
The effect of pentoxifylline on proteinuria in diabetic kidney disease: a meta-analysis

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CRD summary

The review concluded that pentoxifylline may be an efficacious anti-proteinuric agent in patients with diabetic kidney disease, but large high quality trials are required to confirm these findings. Whilst small sample size, low trial quality, and trial differences should be borne in mind, the authors' cautious conclusion appears to reflect the evidence presented.

Authors' objectives

To determine the efficacy of pentoxifylline in adult patients with diabetic kidney disease.

Searching

MEDLINE (to February 2006), EMBASE (1985 to 2005), Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (to first quarter 2006) were searched without language restriction. Search terms were reported. Subspecialty journals (American Journal of Kidney Disease, Journal of the American Society of Nephrology, Kidney International) were handsearched between 1998 and March 2006.

Study selection

Randomised controlled trials (RCTs) with an intervention arm that received oral pentoxifylline and in adults with diabetic kidney disease were eligible for inclusion in the review. Diabetic kidney disease was defined as albuminuria with greater than 30mg/day of albumin, or glomerular filtration rate of less than 60mL/min/1.73m². Trials that included patients with renal transplants or acute renal failure were excluded.

The primary outcome was change in proteinuria, stratified by whether pentoxifylline comparison was with rennin-angiotensin system blockade. Secondary outcome measures were changes in systolic or diastolic blood pressure, and glomerular filtration rate (defined as change in creatinine clearance, measured or calculated).

Included trials compared pentoxifylline (with or without angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) with placebo, standard care, angiotensin-converting enzyme inhibitors (including captopril, ramipril, and lisinopril), or angiotensin receptor blockers. Pentoxifylline doses ranged from 400mg/day to 1,200mg/day; duration of therapy ranged from two to 12 months (medium six months). Most trial populations included patients with diabetes with overt proteinuria and/or microalbuminuria; one trial included patients with diabetes with proteinuria and chronic renal failure. The mean age of included participants ranged from 25 to 65 years. Trials were conducted in Europe, USA, Mexico, Brazil and Iran.

Two reviewers independently assessed studies for inclusion. Disagreements were resolved through discussion.

Assessment of study quality

The quality of the trials was assessed according to the Jadad scale.

The authors did not state how many reviewers performed the validity assessment.

Data extraction

Mean effect size between pre- and post-change for pentoxifylline and control were calculated (a pre-post trial correlation of 0.5 was assumed in order to obtain an estimate of the mean change in standard deviation for trial that reported mean and standard deviation values for baseline and follow-up).

For cross-over group trials, only data from the first period of the trial were included. Trials in which both arms received an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker were analysed as pentoxifylline versus standard care, whereas trials in which pentoxifylline was compared directly with an angiotensin-converting enzyme

inhibitor or an angiotensin receptor blocker were analysed as a separate group.

Trial authors were contacted where additional information was required.

Two reviewers independently extracted data and disagreements were resolved through discussion.

Methods of synthesis

Summary weighted mean differences (WMD) with their 95% confidence intervals (CI) were estimated using a random-effects model. Heterogeneity was assessed using the X^2 and I^2 statistics.

Pre-specified subgroup analysis based on baseline level of proteinuria was performed.

Sensitivity analysis was performed assuming 0.25 and 0.75 as correlation between baseline and final values.

Meta-regression was also carried out to investigate possible sources of heterogeneity.

Results of the review

Ten RCTs (n=476, range 14 to 127) were included in the review; nine parallel group trials and one cross-over trial. Jadad scores were low, with a median score of 3 (range 1 to 4).

Proteinuria: Pentoxifylline was associated with a significant decrease in proteinuria compared with placebo or standard care (WMD -278mg/day of protein, CI -398 to -159; $I^2=97.2%$; 10 trials). There was no difference between pentoxifylline and captopril. Stratification of trials based on baseline urine protein excretion did not change these findings. Subgroup analysis showed that for patients with overt proteinuria (protein > 300mg/d) pentoxifylline was associated with a significant decrease in proteinuria compared to control (WMD -502 mg/day, 95% CI -805 to -198; six RCTs); there was a non significant decrease in proteinuria for patients with micro-albuminuria (three RCTs; p=0.1). The main findings were stable in sensitivity analysis. Results from the meta-regression suggested that baseline proteinuria and study duration were significantly associated with change in proteinuria.

Kidney function and blood pressure: No significant differences were found between pentoxifylline and control groups for change in serum creatinine levels (seven RCTs; p=0.9), systolic blood pressure (nine RCTs; p=0.3) or diastolic blood pressure (nine RCTs; p=0.7). Stratification of trials based on the comparator arm and sensitivity analyses did not change these findings.

Adverse effects were reported in five RCTs and included gastrointestinal symptoms, headache, and dizziness in the pentoxifylline arms. In total, nine patients withdrew because of adverse effects (four from the pentoxifylline arms and five from the control arms).

Authors' conclusions

Pentoxifylline may be an efficacious anti-proteinuric agent in patients with diabetic neuropathy, but large high quality studies are required to confirm these findings.

CRD commentary

The review addressed a focused question and inclusion criteria were clearly defined. A number of sources were searched without language restriction, but no specific attempts were made to locate unpublished papers, so publication bias was possible. Appropriate steps were taken at study selection and data extraction to minimise the likelihood of bias and error, but it was not clear whether similar steps were taken to assess study validity.

Study quality was formally assessed using appropriate criteria; the results were clearly reported. Relevant trial details were summarised in the text and tables. Substantial statistical heterogeneity in the primary outcome suggested that pooling may not have been appropriate. However, potential sources of heterogeneity were investigated.

Whilst small sample size, low trial quality, and trial differences should be borne in mind, the authors' cautious

conclusion appears to reflect the evidence presented.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that high-quality adequately powered trials are needed to determine whether pentoxifylline has an effect on outcomes that are important to patients with diabetic kidney disease, such as time delayed time to dialysis therapy. Future trials should be of adequate duration to see if the decrease in proteinuria is maintained, and should be conducted in patients with significant baseline proteinuria.

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