ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
21 (1999) 931–943

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

www.elsevier.com/locate/jpba

Interference of magnetic resonance imaging contrast agents with the serum calcium measurement technique using colorimetric reagents

Jing Lin [a,*], Jean-Marc Idee [a], Marc Port [a], Andre Diai [b], Christine Berthommier [a], Martine Robert [a], Isabelle Raynal [a], Ludovic Devoldere [a], Claire Corot [a]

[a] *Research Department, Guerbet, Aulnay-sous-Bois, France*
[b] *Laboratoire d'Analyses de Biologie Médicale, Sevran, France*

Received 19 March 1999; received in revised form 28 June 1999; accepted 28 June 1999

Abstract

A possible interaction between either linear (Gd–DTPA–BMA and Gd–DTPA) or macrocyclic (Gd–DOTA) gadolinium complexes used as magnetic resonance imaging (MRI) contrast agents and colorimetric technique reagents for the measurement of serum calcium was evaluated on human serum pools, and its mechanism was investigated by means of UV spectrometry and electro-spray ionization mass spectrometry (ESI-MS). The highest concentration tested was 2.5 mM (corresponding to a putative strictly intravascular distribution of the compound) and the lowest dose was 0.2 mM (i.e. about two elimination half lives). Serum calcium was dosed in duplicate by conventional colorimetric techniques involving *o*-cresol-phthalein complexone (OCP) or methylthymol blue (MTB) as reagents. No interference was detected when mixing Gd–DOTA with serum, whatever the concentration. Gd–DTPA (2.5 mM) did not interfere with the colorimetric technique either. Conversely, the Gd–DTPA–BMA solution induced a concentration-related variation in apparent calcium levels. In the UV experiments, solutions of 2.5 mM MRI contrast media were mixed with OCP or MTB and UV absorption spectra were recorded between 400 and 800 nm. For Gd–DOTA/OCP and Gd–DOTA/MTB, no significant variations in the absorbance were detected. However, in the presence of Gd–DTPA–BMA, the absorbance of OCP and MTB showed substantial and immediate variations over time. The ESI-MS studies showed a complete displacement of Gd^{3+} ion in the case of Gd–DTPA–BMA. In the presence of OCP, we observed the disappearance of Gd–DTPA–BMA and the formation of the free ligand DTPA–BMA and a new complex Gd–OCP with an original stoichiometry of 2/2. Such a phenomenon did not occur in the case of Gd–DOTA and Gd–DTPA. The decomplexation of Gd–DTPA–BMA in the presence of OCP can probably be explained by the weaker thermodynamic stability of Gd–DTPA–BMA compared to that of Gd–DOTA and Gd–DTPA.

* Corresponding author. Present address: Research Dept., Guerbet, BP 50400, 95943, Roissy-Charles de Gaulle Cedex, France. Tel.: + 33-1-45-91-76-72; fax: + 33-1-45-91-51-23.
E-mail address: linj@guerbet-group.com (J. Lin)

0731-7085/99/$ - see front matter
PII: S0731-7085(99)00188-0

Keywords: Magnetic resonance imaging; Gadolinium complexes; Calcium serum levels; *o*-Cresol–phthalein complexone; Methylthymol blue; Analytical interference; Decomplexation; Gadolinium displacement

1. Introduction

To improve lesion identification and characterization, magnetic resonance imaging (MRI) frequently necessitates the administration of contrast media (CM) [1]. These also allow the assessment of vascular morphology and function ('magnetic resonance angiography') [2].

Because of its high paramagnetism (seven unpaired electrons) and its especially long electronic relaxation time, gadolinium, a lanthanide ion, is widely used to improve the contrast during MRI procedures [1]. However, due to its high intrinsic toxicity (mostly interaction with calcium-dependent biological systems and calcium channels [3,4], precipitation tendency above pH 6 and subsequent trapping in the liver and other macrophagic tissues), chelation of this ion by appropriate polyamino-polycarboxylic ligands is mandatory to allow its clinical use.

At present, two structurally-distinct categories of gadolinium chelates are commonly used [1]: (1) the 'macrocyclic' chelates such as Gd–DOTA (or meglumine gadoterate), and (2) the 'linear'

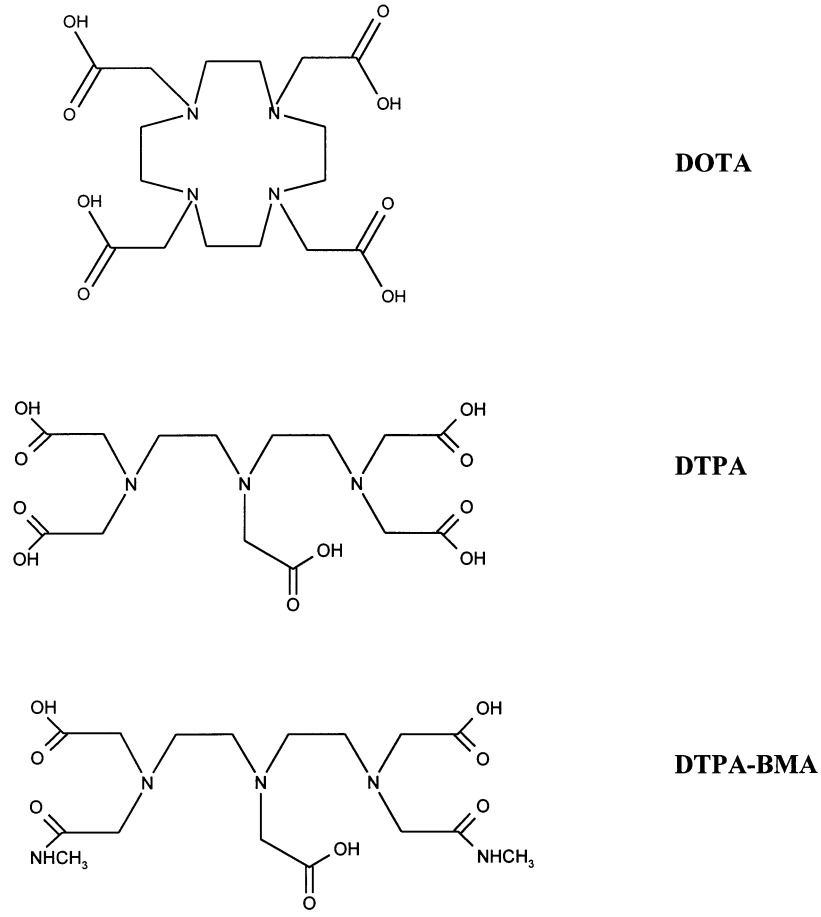


Fig. 1. Structure of the different gadolinium chelates tested: DOTA, DTPA and DTPA–BMA.

chelates such as Gd–DTPA–BMA (or gadodiamide) or Gd–DTPA (or dimeglumine gadopentetate) (Fig. 1).

It has recently been shown that the linear CM, Gd–DTPA–BMA, interferes with the colorimetric determination of serum calcium [5]. This phenomenon can be clinically relevant if colorimetric reagent kits are used for determination of serum calcium after injection of this CM.

Gadolinium complexes differ with respect to the apparent thermodynamic stability constant at pH 7.4 ($\log K'$) and the time necessary to decomplex half of the Gd^{3+} complex molecules ($T_{\frac{1}{2}\,\mathrm{dissoc}}$) [6]. The macrocyclic CM Gd–DOTA has a higher $\log K'$ and a longer $T_{\frac{1}{2}\,\mathrm{dissoc}}$ than Gd–DTPA–BMA [6]. Gd–DTPA has a relatively high $\log K'$ but a very low $T_{\frac{1}{2}\,\mathrm{dissoc}}$ [6]. The aim of the present study was to evaluate the risk of analytical interference with various widely-used MRI contrast agents for calcium measurement in serum, to investigate the mechanisms involved and to discuss the results in terms of structure–activity relationships.

2. Materials and methods

2.1. In vitro experiments on human serum

2.1.1. Preparation of MRI-CM solutions

The studies were carried out using two human serum pools from Institut Jacques Boy (Reims, France) (batches 790170S and 790190S).

Three MRI-CM were tested in their commercial forms: Gd–DOTA (meglumine gadoterate, Dotarem®, Laboratoire Guerbet, Aulnay-sous-Bois, France) (batch 97Gd007A), Gd–DTPA–BMA (gadodiamide, Omniscan®, Nycomed Imaging, Oslo, Norway) (batch 6050151) and Gd–DTPA (dimeglumine gadopentetate, Magnevist®, Laboratoire Schering, Lys-lez-Lannoy, France) (batch 63147). The concentration of all CM was 500 mM.

Test solutions were prepared by diluting the CM solutions in human serum. Tested concentrations were: 0.2, 0.5, 1.0, 1.5, 2.0 and 2.5 mM, except for Gd–DTPA where only 2.5 mM was tested. For 0.2 and 0.5 mM, stock solutions of 50 mM were prepared before dilution. Undiluted samples were used as controls for both serums.

Serum samples were incubated at 37°C for 90 min before analytical measurements.

2.1.2. Colorimetric titration of serum calcium concentration

Serum calcium concentration was measured by two colorimetric methods using respectively *o*-cresol-phthalein complexone (OCP) [7,8] and methylthymol blue (MTB) [9] as reagents (Fig. 2). All measurements were carried out in duplicate.

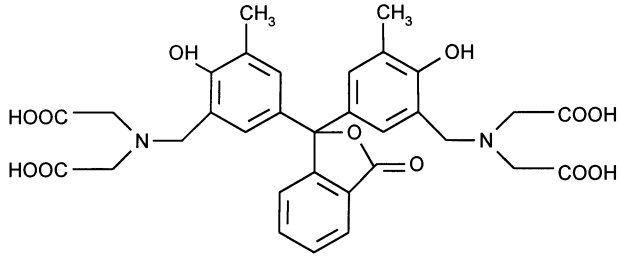
For the OCP method: the serum calcium level was determined using a commercial kit [ref. 61.551, BioMérieux, Lyon, France] of OCP. The titrations were achieved as indicated in package inserts. Absorbance was read at 572 nm. According to the manufacturer, correct linearity is achieved for calcium concentrations below 3.75 mM.

For the MTB method: the serum calcium level was determined using a commercial kit [Uni-Kit II, Roche] of MTB. The titrations were achieved as indicated in package inserts. Absorbance was read at 612 nm. According to the manufacturer, correct linearity is achieved for calcium concentrations below 4 mM.

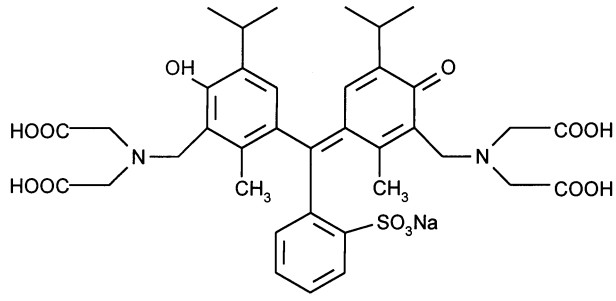
Direct current plasma atomic spectroscopy (DCP-AES) was used to check the plasma calcium levels measured in the first study by means of the OCP method. This measurement was carried out using an ARL Fisons, model SS-7 DCP (Thermo-Optec, Villepinte, France) instrument. Wavelength was 393.4 nm, order 57. Three quality controls were used: 80, 120 and 200 μmol/l. Recovery (R) was: $90\% < R < 110\%$.

2.1.3. Statistical analysis

Data are given as mean ± standard deviation (S.D.). Regression equations were calculated by means of the Number Cruncher Statistical System (NCSS) software version 6.0 (NCSS, Kaysville, UT) to analyse the relationship between the MRI-CM concentration in the sample and percentage change in calcium concentration. Significance was accepted when $P < 0.05$.



OCP



MTB

Fig. 2. Structure of the colorimetric reagents *o*-cresol-phthalein complexone (OCP) and methylthymol blue (MTB).

2.2. Analytical interference between MRI-CM and colorimetric reagents

2.2.1. UV experiments

In order to investigate the mechanism of a possible analytical interference between MRI-CM and *o*-cresol-phthalein complexone or methylthymol blue, solutions of 2.5 mM MRI-CM (Gd–DTPA–BMA and Gd–DOTA) were mixed respectively with OCP or MTB from commercial kits as indicated in package inserts. UV absorption spectra of the mixtures were recorded between 400 and 800 nm every 30 s for 2 min and then every minute (UV spectrophotometer Uvikon 860, Kontron Instrument, Saint Quentin-en-Yvelines, France). All experiments were carried out in duplicate.

2.2.2. ESI-MS experiments

Electro-Spray Ionization Mass Spectrometry (ESI-MS) analysis of different MRI-CM solutions and mixtures of MRI-CM with OCP was performed with a Quattro II mass spectrometer (Micromass, Manchester, UK) equipped with an electro-spray ionization interface and the Masslynx software. For each tested solution, the concentration of MRI-CM and OCP was respectively fixed at 0.1 and 0.16 mM in a mixture of water/acetonitrile/TEA (triethylamine) = 50:50:1. Samples were infused using a Harvard Apparatus syringe pump at a flow rate of 10 μl/min. In each case, 10 scans were acquired in negative mode over the mass range m/z 300–1800 (15 s per scan). The quadrupole Q1 was calibrated in negative mode using a mixture of TFA (trifluoroacetic acid)/NaOH solution as reported by Moini et al. [10].

Typical operating parameters were: 2.5 kV capillary voltage, 0.5 kV HV lens, 50 V cone and 70°C source temperature.

3. Results

3.1. In vitro experiments on human serum: colorimetric titration of calcium concentration

Calcium concentration values for both control serums, measured with both the OCP and the DCP-AES methods are shown in Table 1.

Whereas serum calcium levels determined by the OCP colorimetric method did not vary with respect to the control values in the presence of Gd–DOTA, a clear reduction in the measured calcium levels was observed in the case of Gd–DTPA–BMA: using OCP reagents, at 2.5 mM Gd–DTPA–BMA, the measured decrease was $-66.9 \pm 1.2\%$ (serum I) and $-64.8 \pm 0.9\%$ (serum II) vs control (Fig. 3).

In the case of the OCP colorimetric method, slopes of the relationship between CM concentration in the sample and percentage change in calcium concentration clearly differed with respect to Gd–DTPA–BMA (serum I: slope $= -26.5$, $P < 0.001$, $r^2 = 0.997$, serum II: slope $= -25.7$, $P < 0.001$, $r^2 = 0.997$) and Gd–DOTA (serum I: slope $= 0.87$, $P = 0.08$, $r^2 = 0.481$, serum II: slope $= -0.34$, $P = 0.422$, $r^2 = 0.132$).

Another linear MRI-CM, Gd–DTPA (2.5 mM), did not induce analytical interference with calcium measurement. Measured calcium concentrations were: 2.18 ± 0.03 mM (serum I) and 2.33 ± 0.03 mM (serum II) determined by the OCP method.

With MTB method, whereas serum calcium concentrations did not vary compared to the control values in the presence of Gd–DOTA or Gd–DTPA, an apparent increase in calcium levels was observed with Gd–DTPA–BMA. Indeed, with 2.5 mM Gd–DTPA–BMA, the measured calcium concentration was 3.50 mM vs a control value of 2.65 mM ($+32\%$).

Table 1
Human serum calcium concentration (mM/l) determined by the OCP method and DCP-AES

	Serum I	Serum II
OCP method	2.19 ± 0.01	2.40 ± 0.03
DCP-AES	2.07 ± 0.16	2.49 ± 0.09

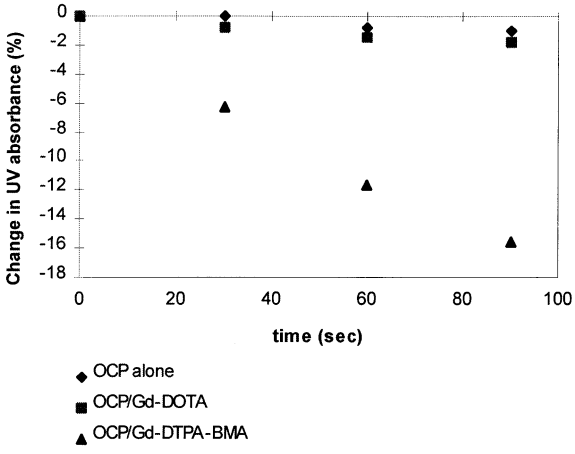


Fig. 4. Variation (in percentage) of UV absorbance of *o*-cresol-phthalein (commercial kit) at 572 nm over time in the presence of Gd–DOTA (2.5 nm) or Gd–DTPA–BMA (2.5 nm).

3.2. UV experiments

In order to understand why only the Gd–DTPA–BMA complex induced an analytical interference with the colorimetric reagent, further experiments were carried out.

Different mixtures of Gd–DOTA or Gd–DTPA–BMA, both at 2.5 mM, with either OCP or MTB were prepared and each was regularly measured by UV spectrometry in order to detect eventual spectral modifications over time. In such experiments, Gd–DOTA and Gd–DTPA–BMA clearly differed (Figs. 4 and 5).

In the case of mixtures of Gd–DOTA/OCP and Gd–DOTA/MTB, no significant variations in the absorbance at respectively 572 and 612 nm were detected. Indeed, the variations were respectively -1.8 and $+0.02\%$ 2 min after mixing. It should be noted that the same order of variation of the absorbance was observed for control OCP (-1%) and MTB ($+0.6\%$) solutions.

However, in the presence of Gd–DTPA–BMA, the UV absorbance of OCP at 572 nm and MTB at 612 nm showed substantial and immediate variations over time. The UV absorbances were modified by -15.6 and $+47.8\%$ respectively after 2 min. Moreover, a further investigation (Fig. 6) showed that, in the case of Gd–DTPA–BMA/OCP, the absorbance at 572 nm continued to decrease for 1 h and then remained relatively stable. The absorbance was decreased by 45.8% from its initial value at 1 h after mixing. On the

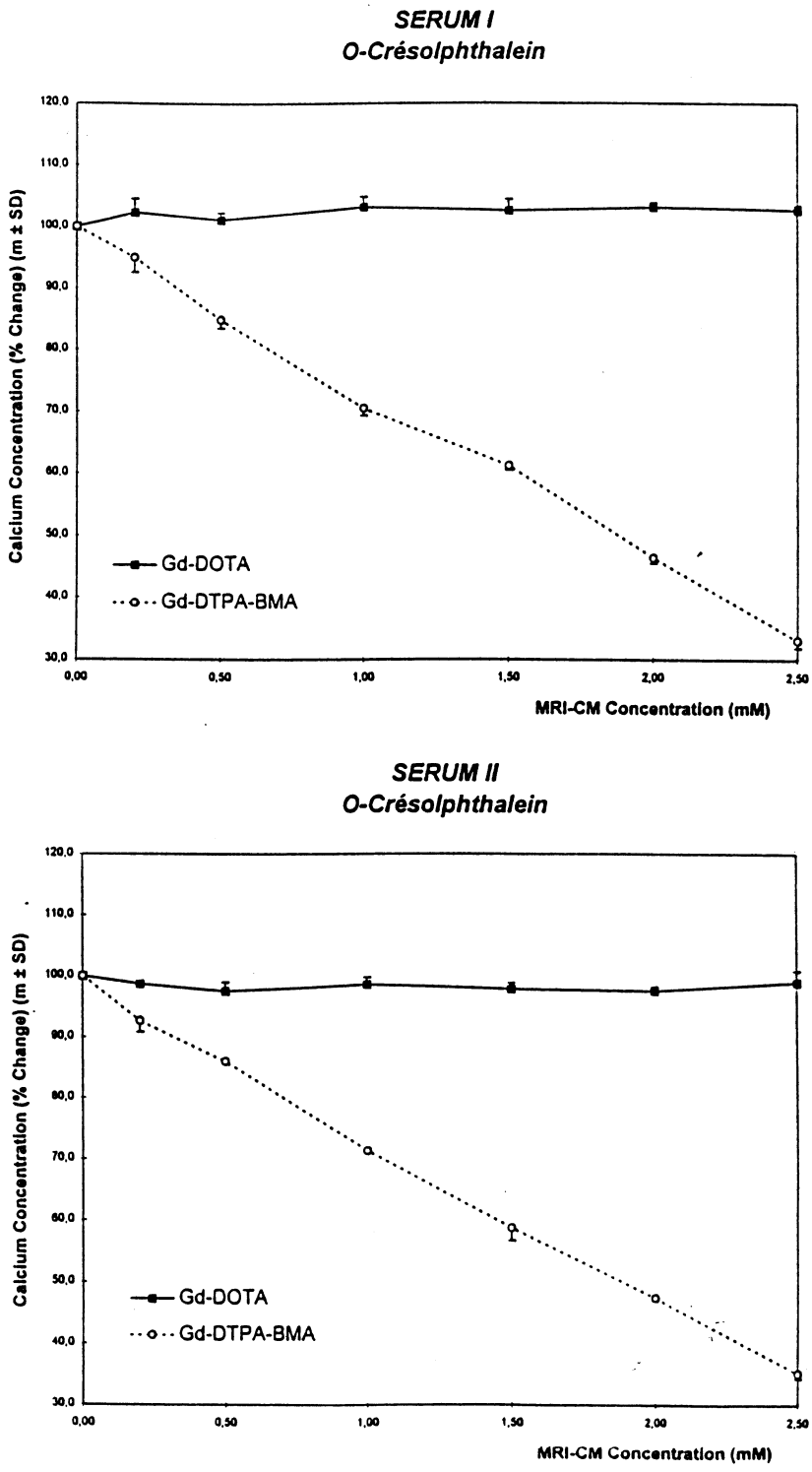


Fig. 3. Effects of Gd–DOTA and Gd–DTPA–BMA (0.2–2.5 mM in the test serum) on the measured calcium concentration using the colorimetric method with *o*-cresol-phthalein complexone for serum I and II.

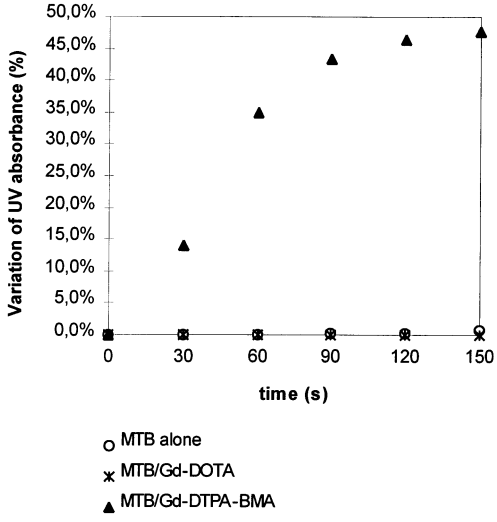


Fig. 5. Variation (in percentage) of UV absorbance of methylthymol blue (commercial kit) at 612 nm over time in the presence of Gd–DOTA (2.5 nm) or Gd–DTPA–BMA (2.5 nm).

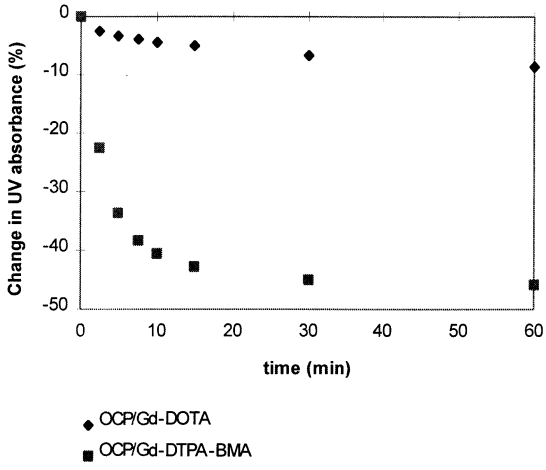


Fig. 6. Long-term variation (in percentage) of UV absorbance of *o*-cresol-phthalein (commercial kit) at 572 nm over time in the presence of Gd–DOTA (2.5 nm) or Gd–DTPA–BMA (2.5 nm).

other hand, the same experiment carried out with Gd–DOTA/OCP showed only a 8.7% decrease at the same time point.

3.3. ESI-MS experiments

Fig. 7 shows the mass spectrum obtained with a control OCP solution (0.16 mM). The molecular ion was clearly detected at $m/z = 635.3$. Peaks detected at $m/z = 502.3$, 520.2, 540.2 and 653.3 were not identified and were probably due to the presence of other compounds in the commercial kit of OCP.

Fig. 8 shows the comparison between the mass spectra obtained with Gd–DOTA only (spectrum above) and the mixture of Gd–DOTA + OCP (spectrum below). The molecular ion of Gd–DOTA at $m/z = 558.0$ was the only peak detected in the first case, and one can note its typical isotopic pattern due to the presence of one Gd^{3+} ion. In the latter case, the spectrum consisted of molecular ions of Gd–DOTA ($m/z = 557.9$) and that of OCP ($m/z = 635.1$). No new signals were detected. Very similar results were obtained when Gd–DTPA was tested instead of Gd–DOTA (data not shown).

However, when the same experiments were carried out with Gd–DTPA–BMA, the results obtained were very different (Fig. 9). The Gd–DTPA–BMA solution (spectrum above) gave a large molecular ion at $m/z = 573.0$ with a minor peak at $m/z = 418.0$ which corresponds to the molecular ion of the free ligand DTPA–BMA. In fact, the commercial solution Omniscan® contains 5% (mol/mol) of Na[CaDTPA–BMA], as indicated by the manufacturer. Because of its much weaker thermodynamic stability constant compared to that of Gd–DTPA–BMA ($\log K_{eq} = 7.17$ vs 16.85) [11], Na[CaDTPA–BMA] dissociated totally under electro-spray ionization conditions in spite of the softness of this ionization method and consequently showed the signal of the corresponding free ligand DTPA–BMA.

On the spectrum of the mixture Gd–DTPA–BMA + OCP (spectrum below), we observed a complete disappearance of the Gd–DTPA–BMA signal (expected $m/z = 573.0$), a significant decrease of the OCP intensity ($m/z = 635.4$) and a marked enhancement of the free ligand DTPA–BMA ($m/z = 418.3$). Furthermore, a new peak was clearly detected at $m/z = 790.3$. The enlarge-

ment of this peak showed a typical isotopic pattern corresponding to a multi-charged signal. Indeed, it is well known that ESI-MS is an ionization technique which generates efficiently multi-charged ions when their molecular weights are superior to 1500. In our case, the difference of 0.5 u.m.a. between every two neighbouring isotopic peaks clearly indicated that the charge state of this ion was $z = -2$. Consequently, the molecular weight of this compound could be calculated by $M = 2 \times 790.3 + 2 = 1582.6$. Interestingly, this molecular weight fits perfectly with that of a dimeric complex: 2Gd–2OCP (theoretical molecular mass = 1583.0). The comparison of the experimental result with the theoretical mass spectrum of 2Gd–2OCP in terms of isotopic pattern showed on Fig. 10 also indicated a great similarity.

4. Discussion

The current study evaluated the risk of analytical interference for serum calcium determination with the commonly used colorimetric technique using *o*-cresol-phthalein complexone and methylthymol blue, in the presence of three MRI-CM, either linear, i.e. Gd–DTPA–BMA and Gd–DTPA, or macrocyclic, i.e. Gd–DOTA.

The serum concentration range of CM in serum samples, equivalent for both agents [12,13], was selected from human pharmacokinetic data. Assuming that the clinical dose is 0.1 mM/kg injected i.v., and for a plasma volume of 40 ml/kg, the maximum serum concentration which could theoretically be expected for a bodyweight of 70 kg is 2.5 mM. This corresponds to a theoretically strictly intravascular distribution (which is never achieved in practice, due to extravasation into the extravascular space). The concentration range selected here is also fully consistent with that chosen by Normann et al. [5].

After i.v. injection of the clinical dose of 0.1 mM/kg, non specific CM are rapidly distributed in the extravascular space ($t_{\frac{1}{2}}\alpha = 3.7 \pm 2.7$ min for Gd–DTPA–BMA), and have an elimination half-life of about 80 min in humans ($t_{\frac{1}{2}}\beta = 77.8 \pm 15.5$ min for Gd–DTPA–BMA) [12]. The lowest con-

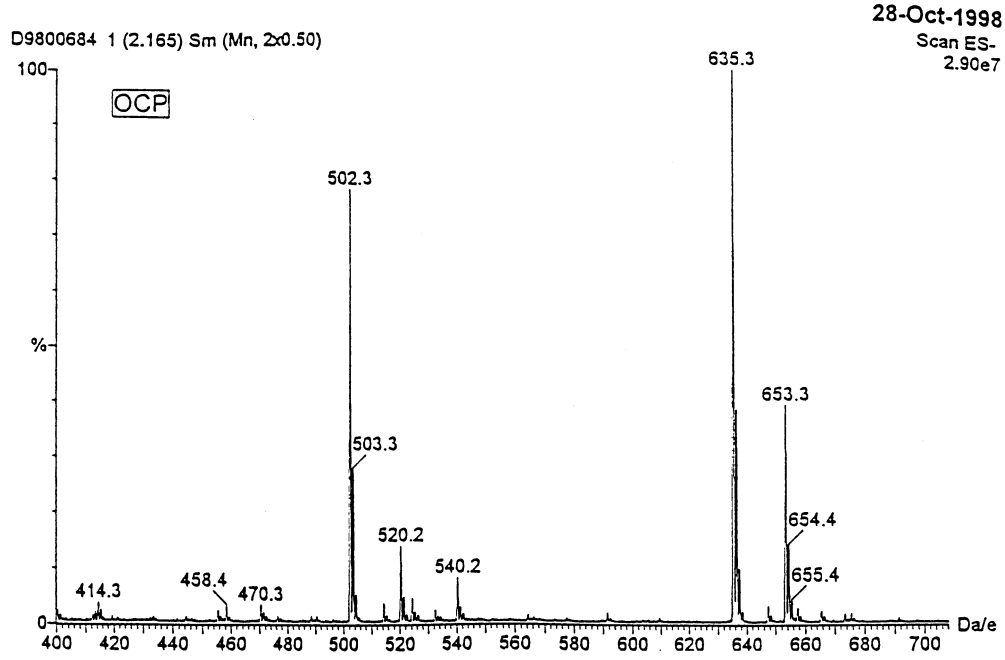


Fig. 7. Mass spectrum of *o*-cresol-phthalein solution (0.16 nm).

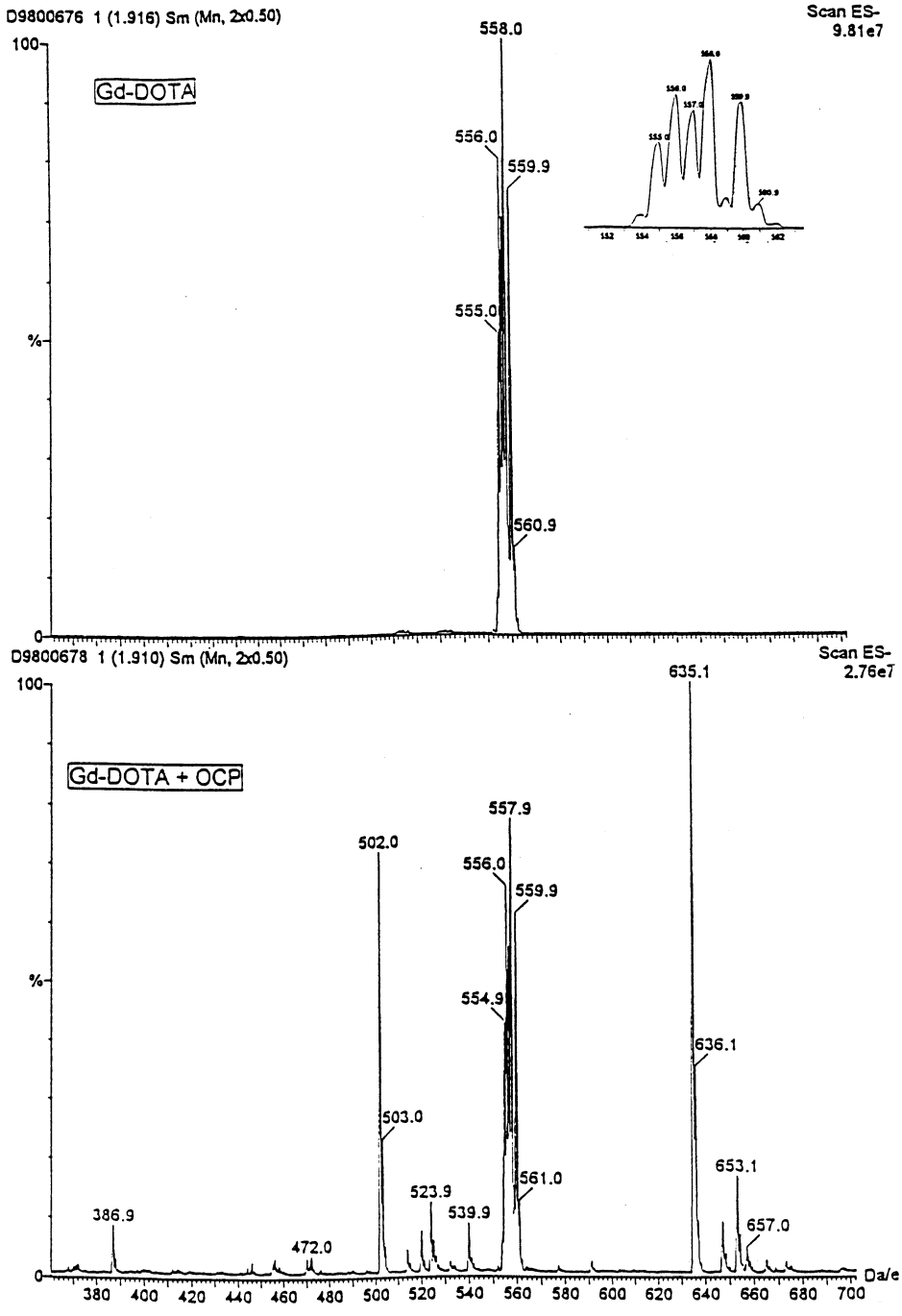


Fig. 8. Mass spectra of Gd–DOTA only (spectrum above) and Gd–DOTA + *o*-cresol-phthalein (spectrum below).

centration selected (i.e. 0.2 mM) corresponds to the concentration obtained at about two $t_{\frac{1}{2}}\beta$.

Our results clearly showed that with the common colorimetric method using OCP [7,8], a sig-

nificant reduction in serum calcium levels occurs in the case of the linear molecule Gd–DTPA–BMA but not when Gd–DOTA was added to the samples, whatever the concentration.

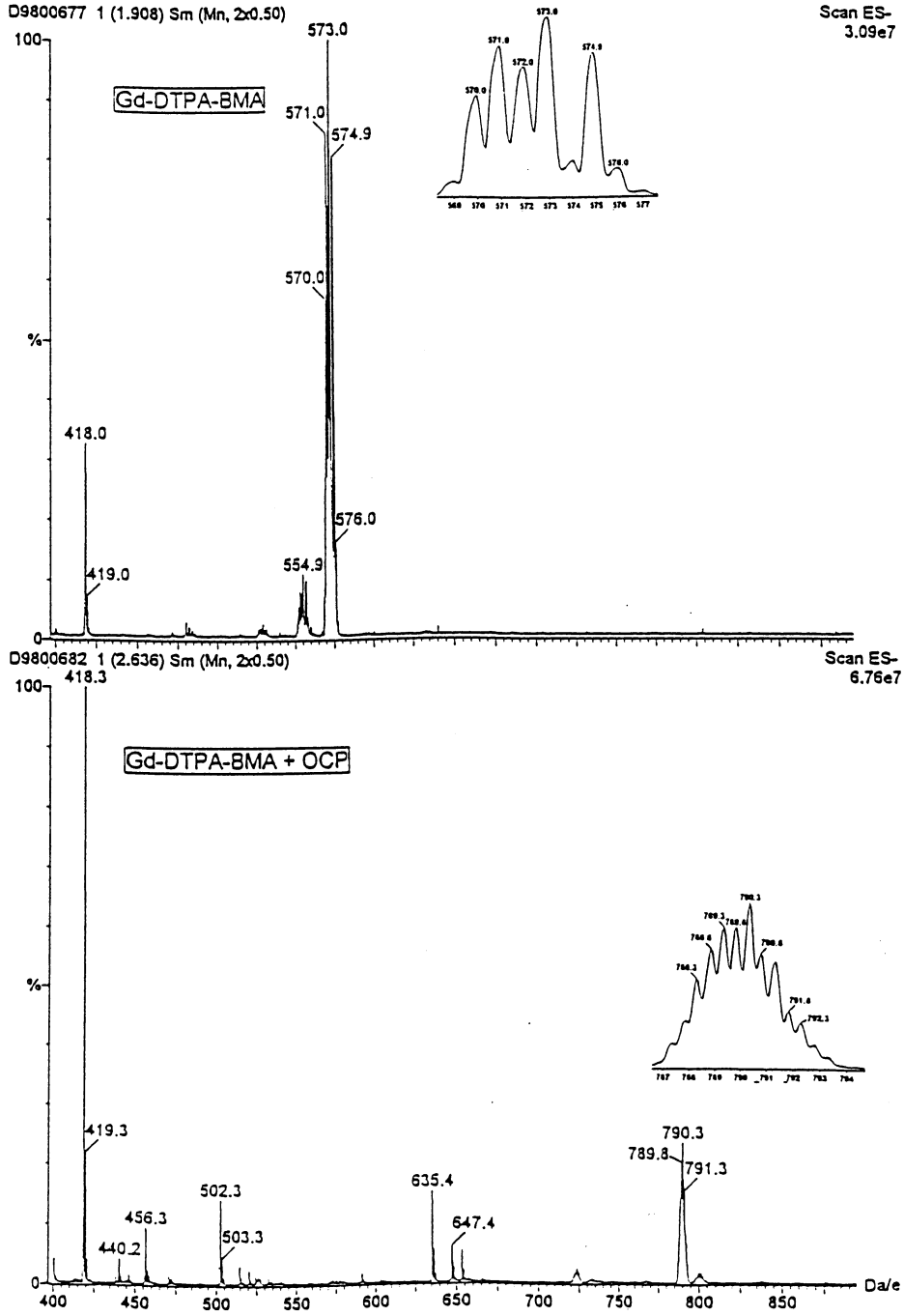


Fig. 9. Mass spectra of Gd–DTPA–BMA only (spectrum above) and Gd–DTPA–BMA + *o*-cresol-phthalein (spectrum below).

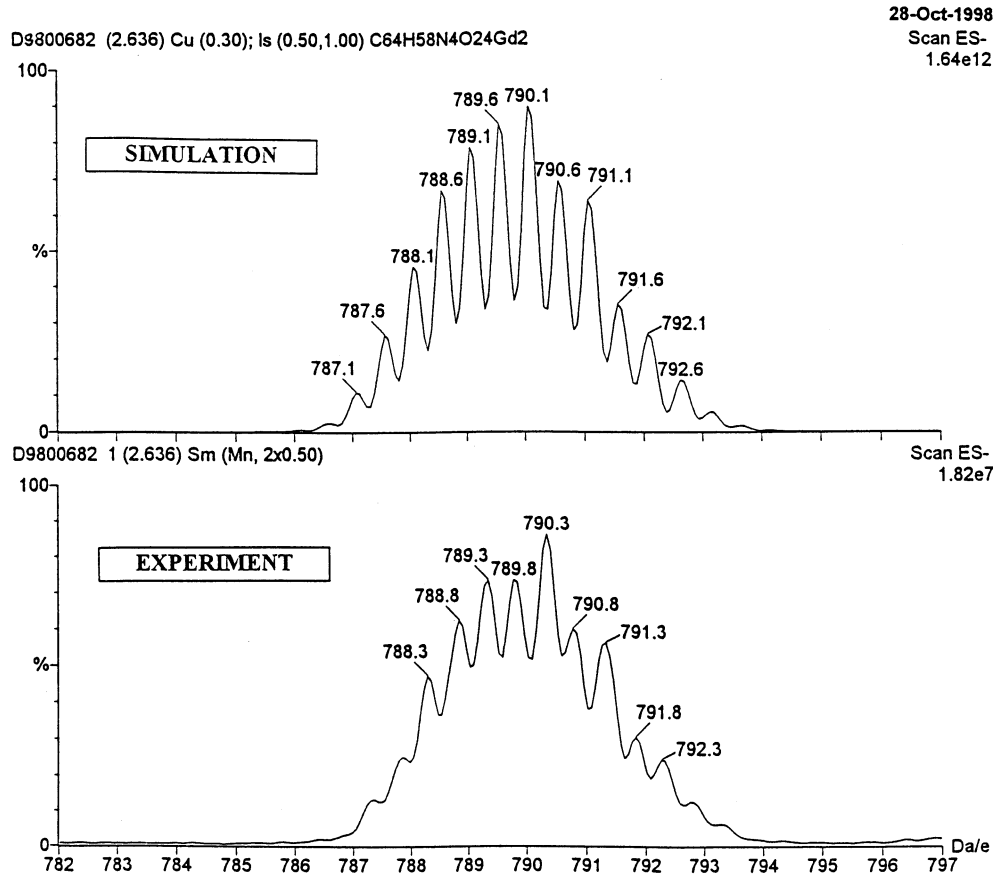


Fig. 10. Comparison of simulated (spectrum above) and experimental (spectrum below) mass spectra of the dimeric complex 2Gd–2OCP (enlarged on the isotopic pattern at $m/z = 790.1$).

We can also point out that no interference was observed with another linear MRI–CM, Gd–DTPA, at a concentration of 2.5 mM.

It has been suggested that Gd–DTPA–BMA undergoes acid-catalysed dissociation and that the so-generated free ligand DTPA–BMA subsequently competes with *o*-cresol-phthalein for the calcium present in the sample, thus leading to apparently and falsely low calcium levels [5].

However, an acid-catalysed dissociation of Gd–DTPA–BMA appears unlikely in our study. Indeed, no acidic conditions were required before the photometric measurements in our conditions. According to the manufacturer's package insert, colorimetric titrations of calcium concentration were carried out at basic pH (pH > 11). Furthermore, the acid-catalysed dissociation hypothesis is invalidated by the fact that Gd–DTPA, which undergoes a fast dissociation in acidic conditions ($T_{\frac{1}{2}\,\mathrm{dissoc}} < 2$ s) [6] did not interfere with the colorimetric technique when subsequently tested at the highest concentration.

In order to explain the reported difference between Gd–DOTA and Gd–DTPA–BMA as regards the serum calcium concentration determined by the colorimetric technique, the mixtures of Gd–DOTA/OCP, Gd–DOTA/MTB, Gd–DTPA–BMA/OCP and Gd–DTPA–BMA/MTB were prepared for a further investigation, in order to monitor possible UV absorbance modifications over time. Irrespective of the colorimetric agent, there were no changes in the UV ab-

sorbance of the reagents with time when the macrocyclic MRI–CM Gd–DOTA was used. Conversely, the presence of Gd–DTPA–BMA clearly changed the UV absorbance of both colorimetric reagents. This marked and immediate change in UV behavior suggests a strong interaction between Gd–DTPA–BMA and both colorimetric reagents.

In order to improve understanding of the nature of this intermolecular interaction occurring only in the case of Gd–DTPA–BMA, ESI-MS analyses were performed using mixtures of Gd–DOTA/OCP, Gd–DTPA/OCP and Gd–DTPA–BMA/OCP. Electro-spray ionization is a convenient and sensitive method of simultaneously detecting the initial Gd^{3+} complexes and their eventual decomplexation in the presence of a ligand competitor, i.e. OCP.

For the macrocyclic MRI-CM Gd–DOTA, no decomplexation phenomenon was observed in the presence of OCP. The same result was obtained with the linear MRI-CM Gd–DTPA. However, in the case of Gd–DTPA–BMA, a complete displacement of Gd^{3+} from Gd–DTPA–BMA by OCP was evidenced in ESI-MS. Indeed, as described by the following equation, the Gd^{3+} ions were totally transferred from their initial ligand DTPA–BMA to the ligand competitor, OCP:

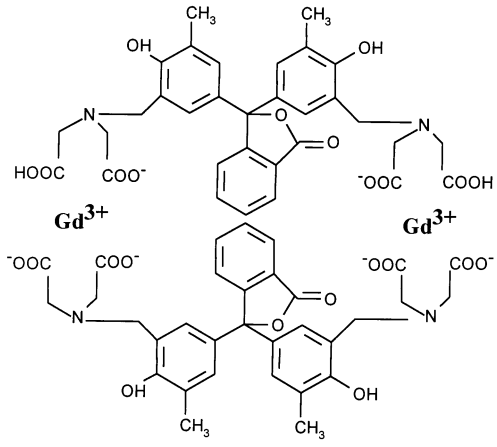


Fig. 11. Hypothetical structure of the dimeric complex 2Gd–2OCP.

$$2\ \text{Gd–DTPA–BMA} + 2\ \text{OCP} \Leftrightarrow$$

$$2\ \text{DTPA–BMA} + 2\text{Gd–2OCP}$$

Subsequently, in ESI, we observed a complete disappearance of Gd–DTPA–BMA and the formation of free DTPA–BMA and a new Gd complex: 2Gd–2OCP. The total displacement of Gd^{3+} by OCP from DTPA–BMA could be related to the weaker stability constant of Gd–DTPA–BMA ($\log K_{eq} = 16.9$) when compared to that of Gd–DOTA and Gd–DTPA ($\log K_{eq}$ respectively 25.8 and 22.1) [6].

It should also be pointed out that the stoichiometry of this dimeric complex is original. Its hypothetical molecular structure is schematized in Fig. 11. It is worth noting that, in this structure, each Gd^{3+} ion is bound by two amine nitrogens and four carboxylic oxygens belonging to two different OCP molecules. In our case, the formation of the monomeric complex Gd–OCP rather than the dimeric complex 2Gd–2OCP is unlikely because of the rigid aromatic part in the middle of the OCP structure which keeps the two amino diacetic acids moieties too far away from one another. Subsequently, the hexa-coordination of the Gd^{3+} ion by only one OCP molecule seems impossible.

The formation of such a dimeric complex could also explain the marked change in the UV absorbance of OCP observed in the presence of Gd–DTPA–BMA. In fact, it is well established that the closeness between two aromatic parts of two molecules often significantly modifies their UV absorbance.

In conclusion, a substantial change in serum calcium levels was observed in the presence of Gd–DTPA–BMA but not of Gd–DOTA or Gd–DTPA (2.5 mM) when using the conventional *o*-cresol-phthalein complexone and methylthymol blue techniques. This discrepancy is not related to acid-catalysed decomplexation of Gd–DTPA–BMA as previously reported, but rather to the existence of an intermolecular interaction between Gd–DTPA–BMA and the colorimetric reagents.

UV and ESI mass spectrometry data demonstrated that there was no intermolecular interaction between Gd–DOTA, Gd–DTPA and the

two colorimetric reagents. On the other hand, in the case of Gd–DTPA–BMA, the OCP proved to be an efficient competitor ligand which can totally-displace the Gd^{3+} ion from its initial ligand DTPA–BMA. This particular behavior of Gd–DTPA–BMA could be related to its weaker stability constant compared to that of Gd–DOTA and Gd–DTPA. Our data may be relevant in the case of serum calcium measurement immediately following an MRI procedure.

References

[1] V.M. Runge, J.W. Wells, Top. Magn. Reson. Imaging 7 (1995) 181–195.
[2] J.F. Debatin, T.F. Hany, Eur. Radiol. 8 (1998) 528–539.
[3] N. Krasnow, Biochim. Biophys. Acta 282 (1972) 187–194.
[4] G.W. Bourne, J.M. Trifaro, Neuroscience 7 (1982) 1615–1622.
[5] P.T. Normann, A. Froysaand, M. Svaland, Scand. J. Clin. Lab. Invest. 55 (1995) 421–426.
[6] M.F. Tweedle, Eur. Radiol. 7 (1997) S225–S230.
[7] C. Anderegg, H. Flaschka, R. Sallman, G. Schwarzenbach, Helv. Chim. Acta 37 (1954) 113–120.
[8] F.H. Pollard, J.V. Martin, Analyst 81 (1956) 348–353.
[9] E.M. Gindler, J.D. King, Am. J. Clin. Pathol. 58 (1972) 376–382.
[10] M. Moini, B.L. Jones, R.M. Rogers, L.F. Jiang, J. Am. Soc. Mass Spectrom. 9 (1998) 977–980.
[11] W.P. Cacheris, S.C. Quay, S.M. Rocklage, Magn. Reson. Imaging 8 (1990) 467–481.
[12] M. VanWagoner, M. O'Toole, D. Worah, P.T. Leese, S.C. Quay, Invest. Radiol. 26 (1991) 980–986.
[13] M.M. Le Mignon, C. Chambon, S. Warrington, R. Davies, B. Bonnemain, Invest. Radiol. 25 (1990) 933–937.