Effects of dexamethasone on peritumoural oedematous brain: a DT-MRI study

S Sinha, M E Bastin, J M Wardlaw, P A Armitage, I R Whittle

Objectives: Glucocorticoids (dexamethasone) are thought to reduce peritumoural brain oedema by decreasing the permeability of neoplastic capillaries and/or enhancing the clearance of extracellular water. Diffusion tensor magnetic resonance imaging (DT-MRI) was used to measure the water diffusion parameters of oedematous and normal brain in a group of patients with intracranial tumours before and after steroid treatment.

Methods: Fifteen patients with intracranial tumours (seven with high-grade glioma, four with metastatic carcinoma and four with meningioma) were examined before and 48–72 h after dexamethasone treatment (16 mg/day). The mean diffusivity (<D>) and fractional anisotropy (FA) were measured for oedematous brain and apparently normal contralateral white matter before and after steroid therapy.

Results: In all three patient groups there was a significant decrease in <D> of oedematous brain after steroid treatment (p<0.01). There was no significant change in FA of oedematous brain after treatment in any of the three groups. There was also no significant change in either <D> or FA of apparently normal contralateral white matter after treatment.

Conclusion: These data indicate that dexamethasone produces a localised reduction in the magnitude of extracellular water molecule mobility, and hence water content, in peritumoural oedematous brain. Furthermore, the magnitude of these changes is similar for both intra- and extra-axial tumours.

In patients with malignant cerebral tumours, the signs and symptoms are due to not only the location and mass effect of the tumour, but also the associated peritumoural oedema. Following several studies that documented a decrease in both surgical morbidity and mortality following glucocorticoid (dexamethasone) treatment,1,2 steroid therapy is now routinely used in the management of patients with brain tumours and peritumoural oedema. Although their modes of action are poorly understood, steroids are thought to play a major role in decreasing oedema formation by reducing the permeability of neoplastic capillaries and/or enhancing the clearance of extracellular water.3

The effects of glucocorticoids on water abnormalities in peritumoural brain can be assessed non invasively using diffusion tensor magnetic resonance imaging (DT-MRI). This technique permits the spatial mapping of the apparent diffusion tensor of water (D) in the brain, from which the mean diffusivity (<D>) and scalar diffusion anisotropy indices, such as the fractional anisotropy (FA), can be determined.4,5 The parameter <D>, which is thought to reflect the average microscopic mobility of water molecules in the extravascular extracellular space,6 can detect and characterise brain oedema, while FA provides a scalar measure of the deviation from pure isotropic diffusion of water mobility in vivo.5 Recent studies have shown that <D> and FA of peritumoural oedematous brain are respectively increased and reduced compared with normal healthy cerebral tissue.6,7 This rise in <D> indicates an increase in the magnitude of water mobility, whereas the decrease in FA suggests a loss of structural organisation within peritumoural brain. These alterations in <D> and FA are thought to arise from a combination of increased water content and tumour infiltration.8 If steroids act by producing a normalisation in peritumoural brain water homeostasis, then this action should reduce <D> and increase FA towards the values seen in healthy brain parenchyma. In this paper this hypothesis is investigated by measuring the water diffusion parameters of oedematous and normal brain in a group of patients with intracranial tumours before and 48–72 h after dexamethasone treatment.

METHODS
Subjects
Twenty consecutive patients presenting with a newly diagnosed, supratentorial, solitary, intracranial tumour were enrolled in this prospective study. Each subject had evidence of oedema on the initial CT scan, but without indication of other concurrent neurological disease. At the time of imaging, none of the patients had (i) begun steroid treatment, (ii) had any prior radiotherapy or chemotherapy, or (iii) undergone any prior cranial surgery. They also had no contraindications to MRI. The local ethics committee approved the study and informed consent was obtained from each patient.

MRI protocol
All MRI data were obtained using a GE Signa LX 1.5 T (General Electric, Milwaukee, WI, USA) clinical scanner, equipped with a self-shielding gradient set (22 mT/m maximum gradient strength and 120 T/m/s slew rate) and a manufacturer-supplied "birdcage" quadrature head coil. The MRI examination consisted of a standard fast spin-echo (FSE) T2-weighted sequence, a DT-MRI protocol described previously, and a contrast-enhanced T1-weighted volume sequence.7 The duration of the examination was approximately 40 min. This protocol was repeated 48–72 h after dexamethasone treatment (16 mg/day) had begun.

To ensure that the slice locations used in the second examination corresponded as closely as possible to those in the first, the subject’s head position and tilt in the first scan were recorded and the patient repositioned in exactly the same manner for the second scan. At least one of the slices

Abbreviations: DT-MRI, diffusion tensor magnetic resonance imaging; DW, diffusion-weighted; EP, echo-planar; FA, fractional anisotropy; FOV, field of view; FSE, fast spin-echo; GBM, glioblastoma multiforme; ROI, region of interest; SD, standard deviation
were generated on a voxel-by-voxel basis and converted into
the fractional anisotropy 5 and the fractional anisotropy 5
acquisition matrix of 128 6 1.0 mm slice gap, a field of view (FOV) of 240
slice position. The acquisition parameters for the DW-EP
aligned to the T 2-weighted (that is anisotropic, and takes a value of 0 for isotropic
planar (EP) imaging sequence in which two symmetric
were collected with diffusion gradients applied sequentially
along six non collinear directions.5 Five acquisitions consisting
of a baseline T2-weighted EP image (G0) and six DW-EP images
(G 1 to G6), a total of 35 images, were collected per slice position. The acquisition parameters for the DW-EP
imaging sequence were 15 axial slices of 5 mm thickness and
1.0 mm slice gap, a field of view (FOV) of 240×240 mm, an acquisition matrix of 128×128 (zero filled to 256×256), a TR
of 10 s, and a TE of 98.8 ms.
After the DT-MRI protocol, 20 ml of gadopentetate dimeglumine (Magnevist, Berlex Laboratories, Wayne, NJ, USA) was administered intravenously. Acquisition parameters for the contrast enhanced T1-weighted volume
sequence were 110 contiguous axial slices of 1.5 mm
thickness, an FOV of 240×240 mm, an acquisition matrix of
256×256, a TR of 7.3 ms, a TE of 3.2 ms, and a TI of
400 ms.

Image analysis
Quantitative co-registered maps of brain water diffusion
parameters for the pre- and post-treatment examinations
were obtained in the following manner. Bulk patient motion
and eddy current induced artefacts were removed from the
component EP images using FLIRT (www.fmrib.ox.ac.uk/fsi), a three-dimensional computational image alignment pro-
gram.11 Firstly, EP images with the same b-matrix were
rigidly aligned to remove patient motion. Secondly, affine transformations were used to align the DW-EP images
acquired with diffusion gradient directions G1 to G6 to
the first gradient direction G1. Thirdly, all DW-EP images
were aligned to the T2-weighted (G0) EP images acquired in the
first examination. Next the set of five EP images collected for
each gradient direction was averaged to give seven high
signal-to-noise ratio images for each slice. From this MRI
data D was calculated in each voxel from the signal
intensities in the component EP images.4 After diagonalisa-
tion of D to yield the magnitude sorted eigenvalues (∆1,2,3),
maps of the T2-weighted signal intensity, mean diffusivity

\[
<D> = \frac{(\lambda_1 + \lambda_2 + \lambda_3)}{3},
\]
and the fractional anisotropy

\[
FA = \sqrt{\frac{(\lambda_3 - <D>^2 + (\lambda_2 - <D>^2)^2 + (\lambda_1 - <D>^2)^2)}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}},
\]
were generated on a voxel-by-voxel basis and converted into
Analyze (Mayo Foundation, Rochester, MN, USA) format. The FA measures the fraction of the total “magnitude” of D
that is anisotropic, and takes a value of 0 for isotropic diffusion (∆1 = ∆2 = ∆3) and 1 for completely anisotropic diffusion (∆1 > 0; ∆2 = ∆3 = 0).

Region-of-interest analysis
The effects of dexamethasone on the brain water diffusion
parameters of peritumoural oedematous brain were quanti-
fied using a previously described region-of-interest (ROI) analysis.7 Blinded as to whether the imaging data came from the pre- or post-treatment examination, the observer (SS)
identified for each slice the largest region of signal
hyperintensity on the T2-weighted EP images which extended
beyond the enhancing tumour margin present in the co-
registered contrast-enhanced T1-weighted volume images.
This oedematous brain region was overlaid on the <D> and FA
parametric maps obtained from both examinations. For
each appropriate slice, values of <D> and FA for the entire
oedematous brain region and apparently normal contralateral
white matter in the centrum semiovale were measured.
Overall mean <D> and FA values were then calculated from
data sets to give volume measures for the two tissue types in
each patient. The volume measurements of <D> and FA were
typically obtained from several thousand voxels in five
to 12 slices for oedematous brain, and hundreds of voxels in a
single slice for apparently normal contralateral white matter
in the centrum semiovale.

Statistical analysis
All data are reported as a mean with one standard deviation
(SD) in parentheses. For each patient the percentage change
in <D> and FA for oedematous and normal brain following
steroid treatment was determined as follows

\[
e(X) = 100\frac{X_{post} - X_{pre}}{X_{pre}}, \text{ where } X = <D> \text{ or FA.}
\]

The percentage change (e) in <D> and FA for both tissue
types was calculated for each patient, and a mean value
(<e>) obtained for each of the three disease groups. To
assess whether changes in these water diffusion parameters
were significant, the mean pre- and post-treatment values
of <D> and FA for each patient were compared using a paired-
samples Student’s t test (SPSS 10.0, SPSS, Chicago, IL, USA),
with p<0.05 being considered statistically significant.

RESULTS
Of the 20 patients initial enrolled in the study, seven men and
eight women (mean (SD) age 58.6 (9.7) years) tolerated both
examinations and had an enhancing lesion on the T1-
weighted volume scan. Of these 15 patients, seven had
glioblastoma multiforme (GBM), four had metastatic carci-
noma, and four had meningioma. In all patients the tumour
type was confirmed histologically, with all surgical proce-
sures performed after the second MRI examination. There
was a significant improvement in limb function in one of the
seven patients with GBM following steroid therapy, while in
the remaining subjects improvement was more limited
and subjective, with the typical benefit being relief from
headache.
Pre- and post-treatment values of <D> and FA for
the remaining patients are shown in table 1, along with their demographic information. Fig 1
shows maps of T2-weighted signal intensity, <D>, and FA
before and after steroid treatment for a representative slice
acquired from a 55 year old female patient with GBM
(patient 1). These maps show the marked difference in the
water diffusion parameters between oedematous and normal
brain, with the former characterised by high values of <D>
and low values of FA. This figure also shows that although
the water diffusion abnormalities of oedematous brain are
not completely resolved by steroid treatment after 72 h, there
is a widespread reduction in the T2-weighted signal intensity.
DISCUSSION

There have been several recent studies using DT-MRI to characterise the water diffusion properties of intracranial tumours. Sinha et al. investigated whether water diffusion parameters could differentiate tumour margin from oedematous brain in nine patients with GBM. They found that while $<D>$ of tumour margin was significantly different from that of oedematous brain, FA was not. Lu et al. measured $<D>$ and FA values in peritumoural brain in 12 patients with high-grade glioma and 12 with metastatic lesions and found that only $<D>$ was significantly different in these two pathologies. Price et al. found evidence for tumour infiltration in high-grade gliomas, when comparing DT-MRI and T2-weighted imaging data from 20 patients with gliomas and metastases. By analysing MRI and biopsy data in 31 patients with astrocytic tumours, Bepup et al. found evidence that the FA values of glioblastoma and anaplastic, diffuse, and pilocytic astrocytoma are largely affected by cellularity and/or vascularity. Changes in the water diffusion parameters of oedematous brain following dexamethasone treatment have previously only been described by Bastin et al. In their small pilot study of six patients with a wide range of tumours, they found evidence for a reduction in $<D>$ of oedematous brain following dexamethasone treatment in one patient with GBM.

The results of the current study show that $<D>$ of oedematous brain associated with high-grade, metastatic carcinoma, and meningioma is significantly reduced 48–72 h after dexamethasone treatment, and that this reduction is of a similar magnitude in all three tumour types. Previous studies have shown that oedematous brain associated with intra- and extra-axial tumours has a much higher proton longitudinal relaxation time ($T_1$) than normal brain, and that dexamethasone reduces these elevated $T_1$ values. Since $T_1$ reflects brain tissue water content, and DT-MRI predominantly measures the mobility of water molecules in the extracellular space, these data suggest that dexamethasone acts by reducing the extracellular water fraction. This reduction then produces the marked decline in $<D>$ of oedematous brain observed above. Interestingly, however, this effect is not sufficient, at least after 48–72 h, to increase axonal organisation, as measured by FA, towards more normal values. Furthermore, since significant differences in $<D>$ and FA were not seen in normal brain, it is concluded that dexamethasone has only a localised effect on brain water content.

The current study has both strengths and weaknesses. Firstly, none of the patients had undergone previous treatment or had recurrent and/or residual tumours. Since the effect of surgery or adjunct therapy on oedematous brain $<D>$ and FA values is not known, excluding such patients makes quantifying the changes in water diffusion parameters after steroid treatment more straightforward. Secondly, by measuring the water diffusion parameters over the entire oedematous brain volume one avoids any subjective bias that may occur when small ROIs are placed in regions of abnormal signal intensity. The main limitation of the paper is the small number of patients imaged. However, even with this number of subjects the effects of dexamethasone on the water diffusion parameters of peritumoural oedematous brain are clear.

CONCLUSION

In this study the effects of dexamethasone on the water diffusion parameters of oedema associated with intracranial tumours and apparently normal contralateral white matter have been quantified using DT-MRI. In all three patient groups, $<D>$ of peritumoural oedematous brain was significantly reduced 48–72 h following steroid treatment,
while FA was approximately unchanged. The water diffusion parameters of normal tissue were also unchanged. These data indicate that dexamethasone produces a localised reduction in the magnitude of extracellular water molecule mobility, and hence water content, in peritumoural oedematous brain. Furthermore, the magnitude of these changes is similar for both intra- and extra-axial tumours. These results also indicate that DT-MRI may provide a sensitive non invasive tool for evaluating the treatment response of peritumoural oedema not only to dexamethasone, but potentially also to other chemotherapeutic agents.

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Table 1

| Values of the mean diffusivity (D) and fractional anisotropy (FA) for peritumoural oedematous brain and apparently normal contralateral white matter (centrum semiovale) pre- and post-steroid treatment for the 15 patients imaged in this study |
|---|---|---|---|---|---|---|---|---|---|---|
| Mean diffusivity, D (×10^{-6} mm^2/s) | Fractional anisotropy |
| | Oedematous brain | Contralateral white matter | Oedematous brain | Contralateral white matter |
| Age/sex | Pre-steroids | Post-steroids | Pre-steroids | Post-steroids | Pre-steroids | Post-steroids | Pre-steroids | Post-steroids |
| Glioblastoma | 1/55/F | 1674 (253) | 1561 (318) | 750 (18) | 740 (24) | 0.15 (0.06) | 0.16 (0.07) | 0.47 (0.10) | 0.47 (0.10) |
| | 2/50/M | 1575 (213) | 1430 (256) | 758 (24) | 766 (22) | 0.15 (0.05) | 0.17 (0.07) | 0.49 (0.05) | 0.48 (0.04) |
| | 3/61/F | 1139 (152) | 1046 (144) | 719 (25) | 716 (22) | 0.21 (0.08) | 0.21 (0.09) | 0.43 (0.05) | 0.42 (0.04) |
| | 4/65/M | 1494 (211) | 1377 (228) | 717 (46) | 711 (46) | 0.18 (0.09) | 0.20 (0.10) | 0.42 (0.08) | 0.40 (0.07) |
| | 5/71/M | 1140 (336) | 1068 (288) | 690 (25) | 704 (22) | 0.22 (0.10) | 0.23 (0.10) | 0.40 (0.07) | 0.41 (0.10) |
| | 7/75/M | 1288 (189) | 1206 (189) | 775 (76) | 757 (67) | 0.20 (0.07) | 0.19 (0.07) | 0.43 (0.10) | 0.41 (0.10) |
| Mean | 1398 (212) | 1291 (191) | 741 (33) | 734 (26) | 0.18 (0.03) | 0.18 (0.02) | 0.46 (0.04) | 0.45 (0.04) |

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