European Journal of Radiology 82 (2013) 768–772

Contents lists available at SciVerse ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Efficacy of diphenhydramine in the prevention of vertigo and nausea at 7 T MRI

Markus Thormann[a,*], Holger Amthauer[a], Daniela Adolf[c], Astrid Wollrab[b], Jens Ricke[a], Oliver Speck[b]

[a] Klinik für Radiologie und Nuklearmedizin, Universitätsklinikum Magdeburg A.ö.R., Otto-von-Guericke Universität, Leipziger Str. 44, 39120 Magdeburg, Germany
[b] Biomedizinische Magnetresonanz, Universitätsklinikum Magdeburg A.ö.R., Otto-von-Guericke Universität, Leipziger Str. 44, 39120 Magdeburg, Germany
[c] Institut für Biometrie und Medizinische Informatik, Universitätsklinikum Magdeburg A.ö.R., Otto-von-Guericke Universität, Leipziger Str. 44, 39120 Magdeburg, Germany

ARTICLE INFO

Article history:
Received 2 August 2011
Accepted 3 August 2011

Keywords:
High-field MRI
7 T
Side effects
Vertigo
Diphenhydramine

ABSTRACT

Purpose: In this study the potential of diphenhydramine in reducing respectively preventing vertigo and nausea induced by the ultra-high static magnetic field at 7 T was evaluated.
Materials and methods: In a prospective, double blinded, placebo controlled, cross-over randomized study the sensations of 34 volunteers before, during and after exposure to the static magnetic field with and without drug respectively placebo administration were quantified. Fast table motion was applied to increase the incidence of otherwise sparse reports of field related sensations.
Results: The strength of vertigo can be reduced by the application of diphenhydramine.
Conclusion: Diphenhydramine, even at a low dose, reduces the strength of vertigo at ultra-high static magnetic fields, may be used preventively, and could pave the way to even higher field strength.

1. Introduction

A continuing and major trend in MR is the use of higher and higher static magnetic field strength to achieve higher signal-to-noise ratio [1]. This can be exploited e.g. for higher spectral resolution in MRS, higher spatial resolution in MR imaging, shorter scan times, or increased sensitivity and spatial specificity of the BOLD response for functional MRI [2–4]. At present, MR systems with field strength of up to 3 T are a standard diagnostic tool and ultra-high-field-strengths, mainly 7 T, are used for research in human subjects [5]. However, it is conceivable, that they will be integrated in clinical applications in the foreseeable future [1].

With the continuing increase in field strength, different side effects related to subjective sensations of the patients become relevant. This could negatively affect patient compliance and acceptance for this new technology [6].

Of all the system hardware components, the magnet with its higher field strength, larger size and longer bore is the main difference to clinical scanners. The gradient system performance is similar to 1.5 T and 3 T systems [6]. The electromagnetic RF pulses have a higher frequency of approximately 300 MHz, but according to IEC limits the power absorption is regulated identically to lower field systems. The acoustic noise caused by the interaction of the gradient system with the static magnetic field can potentially be higher. However, due to effective noise damping within the space of the absent RF body coil, is can be reduced to values similar to 3 T scanners [7].

Previous studies examining sensations related to the static magnetic field have found an increasing number of side effects at field strength of 4 T an higher [6]. Side effects typically related to the ultra-high static magnetic field are vertigo, nausea, metallic taste and light flashes, called phosphenes [8].

Vertigo is, with up to 25% of the examined subjects, the most frequently reported high-field related sensation and the second most field-related disturbing factor for subjects [6]. For a high degree of acceptance it is important to minimize or avoid these physiologic effects if possible.

The current hypothesis for the cause of vertigo as induced by the ultra-high magnetic field is based on two different mechanisms. These are magnetic susceptibility differences between vestibular organs and surrounding fluid and induced currents, acting on the vestibular hair cells. These mechanisms produce misleading signals in the brainstem, similar to motion sickness [9].

Diphenhydramine (DPH) is a first generation antihistamine, frequently used to prevent motion sickness. It works by blocking the effect of histamine at H1 receptor sites in the CNS. DPH is available as an over-the-counter-drug and has relatively rare side effects [10], including anticholinergic effects such as dry mouth, throat or nose, thickening of mucus in nose or throat. Sedative effects may become relevant at DPH blood levels of 30 ng/ml or higher [11,12].

* Corresponding author. Tel.: +49 391 67 13030; fax: +49 391 67 13029.
E-mail address: markus.thormann@med.ovgu.de (M. Thormann).

0720-048X/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ejrad.2011.08.001

The aim of this study was to evaluate whether diphenhydramine can reduce respectively prevent vertigo and nausea induced by the ultra-high static magnetic field at 7 T.

2. Materials and methods

IRB approval was obtained from the local Ethics Committee. All volunteers gave written informed consent prior to their participation in the study.

The study was designed as a prospective double-blinded, placebo controlled cross-over randomized study. The volunteers were randomized in two groups, a drug-group and a placebo-group. Each group consisted of 17 subjects. All participants as well as all persons involved in drug administration and examination were blinded from drug or placebo assignment. The medication consisted of 20 mg diphenhydramine–HCl (diphenhydramine sol., 2 ml, Hevert, Germany) dissolved in 200 ml water or the placebo of 2 ml saline solution dissolved in 200 ml water to provide similar taste and was administered orally.

Subjects were recruited on the basis of the study inclusion and exclusion criteria: The volunteers were between 18 and 65 years of age, did not have any contraindications against MR examinations, especially pacemakers or metal fragments and did not take any drugs or alcohol prior the examination.

The experiments were performed on a whole-body 7 T system (Siemens Medical Solutions, Erlangen, Germany) without the application of gradients or radiofrequency pulses during the exam. The scanner bore had a diameter of 60 cm and a length of 3.6 m.

All subjects were moved into the scanner two times on two different days. In randomized order, subjects received either the drug or placebo on one day and no medication on the other day. The subjects were moved into the bore in the supine head first position and were instructed to keep the eyes closed.

On the day of the drug respectively the placebo application the B0-field exposure started 20 min after oral intake.

The table was moved manually at a velocity of 0.2 m per second, i.e. 10 s into the center of the magnet. This is approximately six times faster than the standard velocity. After moving to the magnet center, the subject was lying in the scanner for one minute and the speed back out of the magnet was identical at 0.2 m/s. The table operator remained in the examination room, so that communication and supervision was ensured.

After each experimental step (moving into the static magnetic field, resting in the isocenter, and moving out), the subjects reported any sensations in a questionnaire. The subjects described and rated the appearance of different possible physiologic sensations such as vertigo, nausea, metallic taste, light flashes and possible side effects of the drug, e.g. drowsiness or dry mouth, on a 10-point-scale separately for the different examination phases. The 10-point-scale reflects an intensity level from 0 = no sensation to 9 = very strong sensation. Additionally, the subjects were asked to report any other cause of discomfort such as bore narrowness or temperature. In ten subjects the blood plasma level of diphenhydramine was determined within 10 min after the B0-field exposure.

3. Statistical analysis

SPSS statistics software, version 17 (SPSS Inc., USA) was used for all data analyses. Data were analyzed non-parametrically. Strength of vertigo was compared using paired Wilcoxon test, occurrence of vertigo was evaluated using McNemar test.

All tests were two sided and a p value of 0.05 was referred to be the level of significance.

Table 1
General sensations.

Sensations	Drug	Drug-control	Placebo	Placebo-control
Nervousness before starting	6	5	3	2
Feeling of insecure standing after exp.	7	6	3	7
Narrowness of the bore	2	2	4	3
Sweating	2	2	1	4
Feeling of heat	3	2	2	2
Palpitations	2	2	2	2
Feeling of coldness	1	0	1	0
Claustrophobia	0	0	1	0
Muscle twitching	0	1	0	0
Unpleasantness generally during moving in	5	9	6	4
Unpleasantness generally during moving out	4	7	3	2

4. Results

34 healthy volunteers (male, $n = 12$; female, $n = 22$; mean age, 28 years; range, 22–57 years) were recruited for this study. All 34 subjects completed both examination days. Therefore 68 questionnaires have been included in the evaluation.

20 of the volunteers did not participate in an MRI examination previously, 8 have already been in a 1.5 T, 4 in a 3 T and 2 in a 7 T scanner. Only the two subjects who already participated in a 7 T study, reported vertigo respectively metallic taste in any prior MR examination. The other subjects did not report any previous experience of side effects during MRI.

Before MRI testing, 6/34 subjects reported that they become vertiginous easily, 24 negated symptoms and 4 answered “I do not know”.

12 volunteers previously used medication against vertigo, thereof 6 dimenhydrinate, 2 metoclopramide and 4 did not know the name of the drug. The doses were unknown. From the 6 volunteers, who previously used dimenhydrinate, 2 felt drowsiness after taking the drug.

None of the volunteers terminated the examinations prematurely. Oral administration of the drug was well tolerated by all subjects.

32 of 34 subjects kept their eyes closed during the first and the second examination. All subjects reported the position on the patient table as comfortable.17 subjects received the drug and 17 participants the placebo medication. The average time between drug intake and examination start was 24 min (range, 17–38 min).

25 subjects reported sensations related to the high static magnetic field exposure. None of the subjects reported tachycardia or faint.

Overall 25 of 34 volunteers reported vertigo at this high table speed, 15 in the drug-group and 9 in the placebo-group.

The occurrence of vertigo did not differ significantly between the drug respectively the placebo group and the control group during all four phases, moving into, resting in, moving out of the scanner, and after the examination (Table 2).

However, differences in the maximum intensity and therewith the ranges of vertigo was detected. The major difference occurred during moving into the scanner ($p = 0.012$). The maximum intensity decreased from 9 to 5 and the median from 2 to 0 compared to the control B0-exposure (Fig. 1).

The drug group showed a trend towards decrease compared to the drug-control group during resting in the scanner ($p = 0.074$), with a decrease of the maximum intensity from 7 to 5, and during moving out of the scanner ($p = 0.094$), with a decrease of the maximum intensity from 7 to 3 (Figs. 2 and 3).

Table 2
Number of volunteers reporting vertigo.

	Vertigo in general	Vertigo during moving in	Vertigo during resting	Vertigo during moving out	Vertigo after examination
Drug	15	7	1	5	5
Drug-control	14	10	11	5	5
Placebo	9	5	6	2	3
Placebo-control	8	4	6	0	3

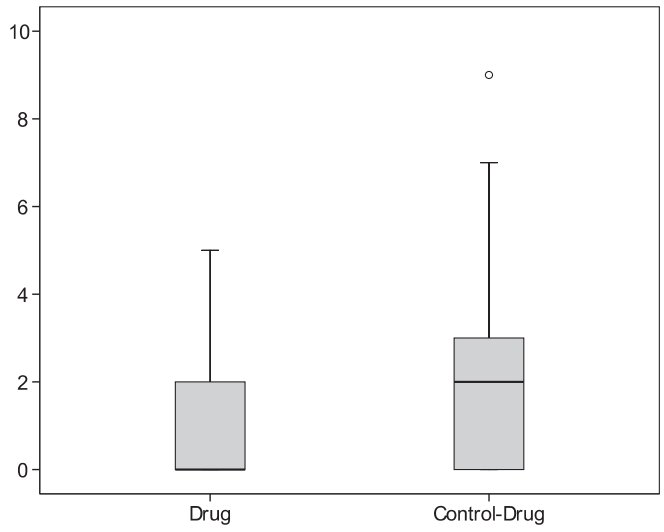

Fig. 1. Strength of vertigo during moving into the scanner. $p = 0.012$.

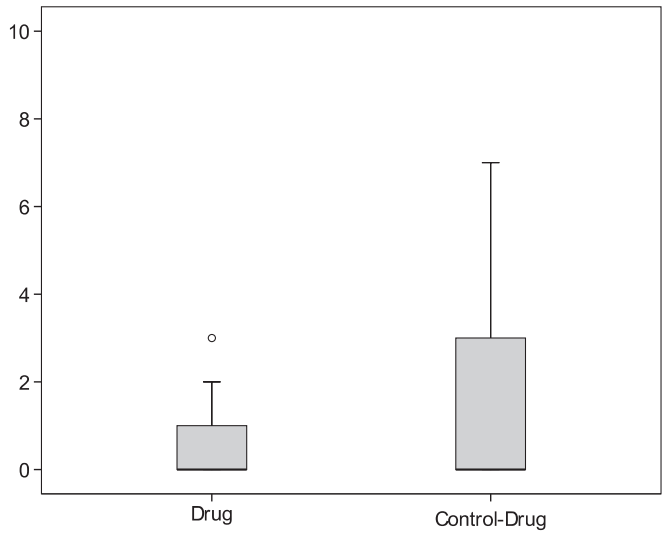

Fig. 3. Strength of vertigo during moving out of the scanner. $p = 0.094$.

The placebo-group did not show a significant difference during moving into the scanner ($p = 0.5$), resting in the scanner ($p = 0.94$) and moving out of the scanner ($p = 0.5$). During all three phases, the placebo group showed a higher maximum rate compared to the placebo-control group.

After the examination, no significant difference in the median of the intensity was present in any of the groups. However, the maximum rating of the strength of vertigo was higher in the control group, compared to the drug group (Fig. 4). The same occurred in the placebo group.

Nausea appeared twice in the placebo group and once in the control-examination of the drug-group. It did not appear under drug administration. However, even though this suggests a trend, based on these low frequencies, no adequate statistical analysis could be performed.

Other physiologic sensations, typically related to field strength of 7 T, occurred, but did not show a correlation to the drug respectively the placebo administration. Light flashes appeared 3 times in the placebo and twice in the placebo-control group; metallic taste was described once in the drug-control group and once in the placebo group.

General sensations, related to MR-examinations, independent to the field strength, appeared, but did not show any correlation to the different groups (Table 1).

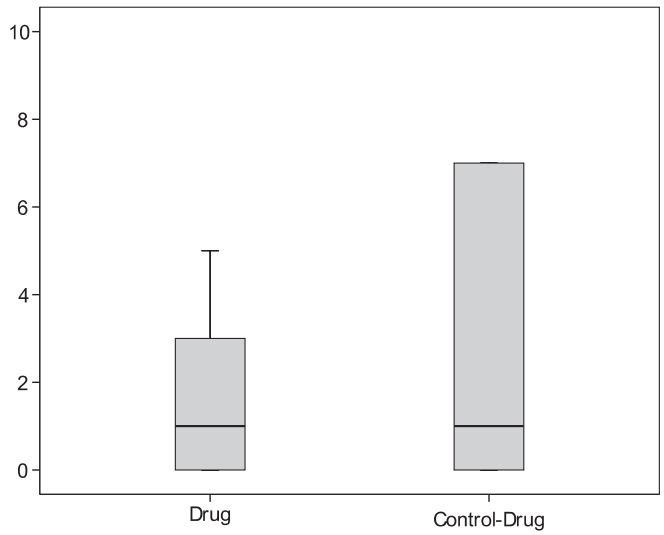

Fig. 2. Strength of vertigo during rest in the isocenter of the scanner. $p = 0.074$.

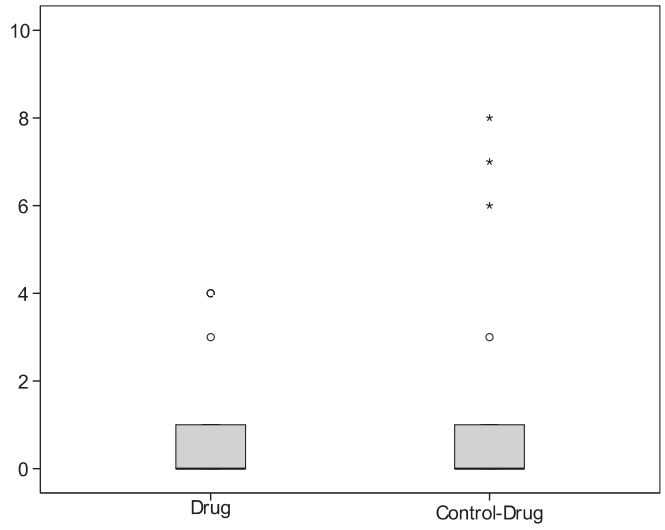

Fig. 4. Strength of vertigo after examination. $p = 0.125$.

Table 3
Newly reported (potentially drug related) sensations after diphenhydramine application.

	Drug	Placebo	Control
Tiredness	1	0	0
Drowsiness	4	0	5
Xerostomia	2	1	1
Headache	1	1	4

Tiredness, drowsiness and anticholinergic side effects that had been associated with diphenhydramine were reported in the drug, placebo and both control groups without any tendency towards the drug administration (Table 3).

None of the measured plasma concentrations of diphenhydramine exceeded the drowsiness level of 30 ng/ml (median 15.1 ng/ml, range, 11.8–20.7).

5. Discussion

To our knowledge, this is the first study that evaluates the efficacy of a drug for the prevention of vertigo, occurring in a strong static magnetic field.

In a previous study it was shown, that approximately 25% of subjects exposed to the field of a whole body 7-T MRI report vertigo, especially during table motion [6]. In order to provoke a high incidence of vertigo-reports, the table speed was increased by a factor of 6, compared to our standard procedure. With this predefined speed, almost 75% of the volunteers reported vertigo during the motion into the magnet, resting, moving out or after the B0-field exposure.

This study suggests that prophylaxis with the antihistamine diphenhydramine reduces the strength of vertigo during examinations in an ultra-high-field MR-scanner.

The antihistamine diphenhydramine is a drug with effects depending on the dose. For blood plasma levels below 30 ng/ml, antiemetic effects without being sedative have been reported [13]. In our volunteers a plasma level of 15 ng/ml was reached after approximately 30 min, which did not suppress but reduce the incidence and rating of vertigo relative to unmedicated conditions. Placebo did not reduce vertigo significantly.

In the analysis also volunteers, who did not notice vertigo in any of the different phases and after the B0-exposure and therefore could not get any improvement of the drug, were included. Nevertheless, significant differences in the strength of vertigo could be detected.

Reports of vertigo did not completely disappear for the drug dose applied. We used a dose as low as possible to achieve a significant effect on the sensation of vertigo and to avoid relevant side effects, mainly drowsiness and tiredness. A higher dose of diphenhydramine (recommended dose: 25–50 mg [14]) is possible, presumably reducing vertigo even further. However the potential side effect of increased drowsiness has to be considered. Whereas this may not be problematic or even helpful for anatomy studies, such side effects may interfere with neuro-cognitive functional studies. On the other hand, subjects' indisposition due to vertigo or even nausea will likely also have an effect on brain function or subject performance. Thus, the consequences of DPH administration as a preventive measure for such exams have to be evaluated further and need to be considered in comparison to field strength related confounds.

A high rate for vertigo during table motion was reported. This supports the proposed mechanisms, that relate vertigo sensations to temporal changes of the magnetic flux in inner ear structures [9], as the only difference to previous studies was the increased table speed.

Other side effects of the ultra-high static magnetic field, such as light flashes and metallic taste, as well as general sensations, occurring during a MR-examination appeared without any correlation to the drug or placebo administration.

The vertigo incidence rate and strength is currently not a major limitation for 7 T examinations in research subjects and patients. However, unpleasant sensations will likely increase at higher field strength [15,16]. Human MRI-systems with 9.4 T, 10.5 T and 11.7 T are currently operational or being installed [17,18]. The preventive application of diphenhydramine may be an efficient measure to allow examination of human subjects at such high or even higher field strength. Future studies may also evaluate other drugs with higher efficacy for the prevention of high magnetic field related discomfort. Possible examples are scopolamine with d-amphetamine [19] or drugs with lower side effects for which an effect on motion sickness is controversial [19,20].

6. Conclusion

Diphenhydramine, even at a low dose, reduces the strength of vertigo at ultra-high static magnetic fields without increased drowsiness and may be used as prevention for high field MR studies.

Conflict of interest

The authors declare that they have no conflict of interest according to the guidelines of the International Committee of Medical Journal Editors.

Acknowledgement

The study was supported by DFG (SFB779).

References

[1] Kangarlu A, Baudendistel KT, Heverhagen JT, Knopp MV. Clinical high- and ultrahigh-field MR and its interaction with biological systems. Radiologe 2004;44(1):19–30.
[2] Breyer T, Wanke I, Maderwald S, et al. Imaging of patients with hippocampal sclerosis at 7 Tesla: initial results. Acad Radiol 2010;17(4):421–6.
[3] Hoffmann MB, Stadler J, Kanowski M, Speck O. Retinotopic mapping of the human visual cortex at a magnetic field strength of 7 T. Clin Neurophysiol 2009;120(1):108–16.
[4] Klomp DW, Bitz AK, Heerschap A, Scheenen TW. Proton spectroscopic imaging of the human prostate at 7 T. NMR Biomed 2009;22(5):495–501.
[5] Schmitt F, Grosu D, Mohr C, et al. 3 Tesla MRI: successful results with higher field strengths. Radiologe 2004;44(1):31–47.
[6] Theysohn JM, Maderwald S, Kraff O, et al. Subjective acceptance of 7 Tesla MRI for human imaging. Magma 2007.
[7] Stadler JDP, Baumgart F, Brechmann A. Reduction of the acoustic noise of a Siemens 7 Tesla scanner. In: Proceedings of international society for magnetic resonance in medicine, vol. 14. 2006.
[8] Schenck JF, Dumoulin CL, Redington RW, et al. Human exposure to 4.0-Tesla magnetic fields in a whole-body scanner. Med Phys 1992;19(4):1089–98.
[9] Glover PM, Cavin I, Qian W, Bowtell R, Gowland PA. Magnetic-field-induced vertigo: a theoretical and experimental investigation. Bioelectromagnetics 2007;28(5):349–61.
[10] Estelle F, Simons R. H1-receptor antagonists: safety issues. Ann Allergy Asthma Immunol 1999;83(5):481–8.
[11] Gielsdorf W, Pabst G, Lutz D, Graf F. Pharmacokinetics and bioavailability of diphenhydramine in man. Arzneimittel-Forschung 1986;36(4):752–6.
[12] Gengo F, Gabos C, Miller JK. The pharmacodynamics of diphenhydramine-induced drowsiness and changes in mental performance. Clin Pharmacol Ther 1989;45(1):15–21.
[13] Scavone JM, Greenblatt DJ, Harmatz JS, Engelhardt N, Shader RI. Pharmacokinetics and pharmacodynamics of diphenhydramine 25 mg in young and elderly volunteers. J Clin Pharmacol 1998;38(7):603–9.
[14] Valoti M, Frosini M, Dragoni S, Fusi F, Sgaragli G. Pharmacokinetics of diphenhydramine in healthy volunteers with a dimenhydrinate 25 mg chewing gum formulation. Methods Find Exp Clin Pharmacol 2003;25(5):377–81.
[15] Vaughan T, DelaBarre L, Snyder C, et al. 9.4 T human MRI: preliminary results. Magn Reson Med 2006;56(6):1274–82.
[16] Ibrahim TS, Mitchell C, Schmalbrock P, Lee R, Chakeres DW. Electromagnetic perspective on the operation of RF coils at 1.5–11.7 Tesla. Magn Reson Med 2005;54(3):683–90.

[17] Vedrine P, Aubert G, Beaudet F, et al. The whole body 11.7 T MRI magnet for Iseult/INUMAC Project. IEEE Trans Appl Superconduct 2008;18(June (2)):868–73.
[18] Vedrine P, Aubert G, Beaudet F, et al. Iseult/INUMAC whole body 11.7 T MRI magnet status. IEEE Trans Appl Superconduct 2010;20(June (3)):696–701.
[19] Wood CD, Manno JE, Wood MJ, Manno BR, Mims ME. Comparison of efficacy of ginger with various antimotion sickness drugs. Clin Res Pract Drug Regulat Aff 1988;6(2):129–36.
[20] Stewart JJ, Wood MJ, Wood CD, Mims ME. Effects of ginger on motion sickness susceptibility and gastric function. Pharmacology 1991;42(2):111–20.