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Evaluation of different low dose of aspirin therapy on renal function in elderly patients

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Abstract

Low dose aspirin is commonly used by elderly people for the prevention of thrombosis. These individuals are more prone to non-steroidal anti-inflammatory drug and aspirin-related adverse reactions, including renal side effects. The effects of the current low dose aspirin regimens (75–325 mg/day) in this regard were previously studied in two cohorts of elderly patients. It is 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 One week after the drug was withdrawn, uric acid excretion returned to normal while creatinine clearance remained low.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. Hence based on above findings the present study was planned for Evaluation of Different Low Dose of Aspirin Therapy on Renal Function in Elderly Patients.

The present study was planned in Department of General Medicine, Jawaharlal Nehru Medical College Bhagalpur, Bihar, India. Total 30 patients of both sexes were evaluated in the present study. The patients were divided in two study groups as Group A and Group B. The 15 cases in Group A patients received the received 100 mg/day Aspirin for 4 weeks and in 15 cases in Group B patients received the 300 mg/day Aspirin for 4 weeks. The data from the both the study group patients were analysed and evaluated.

The data generated from the present study concludes that 300 mg/day aspirin was found to induce a considerably higher changes in renal function and secretion of uric than 100 mg/day. The dosage of 100 mg/day aspirin can be used with more safety during the treatment.

Keywords: aspirin, renal function, glomerular function rate, elders, etc

Introduction

Renal function is an indication of the kidney's condition and its role in renal physiology. Glomerular filtration rate (GFR) describes the flow rate of filtered fluid through the kidney. Creatinine clearance rate (CCr or CrCl) is the volume of blood plasma that is cleared of creatinine per unit time and is a useful measure for approximating the GFR. Creatinine clearance exceeds GFR due to creatinine secretion [1], which can be blocked by cimetidine. Both GFR and CCr may be accurately calculated by comparative measurements of substances in the blood and urine or estimated by formulas using just a blood test result (eGFR and eCCr) The results of these tests are used to assess the excretory function of the kidneys. Staging of chronic kidney disease is based on categories of GFR as well as albuminuria and cause of kidney disease [2]. Dosage of drugs that are excreted primarily via urine may need to be modified based on either GFR or creatinine clearance.

Most physicians use plasma concentrations of waste substances such as creatinine and urea (U), as well as various electrolytes (E), to determine renal function. These measures are normally adequate to determine if a patient is suffering from kidney disease.

However, blood urea nitrogen (BUN) and creatinine in the plasma will not exceed normal ranges until 60% of total kidney function is lost. Hence, a more accurate glomerular filtration rate or its approximation using creatinine clearance is measured whenever renal disease is suspected or careful dosing of nephrotoxic drugs is required.

Elevated protein levels in urine mark some kidney diseases. The most sensitive marker of proteinuria is elevated urine albumin. Persistent presence of more than 30 mg albumin per gram creatinine in the urine is diagnostic of chronic kidney disease (microalbuminuria is a level of 30 mg/L to 299 mg/L urine or 30–299 mg/24 h; a concentration of albumin in the urine that is not detected by usual urine dipstick methods).

Glomerular filtration rate (GFR) is the volume of fluid filtered from the renal (kidney) glomerular capillaries into the Bowman's capsule per unit time [3]. Central to the physiologic maintenance of GFR is the differential basal tone of the afferent and efferent arterioles (see diagram). In other words, the filtration rate is dependent on the difference between the higher blood pressure created by vasoconstriction of the input or afferent arteriole versus the lower blood pressure created by lesser vasoconstriction of the output or efferent arteriole.

GFR is equal to the Clearance Rate when any solute is freely filtered and is neither reabsorbed nor secreted by the kidneys. The rate therefore measured is the quantity of the substance in the urine that originated from a calculable volume of blood. Relating this principle to the below equation – for the substance used, the product of urine concentration and urine flow equals the mass of substance excreted during the time that urine has been collected. This mass equals the mass filtered at the glomerulus as nothing is

added or removed in the nephron. Dividing this mass by the plasma concentration gives the volume of plasma which the mass must have originally come from, and thus the volume of plasma fluid that has entered Bowman's capsule within the aforementioned period of time. The GFR is typically recorded in units of volume per time, e.g., milliliters per minute (mL/min). Compare to filtration fraction.

In clinical practice, however, creatinine clearance or estimates of creatinine clearance based on the serum creatinine level are used to measure GFR. Creatinine is produced naturally by the body (creatinine is a breakdown product of creatine phosphate, which is found in muscle). It is freely filtered by the glomerulus, but also actively secreted by the peritubular capillaries in very small amounts such that creatinine clearance overestimates actual GFR by 10% to 20%. This margin of error is acceptable, considering the ease with which creatinine clearance is measured. Unlike precise GFR measurements involving constant infusions of inulin, creatinine is already at a steady-state concentration in the blood, and so measuring creatinine clearance is much less cumbersome. However, creatinine estimates of GFR have their limitations. All of the estimating equations depend on a prediction of the 24-hour creatinine excretion rate, which is a function of muscle mass which is quite variable. One of the equations, the Cockcroft and Gault equation does not correct for race. With a higher muscle mass, serum creatinine will be higher for any given rate of clearance.

A common mistake made when just looking at serum creatinine is the failure to account for muscle mass. Hence, an older woman with a serum creatinine of 1.4 mg/dL may actually have a moderately severe chronic kidney disease, whereas a young muscular male can have a normal level of renal function at this serum creatinine level. Creatinine-based equations should be used with caution in cachectic patients and patients with cirrhosis. They often have very low muscle mass and a much lower creatinine excretion rate than predicted by the equations below, such that a cirrhotic patient with a serum creatinine of 0.9 mg/dL may have a moderately severe degree of chronic kidney disease.

One method of determining GFR from creatinine is to collect urine (usually for 24 h) to determine the amount of creatinine that was removed from the blood over a given time interval. If one removes 1440 mg in 24 h, this is equivalent to removing 1 mg/min. If the blood concentration is 0.01 mg/mL (1 mg/dL), then one can say that 100 mL/min of blood is being "cleared" of creatinine, since, to get 1 mg of creatinine, 100 mL of blood containing 0.01 mg/mL would need to have been cleared.

Twenty-four-hour urine collection to assess creatinine clearance is no longer widely performed, due to difficulty in assuring complete specimen collection. To assess the adequacy of a complete collection, one always calculates the amount of creatinine excreted over a 24-hour period. This amount varies with muscle mass, and is higher in young people/old, and in men/women. An unexpectedly low or high 24-hour creatinine excretion rate voids the test. Nevertheless, in cases where estimates of creatinine clearance from serum creatinine are unreliable, creatinine clearance remains a useful test. These cases include "estimation of GFR in individuals with variation in dietary intake (vegetarian diet, creatine supplements) or muscle mass (amputation, malnutrition, muscle wasting), since these factors are not specifically taken into account in prediction equations [4].

A decreased renal function can be caused by many types of kidney disease. Upon presentation of decreased renal function, it is recommended to perform a history and physical examination, as well as performing a renal ultrasound and a urinalysis.[citation needed] The most relevant items in the history are medications, edema, . Proteinuria and/or urinary sediment usually indicates the presence of glomerular disease. Hematuria may be caused by glomerular disease or by a disease along the urinary tract. The most relevant assessments in a renal ultrasound are renal sizes, echogenicity and any signs of hydronephrosis. Renal enlargement usually indicates diabetic nephropathy, focal segmental glomerular sclerosis or myeloma. Renal atrophy suggests longstanding chronic renal disease.

Acetylsalicylic acid is a weak acid, and very little of it is ionized in the stomach after oral administration. Acetylsalicylic acid is quickly absorbed through the cell membrane in the acidic conditions of the stomach. The increased pH and larger surface area of the small intestine causes aspirin to be absorbed more slowly there, as more of it is ionized. Owing to the formation of concretions, aspirin is absorbed much more slowly during overdose, and plasma concentrations can continue to rise for up to 24 hours after ingestion [5].

Aspirin, also known as acetylsalicylic acid (ASA), is a medication used to reduce pain, fever, or inflammation. Specific inflammatory conditions which aspirin is used to treat include Kawasaki disease, pericarditis, and rheumatic fever. Aspirin given shortly after a heart attack decreases the risk of death. Aspirin is also used long-term to help prevent further heart attacks, ischaemic strokes, and blood clots in people at high risk. It may also decrease the risk of certain types of cancer, particularly colorectal cancer. For pain or fever, effects typically begin within 30 minutes. Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) and works similarly to other NSAIDs but also suppresses the normal functioning of platelets.

About 50–80% of salicylate in the blood is bound to albumin protein, while the rest remains in the active, ionized state; protein binding is concentration-dependent. Saturation of binding sites leads to more free salicylate and increased toxicity. The volume of distribution is 0.1–0.2 L/kg. Acidosis increases the volume of distribution because of enhancement of tissue penetration of salicylates [6].

As much as 80% of therapeutic doses of salicylic acid is metabolized in the liver. Conjugation with glycine forms salicyluric acid, and with glucuronic acid to form two different glucuronide esters. The conjugate with the acetyl group intact is referred to as the acyl glucuronide; the deacetylated conjugate is the phenolic glucuronide. These metabolic pathways have only a limited capacity. Small amounts of salicylic acid are also hydroxylated to gentisic acid. With large salicylate doses, the kinetics switch from first-order to zero-order, as metabolic pathways become saturated and renal excretion becomes increasingly important [6].

Salicylates are excreted mainly by the kidneys as salicyluric acid (75%), free salicylic acid (10%), salicylic phenol (10%), and acyl glucuronides (5%), gentisic acid (< 1%), and 2,3-dihydroxybenzoic acid.[160] When small doses (less than 250 mg in an adult) are ingested, all pathways proceed by first-order kinetics, with an elimination half-life of about 2.0 h to 4.5 h.[161][162] When higher doses of

salicylate are ingested (more than 4 g), the half-life becomes much longer (15 h to 30 h), because the biotransformation pathways concerned with the formation of salicyluric acid and salicyl phenolic glucuronide become saturated. Renal excretion of salicylic acid becomes increasingly important as the metabolic pathways become saturated, because it is extremely sensitive to changes in urinary pH. A 10- to 20-fold increase in renal clearance occurs when urine pH is increased from 5 to 8. The use of urinary alkalinization exploits this particular aspect of salicylate elimination. It was found that short-term aspirin use in therapeutic doses might precipitate reversible acute kidney injury when the patient was ill with glomerulonephritis or cirrhosis.[166] Aspirin for some patients with chronic kidney disease and some children with congestive heart failure was contraindicated [7].

Low dose aspirin is commonly used by elderly people for the prevention of thrombosis [8]. These individuals are more prone to non-steroidal anti-inflammatory drug and aspirin-related adverse reactions, including renal side effects [9]. The effects of the current low dose aspirin regimens (75–325 mg/day) in this regard were previously studied in two cohorts of elderly patients [10]. It is 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.

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Methodology

The present study was planned in Department of General Medicine, Jawaharlal Nehru Medical College Bhagalpur, Bihar, India. Total 30 patients of both sexes were evaluated in the present study. The patients were divided in two study groups as Group A and Group B. The 15 cases in Group A patients received the received 100 mg/day Aspirin for 4 weeks and in 15 cases in Group B patients received the 300 mg/day Aspirin for 4 weeks. The data from the both the study group patients were analysed and evaluated.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion criteria: Patients on low dose aspirin.

Exclusion criteria: Patients with a history of active peptic ulcer, gastrointestinal bleeding, chronic liver diseases, hyperuricemia, serum creatinine > 1.5 mg/dL (132.6 μmol/L), a significant history of alcohol consumption, or recent use of anticoagulants, aspirin, or non-steroidal anti-inflammatory drugs.

Results & Discussion

Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients who have experienced myocardial infarction (MI) or stroke [11] and is recommended as a secondary prevention strategy for individuals with multiple risk factors such as hypertension, dyslipidemia, obesity, diabetes, and a family history of ischemic heart disease [12, 13]. The American Diabetes Association and the American Heart Association recommend low-dose aspirin (75–162 mg) for adults with diabetes who have no previous history of vascular disease, a 10-year risk of CVD events that is greater than 10%, and no increased risk of bleeding [12].

Table 1: Demographic data

Group	Group I	Group II
No. of Patients	15	15
Dose of Administered Aspirin	100 mg/day	300 mg/day
Age in years	34 – 58	33 - 63
Males	10	12
Females	5	3

Table 2

Group	Group I		Group II	
Dose of Administered Aspirin	100 mg/day		300 mg/day	
Parameters	Baseline	After 4 weeks	Baseline	After 4 weeks
Serum Uric Acid (mg/dl)	5.63 ± 1.29	4.81 ± 1.21	5.75 ± 1.35	5.36 ± 0.89
Fractional Excretion of Uric Acid (mg/dl	44.7 ± 11.4	34.7 ± 8.79	46.7 ± 8.96	27.6 ± 6.78
Uric Acid Clearance (ml/min)	8.59 ± 0.64	7.37 ± 0.86	8.87 ± 0.79	6.78 ± 1.26
Serum Creatinine (mg/dl)	1.38 ± 0.19	1.17 ± 0.14	0.88 ± 0.21	1.34 ± 0.13
Urine Creatinne (mg/dl)	121.5 ± 24.5	129.6 ± 21.8	112.8 ± 13.6	93.4 ± 12.8
CrCl (ml/min)	112.6 ± 14.8	103.7 ± 14.8	117.4 ± 10.9	96.3 ± 11.8
Serum Urea (mg/dl)	27.3 ± 8.8	34.8 ± 5.2	27.6 ± 5.2	33.8 ± 4.9
Urine Urea (mg/dl)	1861.8 ± 289.3	1807.9 ± 246.8	1859.6 ± 271.5	1608.3 ± 278.3

Low dose aspirin is increasingly being used as an antiplatelet to prevent thrombosis and other fatal cardiovascular outcomes in at-risk patients [14]. Elderly patients not only form the majority of these at-risk patients, but they also readily succumb to the deleterious effects of aspirin on renal function [15].

Various studies assessing the elderly among Caucasian populations have shown that 1–2 weeks of low dose aspirin use (75 mg–325 mg/day) caused significant decreases in both creatinine clearance (CrCl) and uric acid clearance, as well as elevations in serum creatinine and uric acid.6–8 These parameters improved upon withdrawal of the drug, but the decline in the glomerular filtration rate persisted 3 weeks posttreatment [16]. Thus, long-term aspirin administration may have clinically important deleterious effects on renal function [17].

Low-dose aspirin therapy has previously been recommended by several key guidelines for primary prevention of CV events in patients with diabetes, although with some inconsistencies [18]. In 2010, the ADA, the

American Heart Association, and the American College of Cardiology Foundation convened a group of experts to create updated recommendations for the primary prevention strategy of low-dose aspirin use in patients with diabetes [19]. They performed a new meta-analysis that included two recent randomized controlled trials of aspirin, the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial [20], and the Prevention of Progression of Arterial Diseases and Diabetes (POPADAD) trial [21]. Both trials enrolled only patients with diabetes and neither showed any significant effect of aspirin to prevent atherosclerotic event.

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 [22]. Supporting this hypothesis is a study on rats following subtotal nephrectomy, where inhibit tion of thromboxane synthesis decreased the progression of renal impairment [23], as well as a study that showed better renal allograft survival in patients treated with low dose aspirin. [24]. Two recent studies on the effects of low dose aspirin in patients with renal disease [25] and diabetic nephropathy [26] found no significant deleterious effects induced by aspirin.

In hypertension, the blood pressure lowering effect of ACE-inhibitors seems to be blunted by aspirin in a dose-dependent manner. The effects of aspirin 100 mg and 300 mg were studied in hypertensive patients treated with ACE-inhibitors. No interaction was noted with 100 mg aspirin, but a significant interaction was observed with 300 mg aspirin [27].

Whether the renal effects of low-dose aspirin in patients with heart failure treated with ACE-inhibitor are dose-dependent, has not been studied previously. High dose aspirin, 500 mg t.i.d., administered to patients with heart failure has been shown to reduce renal sodium excretion [28].

Conclusion

The data generated from the present study concludes that 300 mg/day aspirin was found to induce a considerably higher changes in renal function and secretion of uric than 100 mg/day. The dosage of 100 mg/day aspirin can be used with more safety during the treatment.

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