

COX-2 Inhibitors and Renal Function in the Elderly

Swan SK, Rudy DW, Lasseter KC, Ryan CF, Buechel KL, Lambrecht LJ, et al. Effect of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low-salt diet. A randomized, controlled trial. *Ann Intern Med* 2000;133:1-9.

Study Overview

Objective. To determine if the cyclooxygenase-2 (COX-2) enzyme inhibitor rofecoxib affects renal function in healthy elderly individuals on a low-sodium diet.

Design. Randomized single-dose crossover study and a multiple-dose blinded, randomized study.

Setting and participants. 75 patients aged 60 to 80 years in clinical research units.

Interventions. There were 2 groups in the study. The crossover group ($n = 15$) received 250 mg of rofecoxib, 75 mg of indomethacin, or placebo in single doses. The multiple-dose group ($n = 60$) received rofecoxib 12.5 mg/day, rofecoxib 25 mg/day, indomethacin 50 mg 3 times daily, or placebo for 6 days. Both groups received a low-sodium diet.

Main outcomes measures. Glomerular filtration rate in the single-dose group was calculated by measuring creatinine and inulin clearance. Glomerular filtration rate in the multiple-dose group was calculated by measuring creatinine and iothalamate clearance at baseline and after the first dose was given on the sixth day. Urinary and serum sodium and potassium levels were also measured.

Main results. In the single-dose group, rofecoxib and indomethacin caused reductions in the glomerular filtration rate (using inulin) of 0.23 mL/s ($P < 0.001$) and 0.18 mL/s ($P < 0.003$) compared with placebo. Rofecoxib and indomethacin caused reductions in creatinine clearance of 0.32 mL/s and 0.19 mL/s ($P = 0.002$ and 0.051) compared with placebo; the difference in creatinine clearance reduction did not differ significantly between the 2 drugs ($P = 0.16$). The reduction in urinary sodium excretion was 68.35% for rofecoxib and 48.95% for indomethacin, compared with placebo. The reduction in urinary potassium was significant only for rofecoxib compared with placebo (11.2%, $P = 0.012$).

In the multiple-dose study, rofecoxib in doses of 12.5 mg and 25 mg caused reductions in the glomerular filtration rate (using iothalamate) of 0.14 mL/s ($P = 0.019$) and 0.13 mL/s ($P = 0.029$) compared with placebo. Indomethacin caused a

nearly significant reduction (0.10 mL/s, $P = 0.086$) compared with placebo. Changes in creatinine clearance and sodium and potassium excretion were not significant.

Conclusion

The effects of COX-2 inhibition on renal function in healthy elderly individuals are similar to the effects seen with non-selective nonsteroidal anti-inflammatory drugs (NSAIDs).

Commentary

Use of NSAIDs in the United States is widespread, with 70 million prescriptions filled in 1991 [1]. However, NSAIDs produce unwanted effects on renal function, the gastrointestinal tract, and hemostasis. Inhibition of the COX-1 enzyme is thought to be responsible for the effects on the gastric mucosa and hemostasis (decreased platelet aggregation) [2,3]; such complications led to the development of the COX-2-specific inhibitors. These drugs have been shown to induce less gastrointestinal side effects and less bleeding [4], but their effects on renal function in humans are not well known. Two recent studies involving healthy volunteers showed that celecoxib caused very minimal changes in the glomerular filtration rate [5,6]. The current study is the first to examine the effects of rofecoxib on renal function in humans.

This was a well-designed study. The patient groups in both sections of the study were clearly identified and had similar baseline characteristics. Although different methods of measuring glomerular filtration rate were used in the single- and multiple-dose groups (inulin, iothalamate), studies have shown both methods to be valid [7]. The authors also took care to measure clearance at different times to account for the different pharmacokinetics of indomethacin and rofecoxib. By using 2 different groups, they were able to measure immediate and short-term effects.

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It is important to note that there was a dose-response effect with rofecoxib. The maximum effect was achieved with a dose of 250 mg, which is 5 times the maximum dose recommended by the manufacturer. Also, no effects on blood pressure were observed.

Applications for Clinical Practice

When prescribing COX-2 inhibitors for healthy elderly patients, physicians should follow the same precautions they would when prescribing nonspecific COX-1/COX-2 inhibitors. Further studies should be done to determine the effects of COX-2 inhibitors in patients who have chronic renal insufficiency, liver cirrhosis, or congestive heart failure or who are on diuretics. Until then, these agents should be used with extreme caution in such patients. Finally, studies should explore whether the effects found in this study persist or worsen over a period of time longer than 6 days.

References

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