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Original Research Article

Study of Renal Function after Administration Different Doses of Aspirin in Bihar Region

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Abstract

Aim: The aim of this study to evaluate the renal function after administration different doses of aspirin in bihar region.

Methods: A double-blind, cross-over design study was conducted in the Department of General Medicine, Lord Buddha Koshi Medical College and Hospital, Saharsa, Bihar, India. For 18 months. Patients were divided into two groups and each group received two different doses of aspirin in a randomised order.The volunteers were randomised into two groups (n =20per group). The first group received aspirin doses of 0 mg (placebo) and 160mg. The second group received doses of 80mg and 320mg. The doses were given in a randomised order with at least 14 days wash-out between treatments. The same pre- treatment was given before each dose of aspirin. A total of 40 subjects were included, 30 were women and 10 men. Sodium, potassium, creatinine and osmolality in serum, and sodium, potassium and osmolality in urine, were analysed by standard methods.

Results: The urine flow, GFR, excretion rate of sodium, osmolality clearance and free water clearance 75 min after dosing diminished in a dose-dependent manner. Urine flow, sodium excretion rate and free water clearance were significantly lower with 320mg aspirin vs. placebo and 80mg aspirin. GFR was significantly lower with 320mg vs. 80mg aspirin. Urine flow, sodium excretion rate, osmolality clearance and free water clearance were also significantly lower with the 160 mg aspirin dose than placebo. Urine flow decreased from 6.5 (4.2-7.3) ml/min with placebo to 5.9 (3.5-6.7) with 80mg aspirin, to 4.2 (2.6-5.7) with 160mg and to 2.7 (1.4-4.6) ml/min with 320mg aspirin. table 1. Least square means of the observations 30 to 180 min after dosing showed dose-dependent decreases in urine flow, GFR, excretion rate of sodium, osmolality clearance and free water clearance. However, statistical significance was only shown for dose comparisons of aspirin 320mg vs. placebo and 80mg in urine flow, sodium excretion rate and osmolality clearance and vs. placebo in free water clearance. Statistical significance was also reached for dose comparisons of 160 mg aspirin vs. placebo in sodium excretion rate and free water clearance. With placebo the urine flow was 5.6 (3.8-6.5), with 80mg aspirin 4.9 (3.2-6.0), with 160mg it was reduced to 4.4 (2.6-5.4) and with 320 mg it was further reduced to 3.5 (1.7-4.4) table 2. No significant differences were found between 80mg aspirin and placebo.

Conclusion: We concluded that aspirin deteriorated renal function in a dose-dependent manner in elderly healthy volunteers with an activated renin–angiotensin system from pre-treatment with

diuretics, who were also being treated with ACE-inhibitors. However, the lowest dose which does not cause adverse effects for the individual patient cannot be determined in advance and the risk that aspirin may neutralise the clinical benefits of ACE-inhibitors must be taken into consideration even with low-dose aspirin.

Keywords: GFR, ACE-inhibitors

Introduction

Cardiovascular disease (CVD) is the leading cause of death and disease burden in China and worldwide.[1,2] Low-dose aspirin is the cornerstone of secondary prevention of ASCVD. However, some researchers discovered that low-dose aspirin could raise SUA by a decrease in uric acid excretion, causing hyperuricemia which is a common clinical condition that can be defined as SUA level>420umol/l (7mg/dL) in male or>360umol/l (6mg/dL) in female.[3]

Numerous evidence[4-6] have suggested the existence of an association between elevated SUA and CVD, traditional cardiovascular risk factors, metabolic syndrome, insulin resistance, chronic kidney disease and heart failure.[7–9] Hyperuricemia is an independent predictor not only of all-cause and cardiovascular mortality, but also of myocardial infarction, stroke and heart failure[10] and it may act as a promoter of renal damage for correlating with lower renal glomerular filtration rate and macroalbuminuria.[11] But there are few studies focusing on the effects of low-dose aspirin treatment for a longer time (used to be no more than 2 weeks) on uric acid and its urinary excretion among Chinese elderly patients. Aspirin, also known as acetylsalicylic acid (ASA), is a medication used to treat pain, fever, or inflammation. Specific inflammatory conditions in which aspirin is used 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 heart attacks, ischaemic strokes, and blood clots, in people at high risk. Aspirin 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 similar to other NSAIDs but also suppresses the normal functioning of platelets.[12] Common side effects include an upset stomach. More significant side effects include stomach ulcers, stomach bleeding, and worsening asthma. Bleeding risk is greater among those who are older, drink alcohol, take other NSAIDs, or are on blood thinners. Aspirin is not recommended in the last part of pregnancy. It is not generally recommended in children with infections because of the risk of Reye's syndrome. High doses may result in ringing in the ears.[12]

Material and methods

A double-blind, cross-over design study was conducted in the Department of General Medicine, Lord Buddha Koshi Medical College and Hospital, Saharsa, Bihar, India. For 18 months. Patients were divided into two groups and each group received two different doses of aspirin in a randomised order.

All subjects were pre-treated with the thiazide diuretic bendroflumethiazide, administered as 5mg daily for 6 days i.e. days-6 to -1, bendroflumethiazide was not given on study

days. All subjects were also pre-treated with the ACE-inhibitor enalapril, administered as 2.5 mg daily on days-6, -5 and -4; 5 mg daily on days-3 and -2; and 10 mg daily on day-1and on the study days. The subjects were in contact with oneof the investigators on days-3 to -1; if any adverse events suggestive of too high a dose, e.g. dizziness or tiredness, were reported, the dose was lowered for that subject. The volunteers were randomised into two groups (n =20per group).

The first group received aspirin doses of 0 mg (placebo) and 160mg. The second group received doses of 80mg and 320mg. The doses were given in a randomised order with atleast 14 days wash-out between treatments. The same pre- treatment was given before each dose of aspirin.

Inclusion criteria

Male or female subjects aged 50–70 years.

Exclusion criteria

patients with heart disease, severe renal insufficiency (known GFRb 30 ml/min), peptic ulcer, liver cirrhosis, intolerance to bendroflumethiazide, intolerance to enalapril or any other ACE-inhibitor, intolerance to iohexol, NSAIDs or aspirin.

A total of 40 subjects were included, 30 were women and10 men. Ages ranged from 51–70 years (mean 67 ± 7.8). The group that received the 0 and 160mg doses comprised 15 women and 5 man aged 52–70 years (mean 67 ± 8.6). The group with the 80 and 320mg doses comprised 15 women and 5 men aged 54–69 years (mean 70 ± 7.8).

Sodium, potassium, creatinine and osmolality in serum, and sodium, potassium and osmolality in urine, were analysed by standard methods.

Results

All subjects received the planned doses of diuretics and ACE-inhibitors as the pre-treatment was well tolerated. No adverse effects were reported after the aspirin doses.

The time profiles of acetylsalicylic acid above a con- centration of approximately 40 μmol/l exhibited a pattern suggestive of zero order elimination and thus the areas under the concentration versus time curves showed non-linear in- crease by dose.

Observations of urine flow, GFR, excretion rate of so- dium, osmolality clearance and free water clearance 75 minafter dosing diminished in a dose-dependent manner. Urine flow, sodium excretion rate and free water clearance were significantly lower with 320 mg aspirin vs. placebo and 80 mg aspirin. GFR was significantly lower with 320 mg vs. 80 mg aspirin. Urine flow, sodium excretion rate, osmolalityclearance and free water clearance were also significantly lower with the 160 mg aspirin dose than placebo. Urine flowdecreased from 6.5 (4.2–7.3) ml/min with placebo to 5.9 (3.5–6.7) with 80 mg aspirin, to 4.2 (2.6–5.7) with 160mg and to 2.7 (1.4–4.6) ml/min with 320mg aspirin. table 1. Least square means of the observations 30 to 180 min after dosing showed dose-dependent decreases in urine flow, GFR, excretion rate of sodium, osmolality clearance and free water clearance. However, statistical significance was only shown for dose comparisons of aspirin 320mg vs. placebo and 80mg in urine flow, sodium excretion rate andosmolality clearance and vs. placebo in free water clearance. Statistical significance was also reached for dose comparisons of 160mg aspirin vs. placebo in sodium excretion rateand free water clearance. With placebo the urine flow was 5.6 (3.8–6.5), with 80mg aspirin 4.9 (3.2–6.0), with 160mg it was reduced to 4.4 (2.6–5.4) and with 320mg it was further reduced to 3.5(1.7–4.4) table 2. No significant differences were found between 80mg aspirin and placebo.

Table 1: Urine flow, excretion rates of electrolytes, osmolality clearance and free water clearance measured 75 min after dosing with different aspirin doses (0, 80, 160 and 320 mg) in elderly, healthy volunteers with an activated renin–angiotensin system and treated with ACE-inhibitors (means and 95% confidence limits)

	0 mg	80 mg	160 mg	320 mg
Urine flow (ml/min)	6.5(4.2—7.3)	5.9(3.5—6.7)	4.2(2.6—5.7)*	2.7(1.4—4.6)*◆
GFR (ml/min)	85(67—98)	84(68—100)	79(62—91)	73(57—88)◆
Sodium excretion rate (μmol/min)	108(87—133)	82(59—108)	57(33—81)*	32(10—55)*◆
Potassium excretion rate (μmol/min)	52(31—77)	71(47—93)	43(20—66)*	55(32—78)
Osmolality clearance (ml/min)	2.2(1.7—2.6)	2.3(1.8—2.6)	1.8(1.2—2.4)*	1.6(1.1—1.9)
Free water clearance (ml/min)	3.5(2.3—4.8)	2.9(1.6—4.1)	2.1(0.8—3.5)*	1.5(0.1—2.5)*◆
*p b 0.05 vs. placebo (aspirin 0 mg). p b 0.05 vs. aspirin 80 mg.				

Table 2: Urine flow, excretion rates of electrolytes, osmolality clearance and free water clearance measured 30 to 180 min after dosing with different aspirin doses (0, 80, 160 and 320 mg) in elderly, healthy volunteers with an activated renin–angiotensin system and treated with ACE-inhibitors (least square means and 95% confidence limits)

	0 mg	80 mg	160 mg	320 mg
Urine flow (ml/min)	5.6(3.8—6.5)	4.9(3.2—6.0)	4.4(2.6—5.4)	3.5(1.7—4.4)*◆
GFR (ml/min)	85(73—98)	86(74—99)	79(66—92)	75(62—89)
Sodium excretion rate (μmol/min)	105(83—126)	81(61—102)	60(40—82)*	43(23—65)*◆
Potassium excretion rate (μmol/min)	45(27—63	62(43—80)	39(20—57)	52(34—70)
Osmolality clearance (ml/min)	2.0(1.6—2.4)	2.0(1.6—2.4)	1.6(1.2—2.0)	1.4(1.1—1.8)*◆
Free water clearance (ml/min)	3.1(2.0—4.2)	2.5(1.5—3.7)	2.0(0.9—3.1)*	1.5(0.5—2.6)*
*p b 0.05 vs. placebo (aspirin 0 mg). p b 0.05 vs. aspirin 80 mg.				

Discussion

In this study we have demonstrated that the adverse renaleffects from acute administration of low doses of aspirin to subjects treated with ACE-inhibitors after activation of theirrenin–angiotensin systems are clearly dose-dependent, and are of clinical relevance even after a single aspirin dose as low as 160 mg. However, the effect on GFR is short-lasting and of a magnitude that is probably only of minor clinical importance.

Observations from large-scale clinical trials with ACE- inhibitors have led to the suspicion that aspirin may neutralise the clinical benefits from treatment with ACE- inhibitors. A subgroup analysis from CONSENSUS II found evidence of an interaction between the ACE-inhibitor enalapril and aspirin. The effect of enalapril was less favourable among patients taking aspirin than among patients not taking aspirin at baseline. Aspirin antagonised the effect of enalapril on mortality at the end of the study.[13] In the SOLVD-trial there was less benefit with enalapril among patients taking aspirin; enalapril was shown to be almost inactive in patients taking aspirin.[14] The HOPE-trial observed a highly significant interaction. In the absence of aspirin, Ramipril reduced the primary composite endpoint by 40%, but among those patients taking aspirin only by 15%.[15] The WASH-study, in which patients with heart failure treated with ACE-inhibitors were randomised to no anti-thrombotic therapy, warfarin or aspirin, showed a trend to excess mortality and a significant increase in the risk of hospitalisation for heart failure in patients randomised to aspirin.[16] An observational study of patients with symptomatic heart failure requiring hospitalisation showed an increased incidence of early readmissions for heart failure among subjects treated with ACE-inhibitors and aspirincompared with those only treated with ACE-inhibitors.[17] In the WATCH-study, patients with heart failure and left ventricular ejection fraction b 35% were included and randomised to treatment with warfarin, clopidogrel 75 mg/day or aspirin 162 mg/day. Due to poor recruitment rates thestudy was stopped when only 1587 of the planned 4500patients had been enrolled. There was no difference betweenthe treatment groups for all cause mortality, non-fatal myocardial infarction or stroke, but in the warfarin group compared with aspirin 27% fewer patients were hospitalised for heart failure. Thus, if 17 patients are treated with aspirin, 162 mg/day, instead of warfarin there will be one further hospitalisation due to heart failure. There were also fewer hospitalisations for heart failure with clopidogrel.[18]

A retrospective study of patients hospitalised with aprincipal discharge diagnosis of chronic heart failure and treated with ACE-inhibitors, studied patients in three treatment groups. Group 1 had no aspirin treatment; group2 had an aspirin dose ≤160 mg and group 3 had 325 mg or more aspirin. After an average follow-up of 37.6 months, survival was similar in groups 1 and 2, but was significantlyworse in group 3 compared with groups 1 and 2. Thus, administration of high doses of aspirin was associated with reduced survival.[19] Our finding of a dose-dependentadverse effect on renal function is in accordance with this study.

Several mechanistic studies have been performed to investigate the interaction between ACE-inhibitors and aspirin. In an invasive study of central haemodynamics, enalapril caused significant decreases in systemic vascular resistance, left ventricular filling pressures and totalpulmonary resistance together with a significant increase incardiac output. When enalapril was given on the same day orthe day after 350 mg aspirin, it abolished the enalapril- induced changes in these variables.[20] In another study, ticlopidine, an antiplatelet agent which does not interact with prostaglandin synthesis, reduced systemic vascular resistance more effectively with

enalapril than when enalapril was given in combination with 325 mg aspirin.[21]

In an evaluation of haemodynamic status in patients withchronic heart failure undergoing treatment with ACE- inhibitors after a single dose of 236 mg aspirin, no discernible effect was observed after addition of aspirin. Aspirin significantly reduced plasma TXB_2-levels, but vasodilating PGI_2 was not significantly reduced. The authorsconcluded that the aspirin dose used (236 mg) preferentially blocks formation of the vasoconstricting TXA_2 and that deterioration of the haemodynamic status of patients with heart failure is less likely after addition of low-dose aspirin but that higher doses may be deleterious.[22]

Aspirin 325 mg/day for one week was shown to alter arterial function, assessed by applanation tonometry, com- pared with placebo and aspirin 100 mg/day in patients with chronic heart failure treated with ACE-inhibitors. Thus the alteration in arterial function was dose-mediated.[23] However, using venous occlusion plethysmography, even 75 mg aspirin was shown to inhibit the acute arterial and venous vasodilator response to the ACE-inhibitor captopril in patients with chronic heart failure.[24]

It has been suggested that ACE-inhibitors exert some of their benefits in heart failure by improving alveolar– capillary membrane diffusing capacity and pulmonary gas exchange. These effects have been shown to be counteractedby 325 mg aspirin.[25,26]

The antiplatelet agent clopidogrel, which does not interact with prostaglandin synthesis, was compared with aspirin in patients with heart failure treated with ACE-inhibitors. A significant increase in mean VO_2max was seen in patients receiving clopidogrel in combination with an ACE-inhibitorcompared to those receiving aspirin plus an ACE-inhibitor.[27] In a study of patients with heart failure receiving ACE- inhibitors, an adverse effect of aspirin 325 mg/day on plasma brain natriuretic peptide levels was demonstrated; however, in contrast clopidogrel 75 mg/day had no effect.[28]

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 buta significant interaction was observed with 300 mg aspirin.[29]

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.[30] Our study is the first to show that the adverse renal effects of aspirin, in ACE-inhibitor treated subjects with an activated renin–angiotensin system, are clearly dose-dependent and significant even after a single dose of 160 mg aspirin. In our previous study of patients with heart failure treated with ACE-inhibitors and continuous aspirin, medandose 75 mg/day, we did not find any clinically relevant negative renal effects compared with placebo on a group level.[31] However, we do not know the lowest dose causing clinical deterioration at the individual level. In the present study, there were no significant differences betweenplacebo and 80 mg aspirin, but there was a trend towards an adverse effect. Aspirin 75 mg has been shown to be sufficient to block the vasodilator response to the prostacyclin precursor arachidonic acid in patients with heart failure.[32] meaning that for some patients even low-dose aspirin can cause harmful vasoconstrictor effects. Therefore, it seems unwise to argue that low-dose aspirin is safe for the individual patient with heart failure treated with ACE- inhibitors. Adding low doses of aspirin may cause vasoconstriction

and oedema. In previous observational studies showing the lack of a negative interaction between aspirin and ACE-inhibitors, the doses of aspirin used are notknown.[33,34]

Conclusion

We concluded that aspirin deteriorated renal function in a dose-dependent manner in elderly healthy volunteers with an activated renin–angiotensin system from pre-treatment with diuretics, who were also being treated with ACE-inhibitors. However, the lowest dose which does not cause adverse effects for the individual patient cannot be determined in advance and the risk that aspirin may neutralise the clinical benefits of ACE-inhibitors must be taken into consideration even with low-dose aspirin

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