Renal Effects of Low Dose Aspirin in Elderly Patients

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Abstract

Background: Aspirin is commonly used by elderly patients. In previous studies we found transient changes in renal function induced by low doses of aspirin.

Objectives: To investigate the mechanisms of these effects.

Methods: The study group included 106 long-term care stable geriatric inpatients. Diet and drugs were kept stable. The study lasted 5 weeks; during the first 2 weeks 100 mg aspirin was administered once a day. Clinical and laboratory follow-up was performed at baseline and weekly for the next 3 weeks. The glomerular filtration rate was estimated by creatinine clearance measured in 24 hour urine and serum creatinine, and by the Cockcroft-Gault formula (C-G) equation. Uric acid clearance was determined from serum concentrations and 24 hour excretion of uric acid. Patients with serum creatinine > 1.5 mg/dl were not included.

Results: After 2 weeks on low dose aspirin, measured creatinine and uric acid clearances decreased significantly compared with the initial values in 70% and 62% of the patients, respectively, with mean decreases of 19% and 17%, respectively ($P < 0.001$). Blood urea nitrogen increased by 17% while serum creatinine and uric acid concentrations increased by 4% ($P < 0.05$ for all). The C-G values decreased by 3% ($P < 0.05$). After withdrawal of aspirin all parameters improved. However, 67% of the patients remained with some impairment in their measured Ccr, compared to baseline. Patients who reacted adversely to low dose aspirin had significantly better pre-study renal function (Ccr), lower hemoglobin and lower levels of serum albumin.

Conclusions: Short-term low dose aspirin affected renal tubular creatinine and uric acid transport in the elderly, which may result in a prolonged or permanent deterioration of the renal function. It is suggested that renal functions be monitored even with the use of low dose aspirin in elderly patients.

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Low dose aspirin is commonly used by elderly people for the prevention of thrombosis [1,2]. These individuals are more prone to non-steroidal anti-inflammatory drug and aspirin-related adverse reactions, including renal side effects [3-5]. The effects of the current low dose aspirin regimens (75–325 mg/day) in this regard were previously studied by our group in two cohorts of elderly patients [6,7]. We found that these doses of aspirin were capable of inducing a significant decrease in both creatinine and uric acid excretion within 1–2 weeks. One week after the drug was withdrawn, uric acid excretion returned to normal while creatinine clearance remained low. The consistency of these findings and their potential significance and the mechanisms underlying these effects warrant further research.

The present study was designed to assess the effects of mini-dose aspirin on renal functions in a relatively larger number of elderly patients hospitalized in a geriatric hospital. In order to better estimate the effects of low dose aspirin on renal and tubular function, in this study two methods were used to estimate glomerular filtration rate: measured creatinine clearance and the Cockroft-Gault formula [8].

Patients and Methods

Long-term care patients with a variety of chronic medical conditions, in stable clinical condition during the study period, were recruited to this study after an informed consent was obtained from the patients or their guardians. The study was approved by the Hospital Ethics Committee. Subjects with a history of active peptic disease, gastrointestinal bleeding, chronic liver diseases, gout, hyperuricemia, serum creatinine > 1.5 mg/dl, alcohol consumption, or recent use of anticoagulants, aspirin or NSAIDs were not included. A week before the study a controlled diet consisting of 50–80 g protein and 200–300 mg purine daily was started and maintained for a total of 6 weeks. Other medications (including diuretics) and their dosages were unchanged. Patients whose medical condition deteriorated or those who had to change their medications or diet during the study period were included in the calculations until their dropout. Aspirin 100 mg/day was administered orally or by a nasogastric or percutaneous tube after breakfast for 2 weeks and then stopped, and follow-up continued for a further 3 weeks. Blood and 24 hour urine were collected weekly: before the first dose of aspirin, at the end of each treatment week, and during a further 3 consecutive weeks after discontinuing aspirin. Most patients (87%) had indwelling bladder catheters or a Penrose device, which allows accurate urine collections, while special attention was given to accurate collection in others.

Serum creatinine, blood urea nitrogen, uric acid and albumin were studied by standard methods. Urine creatinine and uric acid were evaluated by 24 hour urine collections for creatinine and uric acid clearances (Ccr and Cu acid). GFR was also calculated using the C-G formula: (140 years of age) x body weight / serum creatinine (mg/dl) x 72, corrected by x 0.85 for women [8]. Patients were also classified according to their renal failure staging [8,9] before and after aspirin treatment.

C-G = Cockcroft-Gault formula
Ccr = creatinine clearance
NSAIDs = non-steroidal anti-inflammatory drugs
GFR = glomerular filtration rate
Cu = uric acid

Statistical analysis

We used Student's paired *t*-test for the weekly changes of all measurements compared to baseline, multivariate analysis of variance with repeated measures (MANOVA) for the overall effect of aspirin during the study period, chi-square for deteriorations in renal failure stages, and Pearson's correlation coefficient for all data – clinical, laboratory, basal or induced by aspirin. Multivariate regression analyses (forward stepwise) were used to identify demographic, clinical, pharmacological and laboratory data as potentially predisposing factors related to the aspirin-induced renal function deterioration (Ccr or C-G, estimated GFR) in the second week of treatment. Basal Ccr and basal estimated GFR were introduced only at the second step of analysis, after all other background variables. The explained variance percentage is expressed by R^2. Significance was considered as $P < 0.05$, two-tailed.

Results

The study group comprised 106 geriatric patients (86 women, 20 men, mean age 80 ± 9 years). Demographic and medical data of the cohort are presented in Table 1. The distribution of patients according to the severity class of renal failure [9] is shown in Table 2. The majority of patients were in stages 2-3 (mild-moderate) renal insufficiency. Ninety-six patients completed the 5 week study, while 10 patients dropped out for a variety of reasons unrelated to the aspirin treatment. Aspirin was well tolerated. No adverse effects, such as allergy, asthma, gastrointestinal complaints, bleeding, hypertension or acute gout, were recorded.

Figure 1 shows the changes in BUN, serum creatinine, Ccr and C-G monitored at baseline, in the first and second week on 100 mg/day aspirin, and 3 weeks following the withdrawal of aspirin. The treatment slightly affected most of these parameters within the first week, reaching statistical significance after the second week of treatment. The mean changes from baseline were +17% for BUN and +4% for serum creatinine. The Ccr and C-G decreased by 19% and 3% respectively. In 21% of patients the Ccr decreased by ≥ 50%. Declines of such a magnitude were not observed with C-G estimated glomerular function.

A significant decrease in Ccr of at least one functional class (definition of the classes is reported in Table 2) was noted in 40% of the patients vs. 21% who improved ($P = 0.008$). However, a deterioration of functional class assessed by the C-G formula was documented in only 16% of the patients (vs. 9% who improved, $P = 0.16$).

During the 3 week post-treatment period renal function gradually improved, but not uniformly [Figure 1]. Mean BUN and Ccr improved, although they remained significantly lower than their pretreatment values by 6% and 16% respectively. As much as 67% of our patients concluded the study with impaired Ccr as compared to their starting values. In contrast, serum creatinine with the C-G method returned to near baseline values 3 weeks after discontinuation of aspirin.

Patients whose renal function declined following 2 weeks of aspirin (70%) tended to be the ones whose Ccr remained low at the end of the study. This was documented by the correlation between the changes from baseline to week 2 with the changes from baseline to week 5, for all the parameters studied ($P < 0.001$ for BUN and Ccr). Less prominent correlation was noted for C-G ($r = 0.26$, $P < 0.05$). The correlation between Ccr and calculated C-G as well as the correlation between the changes of these parameters versus baseline were significant at all tested points of the study (Ccr: $r = 0.25$–0.38, and C-G: $r = 0.32$–0.36, $P < 0.005$).

The effects of low dose aspirin on serum uric acid and Cu acid are shown in Figure 2. An increase in serum uric acid levels

Table 1. Demographic, clinical and basal laboratory data

Age (yrs)	
Mean	80 ± 9
Range	56–98
Gender	
Females	86
Males	20
Previous cardiac history	42 (40%)
Hypertension	46 (43%)
Stroke	47 (44%)
Diabetes	12 (11%)
Diuretic use	21 (20%)
Fed by NGT/PEG	58 (55%)
Body weight (kg)	58 ± 13
Hemoglobin (g/dl)	11.8 ± 1.4
Na (mEq/L)	137 ± 4.4
K (mEq/L)	4.3 ± 0.4
Cl (mEq/L)	100 ± 4.5
Ca (mg/dl)	9 ± 0.6
P (mg/dl)	3.4 ± 0.6
Albumin (g/dl)	3.0 ± 0.5
Cholesterol (mg/dl)	185 ± 53
Triglycerides (mg/dl)	124 ± 64

Clinical data are given in numbers (%) of patients; body weight and laboratory data are given as mean ± SD
NGT = nasogastric tube, PEG = percutaneous gastric tube.

Table 2. Distribution of patients according to the stages of renal failure class based on their basal renal function, as determined by measured Ccr or calculated GFR (C-G)

Stage* (ml/min of GFR)	Ccr (%)	C-G (%)**
1: ≥ 90	20	13
2: 60–89	37	33
3: 30–59	36	44
4: 15–29	7	10
5: <14	0	0

* Stages of renal function based on the American National Kidney Foundation criteria [8,9].
** Calculated GFR by Cockroft-Gault formula.

BUN = blood urea nitrogen

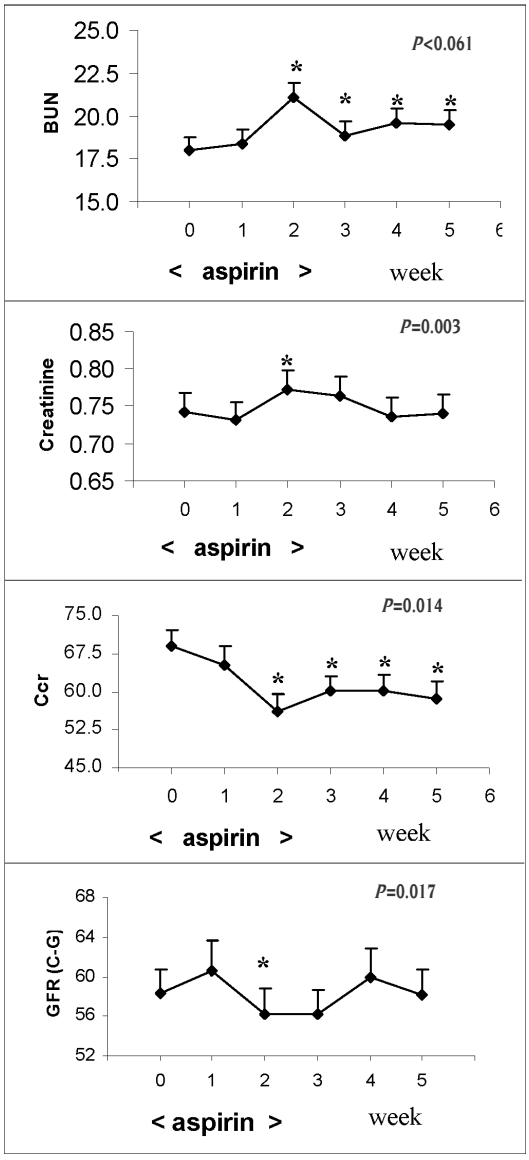

Figure 1. The effect of low dose aspirin on renal function; 100 mg/day for 2 weeks. Levels (mean ± SEM) of BUN (mg/dl), serum creatinine (mg/dl), creatinine clearance (Ccr) (ml/min) and GFR (ml/min) are shown for each week. Statistical significance by MANOVA is shown in the upper right corner. * $P < 0.05$ vs. baseline by paired *t*-test.

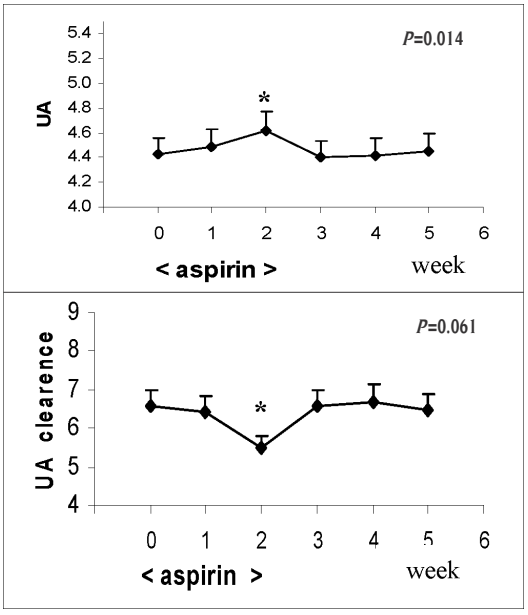

Figure 2. The effect of low dose aspirin on serum levels (mg/dl) and clearance (ml/min) of uric acid (UA), measured weekly. Aspirin 100 mg/day was administered for 2 weeks. All other details are identical to Figure 1. * $P < 0.05$ vs. baseline by paired *t*-test.

in parallel with a decrease of Cu acid were noticed within 1 week, declining further in the second week (+4% and -17%, respectively, $P < 0.005$). Following the cessation of the drug, serum concentrations and renal clearance of uric acid returned to baseline values.

The effects of aspirin on Ccr and on Cu acid were found to be associated. A highly significant correlation between the changes from baseline to week 2 in both creatinine and Cu acid was documented ($r = 0.7$, $P < 0.0001$). However, such correlations were not found between changes in values of C-G and Cu acid.

Normalization of Cu acid following withdrawal of aspirin seemed to be dissociated from Ccr: it occurred rapidly (already on week 3) and completely, as compared to Ccr [Figures 1 and 2]. This is shown also by the non-significant correlation between the ratio of clearance changes (change Cu acid / change of Ccr) in weeks 2–5 ($r = 0.12$, $P = 0.9$).

Factors that may have affected aspirin-induced renal function deterioration were determined by linear multivariate regression analysis. We found that Ccr changes at week 2 were influenced most significantly by the basal Ccr. The higher the basal Ccr the deeper its decrease, both in absolute and relative terms ($R^2 = 0.26$, $P < 0.0001$). The decrease in Ccr was also influenced by low hemoglobin levels ($R^2 = 0.075$, $P = 0.006$) and by albumin levels with borderline significance ($R^2 = 0.027$, $P = 0.08$). These three variables together explain 36% of the changes in Ccr following 2 weeks of aspirin. The change in the estimated renal function by C-G was not significantly influenced by any relevant cofactor.

Discussion

The present study confirms that 2 weeks of low dose aspirin therapy in elderly patients resulted in a significant decrease in creatinine and uric acid clearances. The decrease in Ccr and Cu acid affected the majority of patients. In more than 20% of patients the Ccr decreased more than 50%.

The main finding of our study was only a very mild decrease in the C-G estimated respective values. These differences between the measured Ccr and C-G values suggest a direct tubular effect of the drug. This assumption is further supported by the small changes in serum uric acid levels compared with the unexpected higher changes in Cu acid.

A relatively marked increase in BUN was found in the second week of aspirin treatment (as compared to the modest changes in serum creatinine and uric acid). A possible explanation may be a true decrease in BUN clearance or alternatively a change in its tubular handling. Another hypothetical mechanism may be attributed to aspirin-induced hypovolemia and extracellular volume changes reflected by the significant BUN changes. However, urine output as well as the hemoglobin levels remained stable throughout the study. Although we did not measure the

intravascular or extracellular volumes, the large changes in both BUN and uric acid can be better explained by a tubular transport effect than a hemodynamic effect.

While changes in Ccr and Cu acid correlated well during aspirin treatment, after withdrawal of the drug the Ccr and Cu acid changes no longer correlated. The changes in uric acid clearance were probably the result of the uric acid proximal tubular transport resulting from the aspirin.

Potentiating factors for the deleterious effects of low dose aspirin treatment on Ccr (week 2) were found to be lower serum albumin and lower hemoglobin. Hypoalbuminemia may be linked to increased bioavailability, hence a stronger effect of aspirin on the kidney [2,3]. Hypoalbuminemia and anemia may also be regarded as non-specific indicators of more seriously ill patients [10] within this group, though we were not able to document a direct association of these renal effects of aspirin with co-morbid states or older age.

Interestingly, higher pretreatment Ccr was associated with a more pronounced decrease in Ccr. We do not have a satisfactory explanation for this observation, which is in clear contrast with the well-established effects of NSAIDs and anti-inflammatory doses of aspirin [11]. Very low dose aspirin could affect renal thromboxane/prostacycline equilibrium in situations of impaired basal renal function, by preferentially reducing thromboxane and improving glomerular circulation [12]. Supporting this hypothesis is a study on rats following subtotal nephrectomy, where inhibition of thromboxane synthesis decreased the progression of renal impairment [13], as well as a study that showed better renal allograft survival in patients treated with low dose aspirin [14]. Two recent studies on the effects of low dose aspirin in patients with renal disease [15] and diabetic nephropathy [16] found no significant deleterious effects induced by aspirin.

A limitation of our study relates to the true GFR estimations. Based on the American National Kidney Foundation guidelines, the estimates of glomerular function by C-G and MDRD equations are the best overall indices of the level of kidney function. We also estimated GFR by the MDRD formula and the results were absolutely similar to the results obtained from C-G formula (data not shown). However, in older patients these methods may under- or overestimate the GFR [17-19]. Another limitation is the fact that it was an open-label study with no control group, unlike our previous study [7].

In conclusion, the results of the present study indicate that low dose aspirin administration in elderly inpatients for a short time has a significant effect on their renal tubular function; therefore, long-term drug administration may have an important deleterious effect on kidney function. These observations call for future studies, in younger and healthier patients, and on long-term use of aspirin therapy.

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MDRD = Modification of Diet in Renal Disease

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