared in 2015, describing the historical course of events as clearly as one can and asking the most important question: "Gadolinium – will anybody learn from the debacle?" [1].

The entire affair has been taken over by lawyers, judges, and health administrators and meanwhile its handling has completely gone off course. The companies and people involved seem not to want to collaborate but rather to fight each other. Some people are confused, some try to evade assuming any responsibility for what they have caused and whitewash themselves, some say it's an act of God, some try to make money – while patients suffer and hardly anybody talks about them or tries to help.

The long awaited decision of the London-based European Medicines Agency (EMA) on what should happen with linear gadolinium-based MR contrast agents is many months delayed, most likely due to objections by lobbyists [*]. Meanwhile, the number of examinations with gadolinium contrast agents slowly declines and the indications are curtailed.

The odds are that there will be drastic changes in contrast agent use in the near or medium future. It seems as if manganese-based agents could replace gadolinium agents, at least for selected indications: There is an old new kid in town.

Manganese was the first element applied to enhance pathologies in MR imaging; its use was described by Paul C. Lauterbur, Maria Helena Mendonça-Dias and Andrew M. Rudin in 1978 [2]. They imaged five dogs with myocardial infarctions after injecting a manganese salt solution and were able to highlight the lesions.

Yet, gadolinium became the element of choice for MR contrast agents because of its high relaxivity and patent issues. However, it is an element foreign to the human body whereas manganese is an essential trace element.

The odds are that there will be drastic changes in contrast agent use in the near or medium future: There is an old new kid in town.

The only managnese-based agent approved and sold for clinical imaging was Teslascan (Mn-DPDP), a compound used for liver imaging. As it didn't sell for the indication it was withdrawn from the market some time ago.

In addition to imaging of the liver, manganese-enhanced MRI (MEMRI) with Mn-DPDP has a wide range of potential applications. Research is focused upon both depiction of brain damage and functional mapping of neural pathways to map brain activation independently and with higher contrast than measurements of hemodynamics in fMRI.

Contrary to gadolinium-based compounds, which are unspecific agents, manganese agents can actively track biological processes. Manganese also has an affinity for the myocardium and can act as biomarker in heart disease. It competes with calcium for entry into cardiac cells. There, its ions bind to macromolecules and influence the relaxation of cell and tissue water. Heart diseases gradually inactivate calcium transport mechanisms (due to lower metabolic activity). Thus, manganese uptake is reduced accordingly; manganese-induced changes of tissue relaxation reflect quantitatively tissue calcium homeostasis and thus myocardial viability [3, 4].

During the development of Mn-DPDP as an MR contrast agent for liver studies, it was discovered that this compound and its metabolite, manganese pyridoxyl ethyldiamine (Mn-PLED), also possess therapeutic properties. Mn-DPDP has been studied in cancer patients and in patients with myocardial infarctions. The contrast enhancement in MR imaging relies on the release of manganese from the chelate, the therapeutic activity depends on manganese that remains bound to DPDP or PLED.

Mn-PLED's stabilized derivate calmangafodipir [$Ca_4Mn(DPDP)_5$] has even superior therapeutic properties [5].

MEMRI of the heart is a good example of one of the few promising molecular imaging methods, because the same manganese-based compound can be used for diagnostics and treatment of, e.g., myocardial infarctions, cancer, and drug intoxication – it has *theragnostic properties* –, is inexpensive, and addresses a mass market.

■ It's not only a reshuffle of the card deck; some of the players will leave the card table and will be replaced by others. Small start-ups seem to liaise with distributors without an R&D department of their own, whereas the former big players seem to adopt a *wait and see* attitude.

* **Addendum:** On 10 March 2017, EMA, the European Medicines Agency recommended the suspension of the marketing authorisations of gadoversetamide (Optimark), gadodiamide (Omniscan) and gadopentetic acid (Magnevist, et al.), as well as gadobenic acid (MultiHance).

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Gadolinium contrast: A farewell to well-known brands

Peter A. Rinck

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Nearly 30 years after it was pointed out for the first time at a scientific conference that linear gadolinium-based contrast agents could become unstable *in vivo* and release free gadolinium [1], the long-awaited assessment of the European Medicines Agency (EMA) on gadolinium-based MR contrast agents was published at the end of last week. Expected last November, it came on 10 March [2], and the outcome was slightly different than foreseen by scientists working in the field.

The decision was made and published only some days after one of the major pharmaceutical players in the gadolinium contrast agents market introduced a replacement of their disputed gadolinium contrast agent at ECR 2017 in Vienna. It is a generic that was originally developed and introduced in 1989 by a French company ... "*Honi soit qui mal y pense* – A scoundrel, who thinks badly of it."

At that time, the better binding of the gadolinium ion to the transporting chelate, i.e., the higher complex stability, was attacked as a marketing trick by the competition. Well, it was not. Once again, the transience and volatility of sales and marketing promises became very clear and upsetting. It should be embarrassing to the manufacturer(s), but they can count on the fast-moving radiological consumer market. The slogans of yesteryear to divert attention away from the company leaders' fundamentally wrong assessments are rapidly forgotten by the radiological consumers.

The slogans of yesteryear to divert attention away from the company leaders' fundamentally wrong assessments are rapidly forgotten by the radiological consumers.

It was clear that the misused and abused compounds with severe late adverse effects (nephrogenic systemic fibrosis, NSF) would have to be removed from the market; they were already tagged for withdrawal by the EMA in July 2010, described as "high risk." They included gadodiamide (Omniscan), gadopentetic acid (for instance, Magnevist, Magnegita, and Gado-MRT-ratiopharm), and gadoversetamide (Optimark).

Up to this point, the EMA recommendations are easy to understand. However, the handling of medium-risk compounds is difficult to fathom. Medium-risk compounds include gadofosveset (Vasovist, Ablavar), gadoxetic acid (Primovist, Eovist), and gadobenic acid (MultiHance), of which gadofosveset is not on the market any more.

Gadobenic acid as well as gadoxetic acid are excreted by both the kidneys and the liver, although the percentage of liver excretion is far higher for gadoxetic acid. Still, gadobenic acid is the best enhancing contrast agent on the market. As far as I am aware, there were no direct cases of NSF with gadobenic acid, but there were a small number of "confounding" cases with combinations of gadodiamide. There is no scientific or statistically based reason to damn gadobenic acid and to promote gadoxetic acid for liver examinations, as EMA has now done.

■ The delay in the EMA's decision and the noncommittal verdict punishes all manufacturers, though some are given an unnecessary little piece of chocolate. It does not shed a complimentary light upon EMA. EMA's suspension, described as a "precautionary approach," is a balancing act, locking the stable door after the horse has bolted, and, at the same time, trying to keep all doors open by stating:

"For those marketing authorizations recommended for suspension, the suspensions can be lifted if the respective companies provide evidence of new benefits in an identified patient group that outweigh its risks or show that their product (modified or not) does not release gadolinium significantly (dechelation) or lead to its retention in tissues."

■ As Paracelsus stated: "Solely the dose determines that a thing is not a poison." It stands to reason that if the radiologists using the compounds and the companies pushing off-label use at high dose would have adhered to the recommended dose, much misery could have been prevented.

Perhaps EMA or its predecessors should have made a more thorough and probing evaluation 30 years ago. Or were the authorities and the industry too closely related?

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Spreading the news: Science and the media

Peter A. Rinck

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Last year I wrote about my worries concerning the reports on scientific research published by the lay media – even by those commonly considered serious and reliable [1]. As an example, I chose the articles of two science writers in German dailies about side effects of gadolinium contrast agents. They were mixing facts and opinion in a simplistic way and making sweeping judgments.

Even for well-respected publications, facts in science or research often are of less interest than a good story. Cautiously phrased sentences summarizing the contents of "the latest scientific paper" seem not to attract readers.

The concoction of selected facts, wishful thinking, and opinion as well as negative sensationalism sells; bad news can be good news for publishers.

This can be expected from newspapers and TV, or internet media known for and dedicated to yellow journalism, but not from the leading authoritative publications.

A good tale trumps facts – one only needs an irresistible headline.

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It is sad when trailblazing scientific research is being distorted in this way. However, it is a far more serious issue when faulty research results are taken up by the media in a sensationalist manner, and ends up having harmful, even catastrophic consequences, for patients and the general public, possibly creating a long-lasting negative effect on medical care [2, 3].

Some science journalists have a scientific background, but this does not mean they necessarily can cover science and research for the media -- they need good writing skills and they have to be able to write in an easily understandable, uncomplicated way, be precise, and be good communicators of scientific studies and results to a large public. Few scientists or researchers without a solid journalistic background have this ability.

What makes a good journalist?

Good science journalists possess a broad mind, are good readers and listeners, and know their target audience. They do not rely barely on press releases, but verify facts, vet sources (even if they must read complete scientific papers), have the capability to see through planted stories and possible commercial or political goals, and avoid people who try to steer stories in one direction.

Thus, as outsiders, good science journalists can be more suited to uncover scientific fraud than the scientific community.

The methods of such scams are rather effective. I didn't want to use a recent example – so as not to step on the toes of people whom we meet at conferences and society meetings of our time. Let's pick a well-known 40-year-old example: the scam of Dr. Raymond Damadian's tumor detection machine.

On 21 July 1977, Lawrence K. Altman of the *New York Times* wrote:

"A New York City medical researcher announced yesterday at a news conference that he had developed 'a new technique for the nonsurgical detection of cancer anywhere in the human body.' ... after repeated questioning, Dr. Damadian said that he retracted as "not accurate" the contention that his device had diagnosed cancer anywhere in the body. …

"The manner of Dr. Damadian's announcement was rather unusual. Ordinarily, researchers report their findings at a medical conference or through scientific journal articles. Sometimes, a medical center and its researchers hold a news conference in conjunction with publication of a journal article. …

"Dr. Damadian took the unusual step of retaining [a] public relations and advertising firm which chartered a bus to bring representatives of the news media and financial institutions to Downstate Medical Center from New York [4]."

In another article in the *New York Times*, Grant Fjermedal pointed out major discrepancies between what Damadian claimed and what he had actually accomplished, "discrepancies sufficient to make him appear a fool if not a fraud [5]."

Good public relations

Negative media evaluations can still be good public relations as this famous "radiological" example for the involvement of the press and the spread of fraudulent research revealed. Scientific offenders are not necessarily cast out. Professional societies try to avoid controversies, not exposing colleagues or even friends – nor people or companies with a strong political or financial influence. The truth is being "balanced."

Damadian became famous and rich because he repeated over and over again what outstanding scientific contributions he had made – but through platforms he created and channels he controlled and partly owned. He avoided responsible media.

Commonly, the blame is put on journalists and publishers, the Murdochs of our time. Irresponsible science writing can be caused by scientific illiteracy or a lack of appropriate experience in journalists and, of course, by the newspaper publishers' understandable interest in selling their product; there are also scientific journal publishers and editors who are immodestly greedy.

There is no easy solution. The blame for misleading the public should be shouldered equally by journalists, scientists, journal editors, and research institutions. Usually the topic is swept aside. However, for some months "fake news" and "alternative truths" are the talk of the press and state administrations. It's nothing new; basically, lies and disinformation are as old as mankind.

Recognizing and fighting them is important – in particular in medicine and radiology. They have to be brought up and discussed already at medical school to expose students to the actual spectrum of medical life beyond daily hospital routine. We need analytical and critical radiologists.

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English in medicine and science –
Or: English in the post-Brexit world

Peter A. Rinck

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For many people, perhaps for most who read this column, English is not their mother tongue, in other words, their first language. English is not my first language – nor my second which was Latin; English is my third language. Since I spent many years in different countries, English took over: I wrote scientific articles and books mostly in English, very few are in German or other languages.

The option of a scientific community in favor of one or the other language is only seemingly free.

The option of a scientific community in favor of one or the other language is only seemingly free; some years ago I mentioned in a column:

“The late president of France, Georges Pompidou once stated: 'We must not let the idea take hold that English is the only possible instrument for industrial, economic and scientific communication.'” [1]

He was right, in Europe, it could be Russian or German; he, of course, thought of French. He also highlighted the main feature of international English: its “global” range. He distinguished between the use of a language as a communicative instrument for securing competitive advantages – economic reasons – and the use of a language as a medium for the maintenance of identity, culture, and a distinct civilization.

Nearly one fifth of the population of the European Union speaks German as their first language. English, French, and Italian as first languages are only spoken by some 16% each. However, 47% of EU citizens claim that they speak or can speak English, 31% of them as a foreign language. Very few are able to chat away in French, Italian, German, or Russian as their third or fourth language.

Yet, there is a kind of grass-roots movement critically reflecting the use of English as a language of science – but not of business. Some of the foes of English as the universal language stress that the ubiquity of English ensures Anglo-American superiority around the world, and it is difficult to refute this argument. Although British impact is limited, US-American economic and political influence is strong.

However, the “international” or “global” English spoken abroad has lost a clear cultural identity; it has established itself as a globalized language without a distinct cultural background. Thus, the current discussion about linguistic diversity is also a sign of the globalization debate.

But is the everyday radiological world a global village? Or does the dictate to have to use English lead to cognitive impoverishment and a loss of medical identity and independence?

If you want to dance on an international stage – give talks, publish papers, apply for grants – there is no getting around English. However, teaching is more successfully done in the national languages because it allows a better understanding of contents and distinction of subtleties of a topic.

The same question holds for scientific publications. The expression of nuances is far easier in one's own language … the “radiological” or “medical” English turns into a code of limited vocabulary and stilted and artificial phrases, not only in writing, but also as spoken English. This kind of English is a relative of British, North American, South African, and Indian English, but to many “native” English speakers scientific English is a foreign language they don’t understand.

On the other hand, we used to invite “native speakers” to lecture at conferences only when they spoke clear English; an English tainted by dialects from, e.g., Yorkshire, Arkansas, or India was counterproductive for conference participants with English as a second language. The best teachers were those who spoke English as a second language well and taught with a pedagogical drive. They were understood by most participants who had English as a second language and there were less verbal misunderstandings. On the other hand, native speakers had comprehension problems.

Scientific or global English is distinct from such a personal, individual language: it is the global tool for business, international health care and sales – and the natural sciences. What is essential for the natural sciences and medicine, is not necessarily applicable for the humanities which live and blossom beautifully in other languages than English. For the time being, international English will remain the global business and science language. It is a simple language that can easily be used to communicate with one another and for which there is no imminent replacement.

I have experienced radiologists from the French-speaking part of Belgium talk to their colleagues from the Flemish-speaking part in English. The same holds for Switzerland. German speakers talk in English to their counterparts from Geneva or Lausanne.

However, English will stay or become a second or third tier scientific or medical language in regions of the world where huge populations speak a single language of their own, e.g., in Latin America or China. Those who want to sell or teach here need to speak the local language.

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