Dynamic contrast-enhanced magnetic resonance imaging as a biologic marker to non-invasively assess the effect of finasteride on prostatic suburethral microcirculation

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Introduction

Finasteride, a 5α-reductase inhibitor introduced as drug therapy for benign prostatic hyperplasia (BPH), is also used as a prophylaxis of BPH-associated hematuria and to reduce blood loss at transurethral resection of the prostate (TURP). In 1993, Marshall and Narayan postulated that angiogenesis is critical in BPH and androgen deprivation leads to the suppression of angiogenesis. The first reported use of finasteride to control hematuria associated with BPH was in 1995. The ability of pretreatment with finasteride to reduce perioperative bleeding at TURP was also reported in 2000. One proposed underlying mechanism is that finasteride blocks the conversion of testosterone to dihydrotestosterone, decreasing the expression of vascular endothelial growth factor (VEGF) and inhibiting angiogenesis, which decreases microvessel density in prostatic suburethral tissue. By this mechanism, finasteride significantly reduces blood loss during surgical treatments and suppresses hematuria secondary to BPH.

The important questions to be addressed about finasteride treatment include, what is the optimum dose and how long should the patients be treated. An effective non-invasive tool may be helpful to solve these questions by monitoring the changes in prostatic microcirculation. In this study we investigated dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) of the prostate and assessed the potential of the pharmacokinetic parameters as biomarkers to evaluate microvascular changes in the prostatic suburethral tissue in an experimental dog prostate model.

Material and methods

The study was designed within an interdisciplinary team and approved by the local animal care committee. The subjects of this 4-month study consisted of twelve male beagles (mean age ± SD: 4.4 ± 0.9 years, range 3 to 6 years, mean weight ± SD: 11.3 ± 2.8 kg, range 7 to 17 kg) with an initial palpated prostate diameter larger than 2 cm. The subjects were randomly allocated to one pharmaceutical treatment category and one control category containing six beagles each. The duration of treatment was 3 months. The subjects in the treatment group received a 5α-reductase inhibitor (Finasteride, Merck & Co., Inc., Whitehouse Station, NJ) at a dosage of 1 mg/kg bodyweight. The subjects in the placebo group received 0.4% methylcellulose vehicle only. Investigators were blinded as to subject allocation until the evaluation of the trial was completed.

The subjects were scanned 5 times by MRI: the first baseline (ST1) was carried out 3 weeks prior to the treatment, and the second baseline (ST2) was immediately prior to the initiation of the treatment; Three follow-ups were performed at 4 weeks (ST3), 8 weeks (ST4), and 12 weeks (ST5) after the start of the treatment. MRI examinations were performed on a 1.5 T clinical MRI system (Twinspeed, GE, Milwaukee, WI) using the standard clinical head coil with the subjects imaged in the prone position. DCE-MRI was performed using a 3D spoiled gradient echo (3D-SPGR) imaging sequence (TR/TE/α = 7.5 ms/2.6 ms/25º, field of view = 140 x 140 mm^2, matrix = 256 x 256, in-plane resolution = 0.55 x 0.55 mm^2; NEX = 0.5; 2.0-mm slice thickness, contiguous slices; 26 slices, Acquisition time per volume: 24 s, 32 time points). The extracellular contrast agent Gadoteridol (ProhanceTM, Bracco Diagnostic Inc, Princeton, NJ, 0.2 mmol/kg bodyweight) was intravenously injected at a rate of 0.2 ml/s after 3 time points by a power injector (Spectris®, MedRad, Indianola, PA) followed by a 15 ml flush of saline solution injected at the same rate.

The three slices were selected covering the suburethral tissues just outside and in caudal prostate as depicted in Figure 1, where the 3D MRI modeling of the prostate and the urethra was generated from axial T2-weighted images by the MIPAV (Medical Image Processing, Analysis, and Visualization) application. The Regions of Interest (ROIs) were drawn on the suburethral area of these three slices. By going through all time points, the ROIs were drawn in the center of the contrast-enhanced urethral region during peak enhancement such as the time point 7 and 8, furthermore, these ROIs for each time point were co-registered to compensate for subject motion during scans. The pharmacokinetic parameters evaluated on prostatic suburethral areas included the maximum enhancement ratio (MER, [a.u.]), the time to maximum signal enhancement (T_{max}, [min]), amplitude (A, [a.u.]), and rate constant (k_{ep}, [min^{-1}]). An unpaired Student's t-Test was used to compare the parameters in the baselines as well as the parameters and percentage change in the finasteride and control group. Results for ST3 and ST4 are not shown. Statistical significance was defined as $p < 0.05$. All data was analyzed using SPSS statistical software (SPSS Inc., Chicago, IL).

Results

Of the 12 randomized subjects, 11 had satisfactory image quality for quantitative analysis of the prostatic suburethral regions. One subject in the control group exhibited dramatic motion during the baseline MRI scans. This impeded prostatic suburethral ROI placement, resulting in the exclusion of the subject from this analysis. During the baseline scans there were no statistically significant differences between the finasteride group and the control group regarding age, prostate volume, and all pharmacokinetic parameters (MER, T_{max}, A, and k_{ep}).

At the end of the trial (ST5), the mean time to maximum signal enhancement, T_{max}, in the suburethral portion of the prostate was significantly longer in subjects treated with finasteride compared with controls (2.04 ± 0.64 min versus 0.88 ± 0.34 min) ($p < 0.01$); The amplitude A and rate constant k_{ep} decreased in the finasteride group. The relative change in the prostatic suburethral pharmacokinetic parameter A for the finasteride treated group was -39% ± 36%, which is significantly different from the controls (+61% ± 80%) ($p < 0.05$). Similarly, the relative change in prostatic suburethral pharmacokinetic parameter k_{ep} for the finasteride treated group was -34% ± 44%, significantly lower than the controls (+58% ± 55%) ($p < 0.05$).

Figure 2 demonstrates typical changes in the time-signal intensity curves from baseline (ST1) to ST5 of a subject from the finasteride group. MER in ST1 was 9.68 and decreased to 6.95 in ST5. T_{max} in ST1 was 1.35 min and increased to 2.30 min in ST5. A in ST1 was 11.51 and decreased to 4.11 in ST5. k_{ep} in ST1 was 2.55 min^{-1} and decreased to 1.07 min^{-1} in ST5.

Discussion and Conclusion

Our results showed that the subjects in the finasteride group experienced reduced microcirculation as expressed by the lower and slower contrast enhancement, as quantified by increased T_{max} and decreased amplitude, A, and rate constant, k_{ep} in the prostatic suburethral area. The increase of T_{max} and decrease of A and k_{ep} in the prostatic suburethral area are reflecting a decrease of microvessel density (MVD) and microcirculation mediated by the anti-angiogenic effects associated with decreased VEGF expression. The observed finasteride-induced changes of the pharmacokinetic parameters match findings of other investigators, such as reduced MVD in prostatic suburethral area, reduced blood loss during TURP, and inhibited hematuria after surgery. The anti-angiogenic property also enables finasteride to be used as a prostate cancer treatment, whose efficiency can also be non-invasively monitored by DCE-MRI by providing important information about the relative change in microcirculation and respectively MVD.

In conclusion, DCE-MRI is capable of non-invasively assessing the changes in prostatic suburethral microcirculation induced by finasteride. The quantitative pharmacokinetic parameters show considerable promise for being important biomarkers in drug development of BPH drugs such as 5α-reductase inhibitors by in-vivo monitoring the microvascular changes in the pretreatment to reduce perioperative bleeding at TURP and in the treatment of hematuria and prostate cancer.

References

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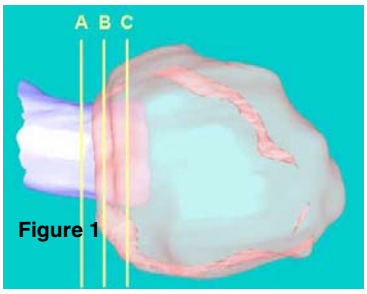

Figure 1

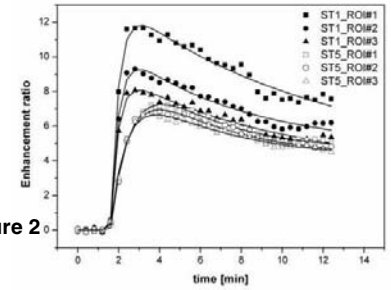

Figure 2