Changes in the transfer constant of a macromolecular MR contrast agent after dexamethasone administration in 9L rat cerebral tumor

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Introduction: The glucocorticoid dexamethasone is a standard treatment for relief of the edema that often accompanies cerebral tumor; relief generally occurs shortly (minutes) after administration. We employed Gadomer (Schering AG), a dendritic gadolinium (Gd) chelate containing 24 Gd nuclei per molecule with a molecular weight of about 17 kD and an effective molecular weight of about 33 kD, and the consensus model[1] to estimate changes in the vascular transfer constant, K^{trans}, the vascular distribution space v_b, and the extracellular, extravascular space, V_{EES} in 5 animals implanted with an aggressive 9L cerebral tumor.

Methods: In an ongoing investigation, 5 male Fischer 344 rats weighing 250 to 300 g were implanted with 10,000 9L cells using methods previously described[2,3]; the resultant population of animals with cerebral tumor was studied using MRI and a magnetic resonance contrast agent (MRCA) about 14 days (mean 14.2 ± 0.8 days, range 13 - 15 days) post-implantation. Tumors were approximately 2 to 4 mm at their largest linear dimension.

MRI studies were carried out in a 7 Tesla, 12 cm (clear bore) Magnex magnet with actively shielded gradients of 25 gauss/cm, 100 µs rise times, interfaced to a Bruker Avance console running Paravision V2.6. RF coils were a Bruker volume resonator for transmission, and an actively-decoupled 2 cm Bruker surface coil for reception. Following established procedures[4], a TOMROP[5] sequence was used to measure R_1 ($R_1 = 1/T_1$) at baseline, and at 145 s intervals following injection of MRCA. Matrix size was 128X64, FOV 32 mm, three 2 mm slices.
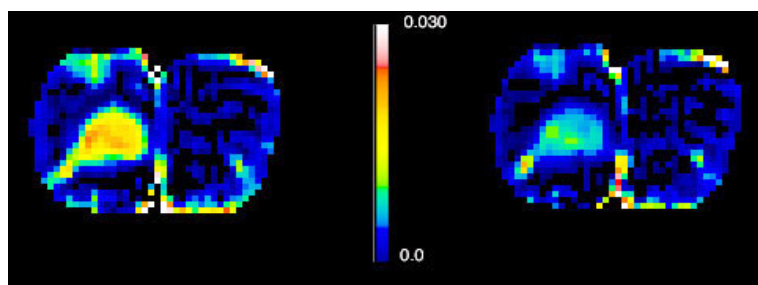
Rat je79: K^{trans} [min^{-1}] before (left) and after (right) administration of dexamethasone. A profound, unevenly distributed, decrease in vascular permeability is easily visualized.

The permeability study consisted of two baseline TOMROP studies prior to the administration of MRCA. Then the next TOMROP sequence was started and Gadomer was administered in a slow push (250 µmol/kg in a 0.3 ml volume in about 2 minutes). During and after the administration of MRCA, 10 iterations of TOMROP were run to follow the tissue concentration of MRCA across a 25 min period. Intravascular dexamethasone (2.4 mg/kg in 0.5 ml) was administered, and a second permeability study was run after an interval of about 90 minutes. Using an approach based on the consensus model of Tofts[1], the parameters vascular volume (v_b), transfer constant (K^{trans}) and efflux constant, k_b were computed. The extravascular, extracellular space (v_{EES}) was estimated from the ratio K^{trans}/k_b. Both region-of-interest (guided by post-contrast T_1-weighted images), as well as pixel-by-pixel whole brain estimates, were generated.

Results and Discussion: In all five animals, the transfer constant decreased after dexamethasone, a decrease that was easily visualized via parametric maps (see figure). Changes in permeability parameters are summarized in the table and compared to the work of Nakagawa et al[6], in which radioiodinated serum albumin (RISA) was used to study the effect of dexamethasone on the rat RG-2 cerebral tumor. Because its size when hydrated is similar to albumin, Gadomer should approximate RISA when used as a measure of vascular permeability. Despite the differences in tumor type, administration schedule, and measurement technique, the agreement between these two studies is striking, particularly the numerical agreement in the change of V_{EES}, which should be independent of the size of the indicator employed. To summarize, dexamethasone treatment appears to reduce not only the leakiness of the BBB, but also the size of the interstitium. Both processes would diminish the formation and flow of edema fluid.

Parameter*	Pre-Dex	Post-Dex	Paired t-test	RISA Values**[6]	
				Pre	Post
V_b [ml/ml]	0.026 ± 0.0072	0.019 ± 0.024	NS	0.030 ± 0.24	0.018 ± 0.009
K^{trans} [min^{-1}]	0.012 ± 0.0072	0.0059 ± 0.0042	$p = 0.001$	0.023 ± 0.009	0.0083 ± 0.003
$V_{EES} = K^{trans}/k_b$	0.11 ± 0.029	0.076 ± 0.055	$p < 0.05$	0.140 ± 0.02	0.080 ± 0.02
*MRI units ** 'Radiological' units, scaled to MRI units by tissue density					

Mean Vascular Leakage Parameters, pre- and post-dexamethasone

Literature Cited:
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