Office-Based Evaluation Of Renal Function In Elderly Patients Receiving Nonsteroidal Anti-Inflammatory Drugs

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Abstract: Elderly patients with multiple diseases who are receiving diuretics are at risk for renal dysfunction from nonsteroidal anti-inflammatory drugs (NSAIDs). Fifty-two elderly patients (mean age = 72 years, range = 63–87 years) with degenerative joint disease and multiple concomitant illnesses were randomly selected to receive ibuprofen suspension (400 mg) or aspirin (650 mg) 4 times a day. Serum creatinine (Cr), blood urea nitrogen (BUN), weight, and blood pressure were measured at baseline and at weekly intervals for 6 weeks. There were no significant changes from baseline in any tests reflective of renal function, no significant differences between ibuprofen and aspirin, and no influence of concomitant diuretic therapy. Ibuprofen and aspirin administered in the doses examined for 6 weeks appear to have little effect on renal function as measured by serum Cr and BUN in a sample of elderly patients for whom these drugs are commonly employed. Concomitant diuretic therapy does not appear to increase the risk. While these drugs are contraindicated in patients with severe hemodynamic insult, they should not be withheld from elderly patients who require this therapy for analgesic/anti-inflammatory effects because of concern for renal impairment. Further prospective research should be undertaken to clarify levels of patient risk and to define appropriate monitoring in such patients. (JABFP 1988; 1: 77-80.)

Recent attention has been focused on the propensity of nonsteroidal anti-inflammatory drugs (NSAIDs) to produce adverse effects on the kidney.[1,2] A variety of renal syndromes have been reported following the use of these drugs, including acute renal failure, interstitial nephritis and proteinuria, papillary necrosis, sodium and water retention, and hyperkalemia.[1] Virtually every NSAID in clinical use has been associated with such reactions, although the propensity of sulindac to produce renal toxicity remains controversial.[3,4]

Prostaglandins synthesized and released by the kidney play a minor role in the regulation of renal blood flow and glomerular filtration rate in normal individuals. However, in animals or patients with prior hemodynamic insult (acute hemorrhage, prior renal disease, congestive heart failure, salt depletion, etc.), renal prostaglandins appear to act as local autoregulatory hormones that support renal blood flow and glomerular filtration. Interference with prostaglandin synthesis by NSAIDs in the presence of prior hemodynamic insult has been shown to alter significantly a person's capacity to autoregulate these important physiologic functions, resulting in the renal toxicity described above.[1] Some authors therefore have attempted to delineate a population of patients with altered hemodynamic states who may be at increased risk for such toxicity. These conditions include cirrhosis with ascites, chronic glomerulonephritis, chronic renal failure, congestive heart failure, systemic lupus erythematosus, diuretic administration, elderly age, and volume contraction.[5,6] It has been suggested that renal function should be closely monitored in these patients.[5,6] When focusing on age alone as a risk factor, as creatinine clearance declines with increasing age, it is reasonable to postulate that some individuals at the lower limit of physiologic reserve may experience further declines in renal function when NSAIDs are employed, particularly if volume contraction associated with diuretic therapy is also present. However, the true incidence of these reactions remains unknown; the risk in any given patient with one or more of these

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risk factors is unclear, and the appropriate monitoring of such patients has not been defined.

To address this issue, we have analyzed the data from a double-blind, randomized, prospective comparison of ibuprofen and aspirin in elderly patients with degenerative joint disease. Because elderly patients with multiple diseases may be at higher risk for the renal toxicity associated with NSAIDs,[5,6] the present study explores: (1) the chronic effects of two popular NSAIDs on commonly used measures of renal function, and (2) the potential influence of concomitant diuretic therapy on the risk of renal dysfunction in this population.

Methods

Ambulatory patients aged 63 years and older with degenerative joint disease requiring therapy with NSAIDs were eligible for inclusion in this multicenter, prospective, randomized study. The study was approved by an institutional review board, and each patient signed a statement of informed consent. A history of concurrent illnesses and medications was carefully obtained and recorded. A physical examination and an electrocardiogram were also performed. Previous NSAIDs were discontinued for an appropriate washout period (1 week), while other medications were continued. Approximately 55 percent of the patients had been taking NSAIDs, most commonly aspirin, ibuprofen, sulindac, and naproxen. Fifty-two patients (mean age = 72 years, range = 63–87 years; 69 percent female, 31 percent male) with degenerative joint disease and multiple concomitant illnesses were randomly selected to receive either ibuprofen suspension (440 mg) or aspirin (650 mg) 4 times daily. Medication compliance was verified by pill counts at each visit. Forty-five patients completed the 6-week study and provide the basis for this report. Seven patients (5 who received aspirin and 2 who received ibuprofen) were discontinued in the first 2 weeks of the study because of adverse effects (primarily gastrointestinal).

Routine noninvasive tests reflective of renal function including serum creatinine (Cr), blood urea nitrogen (BUN), urinalysis, body weight, and blood pressure were measured at baseline (end of washout) and at weekly intervals for 6 weeks. Blood samples for creatinine and BUN were assayed in the clinical laboratories of each participating institution, using a piccurate assay and urease enzyme method, respectively. These tests were selected for analysis because it was believed that they were the ones most likely to be employed by the office-based clinician monitoring these patients. While attempts were made to obtain weekly 24-hour urine collections for determination of creatinine clearance, the difficulty in obtaining a complete collection from these elderly patients rendered these data inadequate.

The statistical procedure used to assess the data was analysis of variance, which controlled for independent variables of NSAIDs, diuretic use, time, and investigator. A significant difference was defined at a level of 0.05. The sample size was sufficient to detect a 25 percent increase in serum creatinine with a 95 percent confidence level.

Results

No significant changes from baseline were noted in any of the simple tests reflective of renal function. Figure 1 shows the mean change from baseline in serum creatinine for all patients during the 6-week period of NSAID therapy. While a small increase in serum creatinine is apparent at week 2, it is not clinically or statistically significant and returns to baseline despite continued therapy. Similar results, demonstrating no significant change from baseline, were seen with the other tests (BUN, blood pressure, weight) and therefore are not presented.

Because the study involved a randomized comparison of two of the most commonly used NSAIDs, we explored the possibility that differences may exist between them with respect to their impact on the tests of renal function that were

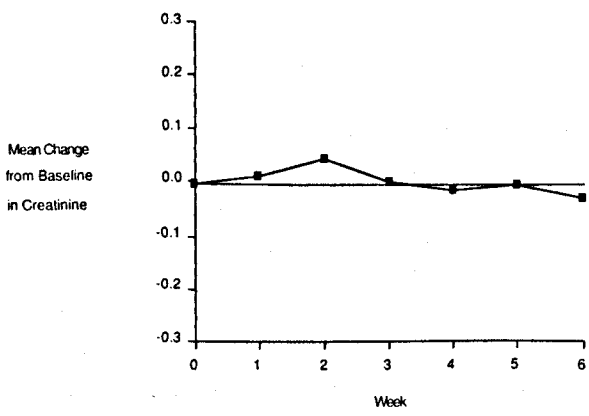

Figure 1. Effect of NSAIDs on renal function displayed as the mean change from baseline in serum creatinine (mg/dL) for all subjects (aspirin and ibuprofen).

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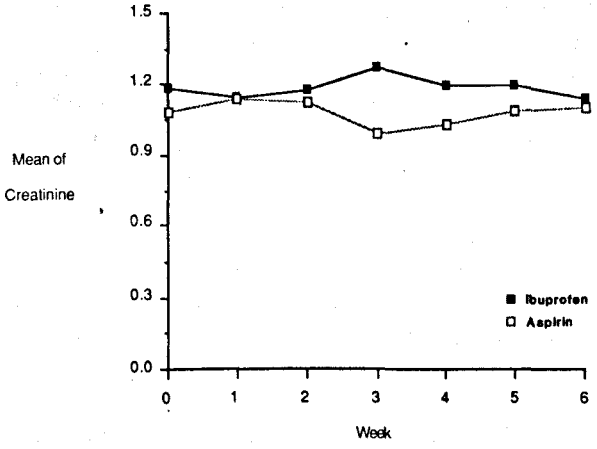

Figure 2. Comparison of the effects of ibuprofen 1,600 mg/day (n = 24) and aspirin 2,600 mg/day (n = 21) on mean serum creatinine (mg/dL).

monitored. As illustrated in Figure 2, no significant differences were noted between ibuprofen and aspirin as reflected by mean serum creatinine measures over the 6-week study period. While the differences at week 3 approached statistical significance, the difference was as much a result of the fall in mean serum creatinine in aspirin-treated patients as it was a result of the mild increase in mean serum creatinine in ibuprofen-treated patients. Consequently, this may simply represent normal variability that occurred in divergent directions at the same time.

Diuretic therapy has been suggested by some authors to be a risk factor for renal dysfunction from NSAID therapy, because diuretics result in relative hypovolemia and, therefore, may stimulate the prostaglandin homeostatic mechanism for maintaining renal blood flow described above. Eighteen of the 45 elderly patients (40 percent) were receiving concurrent diuretic therapy (most commonly hydrochlorothiazide [50 mg/day] for hypertension). When the results of their mean serum creatinine data over time were compared with the remainder of the sample who were not taking diuretics, there was again no significant difference noted between the two groups at any time point (Figure 3).

Discussion

Despite concern regarding the potential renal toxicity of NSAIDs, the present study of a population presumed to be at moderately increased risk for toxicity revealed no evidence of drug-induced renal dysfunction as assessed by simple laboratory tests. Likewise, there was no significant difference between drugs, and the presence of diuretic therapy did not appear to pose any additional risks. Several issues must be considered in explaining these findings.

Because degrees of patient risk for NSAID-induced renal dysfunction are poorly defined, this sample, selected for analysis because of presumed higher risk, actually may have been at very little increased risk. This may suggest that chronologic age in and of itself is not an independent risk factor in that persons aged 63 years and older are still a relatively heterogeneous group. Therefore, advanced age may be simply an indicator of a greater prevalence of those diseases that do enhance the risk of renal dysfunction from NSAIDs. However, even those patients more than 63 years of age with other concurrent conditions such as mild congestive heart failure did not have significant elevations in their measures of renal function. This may suggest that only those patients with more significant degrees of hemodynamic insult (e.g., severe congestive heart failure, prior severe renal disease) are at an increased risk of renal dysfunction from NSAIDs. This is supported by the work of Ciabattoni, et al. who demonstrated a 40 percent increase in mean serum creatinine in 10 patients with chronic glomerular disease who were treated with ibuprofen 1,200 mg/day.[3] However, little data on renal dysfunction apart from the current investigation are available for elderly patients with varying degrees of hemodynamic insult—the population confronted by the primary care practitioner.

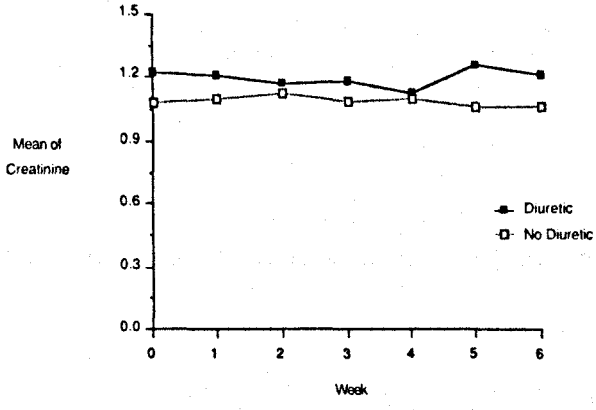

Figure 3. Comparison of the effects of NSAID administration (aspirin or ibuprofen) in patients receiving concurrent diuretic therapy (n = 18) and those not receiving diuretics (n = 27).

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Similarly, the fact that approximately half of these patients had received NSAIDs previously may suggest a selection bias in favor of a history of adequate tolerance of NSAIDs. However, in most of these patients, renal function was not routinely measured following the introduction of NSAID therapy in normal practice, so drug-associated changes were not previously explored in a systematic fashion.

One must also consider the possibility that the simple tests assessed in this study (serum creatinine, BUN, weight, blood pressure) are insensitive to the changes in renal function that result from administration of the NSAID. Consequently, more sensitive measures such as creatinine or inulin clearance may be required to assess smaller changes in renal function that may accompany the administration of NSAIDs in these patients. While attempts were made in the present investigation to assess creatinine clearance, the insufficient collection of a 24-hour urine specimen from many of these elderly patients rendered the data inadequate for analysis. However, in most of the case reports of renal dysfunction associated with NSAIDs and in the work of Ciabattoni, et al.[3] and others, serum creatinine was significantly elevated, suggesting that it is a reliable measure of these renal changes in patients at risk. The possibility also exists that renal dysfunction may have occurred within the first week of NSAID administration and returned to normal despite continued therapy by day 7 when the first blood sample was obtained. It is also possible that the dosage of the two compounds was inadequate to alter significantly the prostaglandin-compensated renal hemodynamic state. This seems unlikely in that significant renal dysfunction has occurred at lower doses of ibuprofen[3] and may occur at lower doses of aspirin in very high-risk patients.[7] These drugs and doses were chosen for study because they are the ones most commonly employed clinically for the management of painful rheumatologic disorders in such patients. However, the possibility that other compounds (e.g., sulindac) may be associated with a lower incidence or severity of adverse renal reactions has been suggested by some investigators.[3,4]

While diuretic therapy has been suggested as a potential risk factor, there may be significant differences between different diuretics. Most of the research to date has been done with furosemide, while little evidence is available on the more commonly employed thiazide diuretics. Our data suggest that these agents in the doses commonly used during chronic administration pose no additional risk of NSAID-associated renal dysfunction in elderly patients with concurrent degenerative joint disease and hypertension.

Conclusion

Ibuprofen and aspirin administered in the doses examined for 6 weeks appear to have little effect on renal function in a sample of elderly patients with painful rheumatologic disease and multiple concomitant disorders as measured by serum creatinine and BUN. These data suggest that the general population of elderly patients is at low risk for developing renal dysfunction associated with NSAIDs. Age alone does not appear to be a significant risk factor for this adverse event. A more careful delineation of the relative importance of each risk factor for renal dysfunction should be undertaken. Until further data are available, it seems appropriate not to withhold NSAID therapy from elderly patients with no or minimal hemodynamic insult (e.g., diuretic therapy) who require these agents for analgesic/anti-inflammatory effects. Moreover, minimal monitoring of renal function appears to be necessary in such patients. For patients with more significant hemodynamic insult (e.g., prior renal disease), the benefit of NSAID therapy should be carefully weighed against the possibility of adverse renal effects, and careful periodic monitoring should be undertaken.

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