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Do we need so many gadolinium chelates?

Peter A. Rinck



This column has the same title as two refresher courses at the European Congress of Radiology in Vienna 1995 and 1997. It is a provocative question because whatever your answer, you either lie or step on somebody's toes. It would be easy to respond "yes" or "no" or "of course, because all pharmaceutical companies want to make a profit". But first it is essential to look at the facts.

Gadolinium is a rare earth metal that offers an extremely strong degree of relaxation enhancement, and therefore seems to be the best foundation for paramagnetic contrast agents. It has to be chelated to organic ligands to decrease its toxicity and facilitate delivery to the desired region of the body.

The gadolinium class of magnetic resonance contrast agents consists of a number of chelates. Chelates come as stretched, or linear, or cyclic or macrocyclic molecules. Their number is increasing every year. It is this expansion that leads to our question. Before attempting to determine whether we need so many gadolinium chelates, however, a far more important question must be addressed: Do we need gadolinium chelates at all?

Ten years ago the response to this question was equivocal, but today it is clearly affirmative. Administration of a gadolinium contrast agent often renders an MR examination conclusive, delivering a straight diagnostic answer. Nonetheless, there are only a few publications dealing with this topic that include a large patient population.

In one of the few prospective studies, Elster et al. reported in 1989 that in 3% of all patients enrolled, lesions were detected after contrast that were not otherwise apparent in precontrast T1- or T2-weighted images [1]. Contrast-enhancing lesions were seen in 20% of patients, and in 75% of those cases radiologically useful information was revealed. Lack of enhancement was found useful in an additional 22% of cases. A number of other papers have underlined the added benefit of gadolinium-containing contrast agents.

The first gadolinium chelate was brought to the market in the late 1980s. It was Gd-DTPA, Schering's Magnevist. It enjoyed a kind of monopoly position in most countries of the world. Between 1988 and 1991 more than 5 million patients underwent examinations with Magnevist. The only competitor was Gd-DOTA, which was marketed in some countries by Guerbet as Dotarem.

For some years there was no other competitor. In Spain, Schering competed with itself by selling Gd-DTPA through the Spanish company, Juste, under the trade name Magnograf. And in China, Gd-DTPA is available as a copied product, with the Chinese apparently not paying license fees to Schering.

Two new products were introduced in 1993, both slightly different from the first ones. Nycomed's Omniscan, or Gd-DTPA-BMA, and Squibb Diagnostics' (now Bracco's) ProHance, or Gd-HP-DO3A, possess a lower osmolality and are neutral or nonionic. Their manufacturers claim that the safety indexes of their nonionic products are better than those of the earlier products.

This will be difficult to prove, however, because even Magnevist seems to be at least one order, perhaps even two orders, of magnitude safer than ionic x-ray contrast agents. In other words, hundreds of millions of examinations are needed to prove the manufacturers' claim because all these agents are safe in the first place.

New agents on the way

At least three more gadolinium-based contrast agents will hit the market in the foreseeable future. Mallinckrodt will have a gadolinium compound of its own called Optimark, Bracco will introduce its Gd-BOPTA as MultiHance, and Schering its Gd-EOB-DTPA as Eovist. The latter two agents will be used not only for the same indications of the compounds sold today, but also for liver and myocardial examinations, for example, because of their specific distribution to these organs.

Gd-BOPTA combines hepatocyte specificity with plasma kinetics similar to that of the four traditional gadolinium agents and relaxivity modulated by serum protein concentration. The latter behavior may have implications for the detection of blood-brain barrier disruption after ischemic insults and in tumors.

Even more gadolinium agents are on their way. Gd-DTPA-albumin, GD-DTPA-dextran, and Gd-DTPA-polylysine could facilitate MR angiography and help to assess myocardial and cerebral ischemia, pulmonary embolism, vascularization of tumors, and tumor perfusion. Altogether, today, some ten compounds are sold for routine use or are on their way to the market. There are numerous other gadolinium chelates still in the laboratories of their developers.

To my knowledge, to date none of the new contrast agents has so far been rejected by the regulatory and licensing authorities. In the future, however, approval might become more difficult to obtain because the regulators will require proof of additional diagnostic benefit of the new compounds compared to those already on the market.

New contrast agents must be innovative, yet the initial four already competing on the market, and some of those still to come are very similar. Three major factors influence the evaluation of these products: firstly, efficacy; secondly, relative biological tolerance profiles; and thirdly, price.

There is a general consensus that Magnevist, Dotarem, ProHance, and Omniscan are similar in their efficacy; this consensus exists because there is no proof to the contrary.

Furthermore, it is difficult to test two different contrast agents in the same patient at, more or less, the same time. It even might be considered unethical. I have heard about some such comparative studies being conducted and about results giving preference to a particular contrast agent. However, nobody has dared to publish them.

In terms of acute safety aspects and relative tolerance profiles, the agents do not differ substantially. So the basic difference between these contrast agents is price, and a subtle price war is already going on.

Undoubtedly, today's unspecific agents were a big step forward in MR imaging and medical diagnostics

in general. However, the development of new ligands for these traditional unspecific indications is not worthwhile. What is both desirable and necessary are new compounds with higher specificity.

However, there seems to be a simple rule: The better the specificity, the smaller the market will be.

There might be one exception: blood pool, i.e., angiographic agents, should be introduced as soon as possible because there is a need for MR angiography with less pitfalls, which means with an MR angiographic contrast agent.

In this case, there is a substantial market because contrast-enhanced MR angiography will cut a big slice out of the conventional and CT angiography cake.

Nuclear medicine connection

For other specific applications, new impulses will come from nuclear medicine. Always remember that DTPA was a ligand used first in nuclear medicine, yet researchers in MR imaging have only looked into radiopharmaceuticals with a half-opened eye.

For a long time nuclear medicine was considered a discipline that was "supposed to die" – but it appears to be expiring very slowly. Many observers thought nuclear medicine would be replaced by MR imaging and MR spectroscopy, but it looks instead as if MR spectroscopy has been replaced by nuclear medicine.

In the meantime, spatial resolution in nuclear medicine has improved and new radiopharmaceuticals have been introduced. I still believe that MR imaging has a more important future for mankind than nuclear medicine, but this should not prevent us from trying to learn from nuclear medicine and to develop higher-specificity MR contrast agents based on the results of nuclear medicine research.

There is another aspect to the debate about whether we really need so many gadolinium chelates. Just as the automobile, the electronic, and the tourist industries have to some extent developed into consumer industries, so has medicine.

New products are developed and sold, many of them are hardly essential for the survival of mankind. However, they do create income and employment for thousands of physicians, scientists, clerks, and work-

ers. As long as they do not harm people, they are welcome. In the case of gadolinium contrast agents, the new products may have a positive impact on cost-containment, because prices are likely to fall as competition intensifies.

In the end, whether we need so many gadolinium chelates depends on where we live. In socialist societies or those with restrictive healthcare systems the policy followed is “That’s what we have, that’s what you get”. In many Central and Western European countries, in the U.S.A., in Japan, and in some other nations the answer is (still) different: You get a selection of goods, which also include contrast agents. If a product is not good or too expensive it will be eliminated.

■ **Footnote:** Within a few years, the landscape in MR contrast agents has completely changed. A number of companies has disappeared and the aftermath of the NSF scandal has left its traces.

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News from the ultrasound front: Avoiding abuse and overuse of ultrasound

Peter A. Rinck



Sometimes you hear or read statements that are beyond belief. The March issue of the U.S.-American edition of *Diagnostic Imaging* contained quite a stunning article with the title “Ultrasound Portraiture: Glimpses of Fetal Space”. The authors propose that they may distinguish states of serenity and distress, hunger and pain from viewing the face of the fetus in utero with ultrasound. In the future, prenatal face viewing performed by ultrasound will be requested and eventually demanded as part of each ultrasound study, they suggest. Images should be in pseudocolors – preferably in gold tones, which promote a feeling of warmth and emphasize the notion of an ultrasound probe as a sonic “flash-light”.

It is the authors’ impression that “frontal views ... provoke comments about resemblances within the family, while more idealized profile views tend to elicit comments about projected futures or anticipated personal attributes.”

Because of the clarity of the images it provides, an endovaginal probe should be used to view the face whenever the fetus is in a prone or semiprone vertex position, the advise [1].

Is the ultrasound operator going to become the prenatal family photographer of the 1990s?

■ Not everybody seems to like this idea. At the time of publication of the article, the International Herald Tribune, a U.S. newspaper published in Paris, printed the following short note (25 February 1995):

“An ultrasound videotape of a baby swimming in the uterus is a useful diagnostic tool for doctors. But such tapes should not be made simply as souvenirs for the expectant parents, according to the [United States] Food and Drug Administration. It has warned non-medical companies that offer to make such videotapes that they risk seizure of their equipment. Ultrasound can produce physical effects in tissue, such as a rise of temperature. ‘Although there is no evidence that this can harm the fetus,’ an agency

spokesman said, ‘public health experts agree that casual exposure to ultrasound, especially during pregnancy, should be avoided.’”

In the year of Roentgen’s centenary, we have all seen the x-ray pictures of both Herr and Frau Roentgen’s hands. They are a great souvenir in the history of roentgenology and medicine itself. However, radiation protection regulations do not allow such souvenirs to be available today. Are the ultrasonic smiling baby faces going to have the same fate?

There is no evidence that B-mode scanners lead to any deleterious effects, particularly on fetus or mother when used for routine clinical scanning during pregnancy. However, some Doppler equipment has the potential to produce a biologically significant temperature rise, specifically at bone/soft tissue interfaces. Doppler flow studies in the fetus work with intensities at which thermal effects cannot be excluded.

Lower costs?

There are other arguments against unrestricted and medically unsolicited overuse of ultrasound. It adds to the cost explosion in the healthcare system. I hear your argument that ultrasound is the cheapest diagnostic imaging modality. In the same manner, you can argue that a motorcycle is cheaper than a car. But if you buy ten motorcycles you will spend more money on acquisition, running costs, and maintenance than for one car.

At the opening session of the Annual Meeting of the Radiological Society of North America in 1994, radiology chairman Christopher R.B. Merrit of the Ochsner Clinic in New Orleans, quoted the direct cost of an ultrasound examination at US\$ 28.90. Direct costs of a plain x-ray were US\$ 11.93; of fluoroscopy US\$ 42.23; of CT US\$ 77.65; and of MRI US\$ 143.04 [2].

In Germany, at least 30,000 non-radiologists (three times more than the total number of radiologists) perform x-ray and/or ultrasound examinations, especial-

ly in internal medicine, orthopedics and pediatrics. Total expenditure on ultrasound is three times higher than on CT and MRI combined. It should be asked, then whether the diagnostic outcome of ultrasound is proportionally three times higher?

In 1958, C. Northcote Parkinson published his famous book entitled *Parkinson's Law*. His law basically boiled down to the following: Put a typewriter in the desert and a bureaucracy will grow around it.

Similarly, Rinck's Law on Ultrasound states: "Put an ultrasound machine anywhere and there will be an explosion of unnecessary examinations with this machine – or, if it's hidden behind the door, no examinations at all." I can hear the outcry. But if you start reading recent publications on ultrasound, you will find some statements by developers and users of this imaging modality which are quite critical of certain of its applications.

Dubious applications

Some time ago, a friend of mine had knee problems. After clinical examination by an orthopedic surgeon, x-rays of his knees were taken, then he underwent an ultrasound examination. Neither of the imaging studies was conclusive, so he was referred to MR imaging.

This is not an uncommon occurrence. During the last years, people have started using ultrasound in orthopedics, for instance, to examine the menisci and cruciate ligaments. This adds one more examination to the list, but the question: "Why use ultrasound?" remains a taboo.

In a recently published paper on ultrasonography in arthritis of the knee, the authors conclude:

"The present study confirms that US is a reliable method for demonstration of joint effusions and Baker's cysts. The synovial membranes of the suprapatellar recess could be identified in approximately half of the patients ... Although cartilage evaluation by US seems reliable, the clinical value is limited, because the weight-bearing areas are inaccessible. Since MR imaging additionally may provide information about early pannus-induced cartilage and bone erosions, the synovial membrane volume, and the inflammatory activity of the joint, MR imaging for the moment must be preferred second imaging modality to con-

ventional radiography in rheumatoid arthritis and osteoarthritis, except when Baker's cysts are suspected." [3]

Cranial sonography is also increasingly used in the detection of intracranial changes and complications in infants. The following is the conclusion of a study in 58 infants conducted between 1988 and 1993 at the Massachusetts General Hospital in Boston:

"Current cranial sonography protocols in ECMO (extracorporeal membrane oxygenation) patients are not maximally efficacious. Incorporation of an analysis of clinical parameters routinely followed in these neonatal intensive care unit patients should identify those at increased risk of acute intracranial hemorrhage, increasing the yield of this sensitive but time and cost intensive modality." [4]

Ethics

There is also the medical ethics issue to consider.

In China and some other Asian countries, demographic statistics show a significant change in the composition of the younger population. The share of the male population has increased substantially during the recent years, and in some areas of China it has become almost impossible for young men to find a woman to marry. Bachelorhood is the grim prospect for many young Chinese men. Kidnapping and trading of women has increased sharply.

This change in population structure has been aided by ultrasound. In the eyes of a great number of Chinese, it is better to have sons than daughters, so when ultrasound examinations reveal the sex of the fetus to be female, it is aborted. Although both China and India have introduced legislation to ensure against this abuse, it nevertheless continues.

A positive contribution to diagnostics

The abstract of a refresher course at the 1995 European Congress of Radiology describes ultrasound in a typical manner as follows:

"Ultrasound is simple, rapid, inexpensive, dynamic, and can be repeated as often as necessary without known hazard to the patient. It does, however, require dedication, skill and experience. When properly integrated with the clinical data and the results of other radiological examinations, US provides a

wealth of information which has a crucial impact on therapeutic management.” [5]

This description should be kept in mind and ultrasound should be used accordingly. Furthermore, ultrasound is versatile, able to image solid organs, vessels, and the fetus in a variety of clinical settings, and quite importantly, the equipment is portable and can be brought to the patient. Personally, I would like to emphasize the need for “proper integration” of ultrasound.

As with any diagnostic imaging modality, there are two major risks associated with ultrasound: misdiagnosis and overuse. Because ultrasound is far more operator-dependent than other methods, the risk of misdiagnoses is higher than with other modalities. Therefore, it is essential that training deals not only with how to use the technique but also when to use it with prudence. Unfortunately, such training is not available or required in all countries, including some in Europe.

Recent undesirable trends are overshadowing the positive contribution that ultrasound makes to diagnostics. Unless action is taken to reverse these trends, the risk is that ultrasound will be remembered as the not-so-ultracheap and ultra-abused imaging modality of the last decade of the 20th century.

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Drawbacks of the information autobahn

Peter A. Rinck



It is difficult to pick up a magazine or journal these days without being confronted with the information superhighways. Everybody is talking or writing about them, so I have decided to join the crowd. It is not a bad idea to give this subject some thought before we are totally immersed.

The information superhighways allow all kinds of information to be shared, facilitate education, and provide access to libraries and galleries worldwide. The exchange of information is faster and dissemination of knowledge more widespread because of distant learning, and it is claimed that even the environment benefits because people do not have to drive to the office but can work from home.

Those using the superhighways are singing the praises of this new tool. Like highways for automobiles, the information superhighways or data autobahns are great, wide, fast roads that are free or inexpensive. In medicine, it seems that many problems can be eased by this technology.

Let us imagine one typical situation in radiology – or in clinical medicine at large – where the highways can contribute to the patient's advantage: A patient has been referred for a diagnostic follow-up, but the original hard copies are not in the hospital archives. They are somewhere in London, Paris, Amsterdam, or the building next door. In any case, they cannot be found. Everybody is familiar with this situation. Now, there are two possibilities: there is a backup on tape or disk (which usually cannot be retrieved), or the original examination was made somewhere else and cannot be retrieved.

Consider the future: you walk to the next computer with an internet or PACS (picture archiving and communication system) connection, log on, and within seconds you have the original images on-screen, regardless of where in the world they are being stored. In another situation, a patient has Hotzenplotz disease and you want to know how many cases of the disease there have been in San Marino and how they have been treated there. You walk to the next computer with an Internet connection, log on, and within seconds the answer is displayed on-screen.

No quick fix

Attending conferences, reading magazines, or watching television can give the impression that computers and Internet will solve every conceivable question. In medicine, computers contribute to a patient's faster and better recovery. The patient's medical history is available on Internet. E-mail makes the health system cheaper.

There is no doubt about the benefits that information superhighways will bring, but the mental picture of the highway analogy contains not only fast-moving and smooth-flowing traffic but also pollution, noise, accidents, congestion, and a ruined landscape.

Few people have thought about the drawbacks of the data autobahn.

The overwhelming enthusiasm of today might soon give way to more sobering thoughts, and it is worth considering some of them in order to keep a sense of perspective.

Supporters of the information superhighways assert that medicine is one of the main areas of application and benefit.

A common example is of a small community hospital or clinic connected to experts in big faraway medical centers. With difficult or uncertain cases, all the data is sent to these experts via a telephone line or fiber-optic cable, and the experts then return the diagnosis. Ideally, this scenario implies that the patients will receive the right treatment faster than if it had first been necessary to transport them to the big medical center.

The main problem of many small hospitals is the lack of high technology equipment to obtain data, not the lack of an expert. It may well be the case that such small hospitals would spend valuable resources connecting themselves to the superhighway, thus using resources that could have been better used purchasing diagnostic equipment or educating and training a medical doctor to deal with the patients locally.

Beware of the superhighway barons

The next point concerns access, and the problem of haves and have nots. The promise is of easy and free (or, at least, very cheap) access to the information superhighways for all. A student of mine told me that it does not cost anything, but he is not in charge of paying the university's telephone bill; he did not have to buy the hardware and software he uses; nor does he read the business pages of the newspapers.

Just as the 19th century had its railroad barons, the late 20th century will have its information superhighway barons, making millions of dollars out of high technology telephone lines, hardware, software, and most importantly, fees.

Easy and free access is a public relations slogan. Access still depends on availability of equipment, connections and networks which are not necessarily cheap or easy for everybody. The concept of easy and free access assumes the prior availability and understanding of the supporting technology. The entire continent of Africa possesses less telephone lines than Sweden, so it is difficult to see how Africa can be connected to the superhighways.

Will all the world's information be accessible? Of course not. This is another marketing slogan.

The superhighways will convey only information from those computers linked to the system – if you can find it because the internet is chaotic. Other information will not be accessible. On the other hand, whatever information is on the highway can hardly be protected any more.

Copyright does not count, and intellectual theft will become increasingly widespread and cannot be punished because nobody is enforcing the laws. As soon as you are connected to the highways, it will become difficult to lock your garage and house doors. All the big and small brothers can – and will – watch you.

Data autism

Is it really necessary for everybody to participate in the information society? It is claimed that if you do not become a member, you will be isolated.

However, there is another point of view: you become isolated as a member of the information society because you start living in an artificial world fenced in by computers and telephone lines. In other words,

you degenerate into data autism. This leads to the next potential problem of dependency and habit, whereby the user becomes so used to or dependent on the technology that the options or alternatives are no longer considered.

The telefax addicts are a case in point. Many people have seemingly forgotten that mail and telephone exist, communicating only by telefax, to the extreme of sending a 50-page document by fax when it could have been sent by mail (or kept, because nobody will read it anyway).

Given easy and free access, is the point going to be reached where people only communicate through computer networks? Will, for example, congresses and other scientific meetings become obsolete? Users of the superhighways are able to order tickets for travel and entertainment from home, but will there really be any need for tickets? From their computers, users can connect to wherever they want to go to and to whatever they want to hear or see.

Will books or the printed media in general disappear, as some people predict? Will all scientific information be provided through the computer? Incidentally, journal articles published 10, 20, or 100 years ago can easily be read, but can a computer access and decipher diskettes that are 10 years old? Probably not, because reading them is as difficult as deciphering the Dead Sea scrolls.

Another point often overlooked is that the information society is based on permanent change. What was taken for granted yesterday will change today. The high-technology wonderland needs permanent change to earn money, and it is big business. It does not create new thoughts or new mental results, but it offers solutions for new vehicles to transport, transform and store information. These vehicles are consumer goods that will be obsolete in five years.

Depending in whom you talk to, the opinions about the information superhighways vary from "I do not really care because I do not understand anything about it" to "I can't wait until it is all set up and I can use it for everything". In between these two extremes, one finds animosity, fear, excitement, and brainstorming to discover applications for the technology.

For users of technology and information, the prospects are mostly fascinating. Much has been said and written about the new possibilities, the irrele-

vance of distance and difficult access, and the dream future of democratic distribution of information. However, it is because we have been bombarded with propaganda and commercials about the advantages of the information superhighways that the possible drawbacks must be kept in mind. We must do this for our own good and to keep alive the different and independent cultures that are the backbones of our civilization.

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