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EFFECTS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ON HYPERTENSION CONTROL USING ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND THIAZIDE DIURETICS
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ABSTRACT

Objectives: **To determine the impact of three non-steroidal anti-inflammatory drugs on the efficacy of two anti-hypertensive drugs.**
Design: **Fifteen women with arthritis and hypertension who were receiving lisinopril and HCT, and administered sequentially in random order ibuprofen, sulindac, and diclofenac for one month each, with an intervening two-week washout period between each treatment period. During the washout period, subjects received paracetamol.**
Setting: **Hypertension Clinic, Medical Centre, Harare, Zimbabwe.**
Subjects: **Fifteen female hypertensive women with documented arthritis.**
Main outcome measures: **Blood pressure at the end of two weeks of paracetamol was compared with blood pressure after one month of treatment with each of the NSAID.**
Results: **Mean blood pressure was unchanged before and after all NSAIDs: 108 ± 7 versus 107 ± 9 for diclofenac, 108 ± 9 versus 108 ± 9 for sulindac, and 108 ± 8 versus 107 ± 9 for ibuprofen. The 24 hour urinary sodium excretion was not significantly different.**
Conclusion: **The three NSAIDs investigated did not neutralise the antihypertensive effect of the combination of lisinopril and HCT, and hence the blood pressure lowering action of the combination may not be prostaglandin dependent.**

INTRODUCTION

Prostaglandins induce vasodilatation and natriuresis and thus, can lower blood pressure (BP). By blocking these actions, non-steroidal anti-inflammatory drugs (NSAIDs) can increase BP. In the United States, an estimated 50 million individuals take NSAIDs at least once yearly, but NSAIDs do not increase BP in all of these subjects. Reasons for these variable effects include the fact that NSAIDs interfere with the actions of many anti-hypertensive agents, they may not affect BP in the normotensive population; in addition, some NSAIDs may affect BP in some individuals more than others. For example, anti-hypertensive agents whose BP lowering actions are not dependent on prostaglandins (such as calcium channel blockers) are not influenced by NSAIDs, whereas the anti-hypertensive action of many other agents, including angiotensin-converting enzyme (ACE) inhibitors and diuretics, is susceptible to interference by NSAID(1,2).

Not all NSAIDs affect BP equally; certain NSAIDs, such as indomethacin, are more likely than others to cause hypertension. Several studies(3,4) have demonstrated that ibuprofen increases, whereas sulindac appears to have little effect on BP. In a meta-analysis by Pope *et al*(5), the normotensive population did not seem to be at risk for elevation in BP due to NSAID use, and indomethacin and naproxen caused the highest increase in BP, whereas others were not as damaging. However, one of the limitations of this meta-analysis was that the trials included were heterogeneous for anti-hypertensive agents used. Therefore, the relative role of specific anti-hypertensive agents, if any, could not be determined. Although it has been shown previously that NSAIDs dampen the anti-hypertensive effects of ACE inhibitors and diuretics administered individually(6,7), the effects of NSAID on ACE inhibitors used in combination with a thiazide diuretic has not been examined.

MATERIALS AND METHODS

This study evaluated the effects of three different NSAIDs in a group of patients taking both the ACE inhibitor lisinopril and the diuretic hydrochlorothiazide (HCT) for BP control.

Fifteen African hypertensive women above 45 years, who had clinical and radiological evidence of osteoarthritis of the knees, hips, or hands, and whose BP was controlled (sitting, diastolic BP <95 mm Hg) by the combination of lisinopril 10 to 40 mg daily and HCT 25 mg, daily were enrolled in the study. (Patients had documented and recorded blood pressure measurements dating back at least three years). All had initial untreated blood pressures defined as moderate or severe hypertension (BP >160/100) as defined by the World Health Organisation. The nature of the study was fully explained and informed consent obtained. Once enrolled, patients were placed on paracetamol 500mg up to eight tablets per day for pain, as needed. After two weeks, BP was measured as described in standard textbooks, with the patient in a sitting position, using a mercury sphygmomanometer. The patients were allowed to sit for several minutes in a quiet room before beginning blood pressure measurement. The standard cuff with a bladder that was 12-13cm by 35cm was used. Where patients were obese a larger

bladder was used. Phase V of the Korotokoff sounds was used to determine diastolic blood pressure. Blood pressure was always measured in both arms and the sphygmomanometer was always placed at the heart level whatever the position of the patient. Weight was noted, and 24 hour urine collected for electrolyte, and creatinine. In addition, glomerular filtration rate (GFR) was measured using inulin clearance. The patients were then given either diclofenac 75mg two times a day, sulindac 200 mg two times a day, or ibuprofen 800mg three times a day for one month in an order predetermined by a randomisation code. At the conclusion of one month, the battery of tests was repeated and the next cycle was initiated using another NSAID, with an intervening two week period of paracetamol therapy. Compliance with both anti-hypertensive and NSAID was assessed by tablet count at each weekly visit. Compliance of less than 80% on two consecutive visits was considered a reason for withdrawal from the study.

RESULTS

The results are expressed as mean±SEM. The mean age was 53.8±0.82, mean weight 87.3±2.8kg and the height 142±0.8cm. Acute renal failure, defined as a decrease in GFR of >25% occurred in four of the fifteen subjects in the ibuprofen group, one of the fifteen in the sulindac group and none of the fifteen in the diclofenac group, the difference in the incidence of acute renal failure did not achieve statistical significance. On stopping the NSAIDs renal function recovered over a period of several weeks. All patients that were found to have acute renal failure recovered by the end of the study.

Table 1

Comparison of blood pressure before being the NSAID (after a two week washout period with paracetamol), to blood pressure after a one month of administration of each of the NSAID

	Diclofenac (n=15)		Sulindac (n=15)		Ibuprofen (n=15)	
	Pre	Post	Pre	Post	Pre	Post
SBP (mmHg)	140±5	138±6	142±4	141±6	1381±4	140±5
DBP (mmH)	87±3)	88±2)	80±2	82±2	83±2	84±2
MAP (mmHg)	109±7	108±9	109±9	106±9	108±8	109±9
Na/Cr (mmol/g)	104±24	132±39	112±34	121±32	122±34	100±30
Acute renal failure	0	0	0	1	0	4

P<0.05

Table 1 lists baseline blood pressure at the end of the two week period of paracetamol treatment and after one month of treatment with each of the NSAIDs. Pre-NSAID BP was no different from the BP after NSAID administration among any of the three NSAIDs studied. Table 1 also lists sodium/creatinine ratio obtained from 24 hour urinary collections.

DISCUSSION

NSAID blockage of prostaglandins has been shown to interfere with the anti-hypertensive actions of ACE inhibitors and thiazide diuretics administered individually(8). In the fifteen subjects taking lisinopril and hydrochlorothiazide, three different NSAIDs did not interfere with BP control. Urinary sodium excretion measured as Na:Cr ratio was increased after use of both sulindac and diclofenac; it was decreased with the use of ibuprofen. This difference may be related to the less prominent effect of diclofenac and sulindac on the kidney. The difference, however, was not statistically significant. In addition to blocking the conversion of angiotensin I to angiotensin II, the ACE inhibitors lower BP by other avenues(9,10) including effects on bradykinin, prostaglandins, and the sympathetic nervous system. It has been shown that ACE inhibitors are less effective in African-Americans than in whites(11,12). This may be related to low levels of renin found in the black hypertensive population. ACE inhibitors decrease BP in blacks but their BP lowering action is thought to be related to factors other than ACE inhibition, such as increased levels of bradykinin(13,14). This assertion is supported by the higher incidence of ACE inhibitor-related cough symptoms in black subjects(14). Because the vasodilatory effect of bradykinin is prostaglandin dependent(15), the BP lowering action of ACE inhibitors in these subjects appears to be prostaglandin dependent and, therefore, subject to interference by NSAIDs(6).

Thiazides in low or very low doses potentiate the antihypertensive actions of enalapril in patients with low renin hypertension(16). This synergistic effect of thiazides is attributable in part to salt depletion and renin stimulation. Accordingly, the combination of ACE inhibitors and diuretics works as well in blacks as in whites(11,12). In this instance, the antihypertensive action of ACE inhibitors is primarily due to blockage of the conversion of angiotensin I to angiotensin II. Hence, NSAIDs would not be expected to have as much effect on BP control in a subject on both an ACE inhibitor and a diuretic as NSAID would have in subjects using an ACE inhibitor alone. Other possible explanations for the lack of effect of NSAIDs on BP may be related to the following: (i) the choice of NSAID. Although the adverse effect of indomethacin on BP has been well documented, evidence for other NSAIDs is not as solid(5). Both diclofenac and sulindac are relatively renal sparing and in the case of sulindac, lack of an increase in BP has been documented. However, several investigators(3,4) have documented an increase in BP with ibuprofen; (ii) the choice of ACE inhibitor. The action of captopril seems to be prostaglandin dependent, whereas there are not much data on other ACE inhibitors. However, there is no reason to believe that lisinopril acts differently and; (iii) the order of administration of NSAID and ACE inhibitors/thiazide diuretics may be important. In a study by Quilley *et al*(7), pre-treatment with indomethacin attenuated the anti-hypertensive effect of captopril, but the addition of indomethacin for a few days after captopril administration had no effect on BP control. It is possible that one or several of these factors may play a role.

In conclusion, administration of ibuprofen, sulindac,

or diclofenac does not increase BP in patients who have stable BP on lisinopril and hydrochlorothiazide. However, this study examined fifteen black women and our data may not be applicable to other populations, such as whites or black men. In this study because ibuprofen was likely to cause acute renal failure, we recommend either sulindac or diclofenac for use in this group of subjects. However, in order to extend these observations to other groups, it would also be important to conduct similar studies in male hypertensives and in patients of different ethnic origin.

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