Effects of naproxen and naproxcinod on intra-renal oxygenation during water-loading as evaluated by BOLD MRI

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to alleviate pain [1]. While these are considered relatively safe for acute and short term use, there are well known adverse effects in chronic users [2]. While the gastrointestinal issues are a major concern in chronic users, NSAID associated nephrotoxicity is also well appreciated in the clinic [3]. Since there are really no alternatives to pain medication for arthritic patients, and with the growth in older population this is a major healthcare concern.

While disease modifying osteoarthritic drugs are under development, there has been an alternate approach where the NSAIDs are combined with nitric oxide (NO) donors to compensate for the effects of prostalgandin inhibition. One such drug is naproxcinod (NicOx, France), previously HCT 3012 and AZD3582, currently in Phase III clinical development. While pre-clinical and clinical data indicates that the drug is as effective in pain management compared to naproxen, it is associated with less GI adverse effects [4, 5]. A small blood pressure reduction was also suggested [4, 5]. However, there has been no other hemodynamic or physiological correlates reported to-date.

Using BOLD MRI, it was previously documented in healthy human subjects a significant reduction in R_2* during water-loading which was abolished when pre-treated with naproxen [6]. In the current study, we have extended these findings to rats, and further compared the response to those pretreated with naproxcinod.

MATERIAL AND METHODS

The study protocol was approved by the Institutional Animal Care and Use Committee. Eighteen male Sprague Dawley rats (weight 317.6±6.8 g, Charles Rivers, US) were dosed by gavage with vehicle (carboxymethycellulose/DMSO), naproxcinod (14.5 mg/kg) or equimolar naproxen (10mg/kg) for two weeks. On the day of experiment, rats were anesthetized with Ketamine (60-100 mg/kg ip) and thiobutabarbital (Inactin, 100 mg/kg ip). A catheter (PE-50) was placed in femoral vein.

MRI acquisitions were performed on a short bore Signa Twin speed 3.0T (GE Healthcare) using a multiple gradient echo sequence (TR/TE/Flip angle / FOV /BW /matrix/Thk/NXE = 70ms/4.4-57.7ms /30^o /10cm/42 kHz /256x256 /2mm /10) to acquire 16 T_2* weighted images. A quadrature extremity coil was used for signal reception. The signal intensity *vs.* time data was fit to a single exponential function to generate R_2* map using the FUNCTOOL (GE Healthcare). After obtaining a set of baseline images, hypotonic glucose-saline (0.25% NaCl, 0.5% glucose) [7] at 1.5ml/100g body weight/hr was infused IV for 2 hours to induce the water-diuresis. R_2* maps were obtained every 3 minutes for 2 hours. Regions of interest (ROI) were placed on renal medulla to obtain values for the mean and standard deviation of R_2*. An increase in R_2* implying a decrease in oxygenation and *vice versa*. The statistical significance of the differences between pre- and post-diuresis R_2* was evaluated by two-tailed paired Student's t-test.

RESULTS

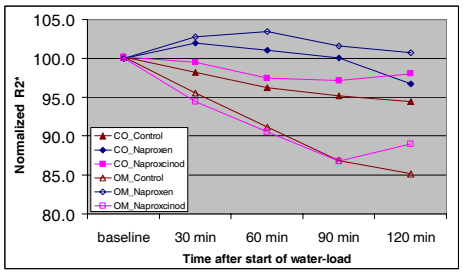

Figure 1. Summary plots showing R_2* response in the cortex and medulla to water-load in the three groups of animals.

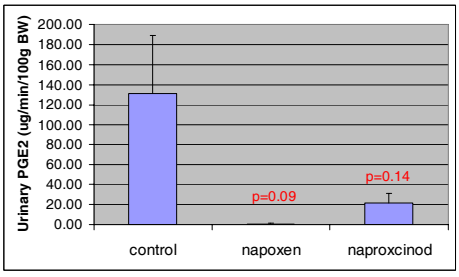

Figure 2. Summary of urinary PGE2 measurements. Data expressed as mean±SE. p values shown are in comparison to the controls.

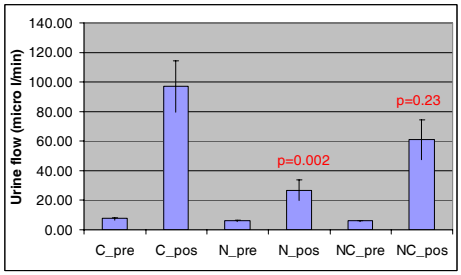

Figure 3. Summary of pre- and 90 min post-water-load urine flow. Data expressed as mean±SE. C: control; N: naproxen; NC: naproxcinod. p value w.r.t. C_pos.

As expected, in control rats there is a significant shortening of R_2* during water-load, which was completely abolished in the naproxen group consistent with previous human findings [6]. The novel finding is that in the naproxcinod group the response to water-loading was almost intact (Figure 1), even though the urinary PGE2 data showed substantially reduced levels in both naproxen and naproxcinod groups. The inter-animal variability was relatively high both in the control and naproxcinod groups resulting in no statistical significance (Figure 2) even for the naproxen group, where the urinary PGE2 levels were consistently very low.

The urine flow rate increased in all groups during water-load (90 min) compared to baseline, which was comparable between groups. Both naproxcinod and naproxen groups had less of increase in urine flow during water-load compared to the control group (Figure 3), but only the naproxen group reached statistical significance.

DISCUSSION

While the BOLD MRI observations during water-load clearly suggest differences in responses between naproxen and naproxcinod, it is not yet clear if they are necessarily related to the NO donation. While the urinary PGE2 was substantially lower in the naproxcinod group compared to controls, they were not as low as the naproxen group.

Figure 3 suggests that there is a significant reduction in the increase in urine flow during water-loading in the naproxen group compared to controls. It is possible that differences in water content could potentially contribute to the MRI observations, but to what extent is not yet clear. While it has been shown previously that the observed R_2* responses during water-loading are not related to water content changes [8], those were based on human studies which also failed to show any significant difference in the urine flow when pre-treated with a COX inhibitor [9].

CONCLUSION

Preliminary results presented here suggest that naproxcinod may have less nephrotoxicity in rats. Further studies with larger number of animals, and probably other confirmatory studies are needed to fully validate these observations. Studies in hypertensive rats or in other renal impaired models may also be important to fully elucidate the benefits. Future studies should acquire both R_2 and R_2* measurements to verify the contributions from potential changes in water content.

ACKNOWLEDGEMENT

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REFERENCES:

[1].*Curr Opin Anaesthesiol*, 2001. **14**(4): p. 417-21.[2]. *Thromb Haemost,* 2006. **96**(4): p. 407-12. [3]. *Vnitr Lek,* 2006. **52**(7-8): p. 686-90. [4]. *J Pharm Pharmacol,* 2005. **57**(12): p. 1539-54. [5]. *Arthritis Rheum*, 2005. **53**(6): p. 827-37. [6]. *Kidney Int,* 2006. **70**(1): p. 139-43. [7]. *Journal of Physiology* (2002), **542(1):** 315-322. [8]. *Circulation* 1996, **94**(12):3271-5. [9] *Kidney Intl* 1999, **55**(1):294-8.