# The Effect of Nonsteroidal Anti-Inflammatory Drugs on Blood Pressure in Patients Treated With Different Antihypertensive Drugs

Trefor Morgan, MD; Adrianne Anderson, MB, BS

*Hypertension and arthritis are both common diseases in the older age group and require pharmacologic treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs) alter renal function if given in high enough doses, reducing renal blood flow and the glomerular filtration rate and causing sodium retention. In salt sensitive subjects, this retention of sodium will cause blood pressure to rise. Salt sensitivity is more common in elderly patients, in diabetics, and in people with renal failure. When most antihypertensive drugs are used, people become salt sensitive, as shown by the additive effect of salt restriction or diuretics on blood pressure response. The responses to dihydropyridine and possibly other calcium channel blocking drugs are not affected to any major extent by sodium intake or by diuretics. Studies are described which indicate that indomethacin elevates blood pressure in elderly people treated with enalapril, but not in people whose blood pressure is controlled with amlodipine or felodipine. It is unclear whether the various NSAIDs have different effects on blood pressure. It is proposed that if the same analgesic effect is achieved with the same amount of cyclooxygenase inhibition, the response will be similar. Aspirin, used in a prophylactic dose, does not inhibit to this extent and does not elevate blood pressure. If elderly people require NSAIDs, it would appear that dihydropyridine calcium channel blocking drugs are more effective at lowering and maintaining blood pressure control and should be one of the drugs used. If patients are on other antihypertensive agents, it is important to monitor blood pressure when a NSAID is added to therapy. (J Clin Hypertens. 2003;5:53–57).* ©2003 *Le Jacq Communications, Inc.*

*From the Department of Physiology, University of Melbourne, and Hypertension Clinic, ARMC, Heidelberg, Australia*
*Address for correspondence:*
*Trefor Morgan, MD, Department of Physiology, University of Melbourne, Parkville, Vic. 3010, Australia*
*E-mail: t.morgan@physiology.unimelb.edu.au*
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In the older age group, people frequently have multiple problems. A large number of people on drug treatment for hypertension have arthritis that requires medication for pain relief. Most of the agents used for pain relief inhibit cyclooxygenase (COX).[1] This provides the mechanism for pain relief probably by COX-2 inhibition,[1] but also has effects on renal function, leading, in some people, to reductions in renal blood flow, the glomerular filtration rate, and sodium and potassium excretion.[2–4] The associated fluid retention that can occur may cause elevation of blood pressure and hyperkalemia.[5,6] These effects do not cause clinical problems in most people, but certain people on various drugs and with renal impairment may be particularly prone to complications.

The effects of nonsteroidal anti-inflammatory drugs (NSAIDs) have been investigated in people with and without elevated blood pressure, and the effects were reviewed in a meta-analysis in 1994.[7] Three important questions need to be addressed. First, do all NSAIDs have a similar effect on blood pressure? Second, is the response of blood pressure to an NSAID similar when patients are on different antihypertensive

medications? Third, do all patients respond in a similar manner, and if not, what determines who will have an elevation in blood pressure? This brief review will attempt to answer these questions by reporting the results of our own studies and reviewing them in the context of the reported literature.

## METHODS

Two studies have been undertaken.[8,9] The first study[8] was in patients age >55 years (mean, 67.2). The patients had been treated with either enalapril (20 mg) or felodipine (5 or 10 mg) as monotherapy, and blood pressure had been controlled for at least 3 months. Blood pressure was measured at the clinic 24–26 hours after a dose of antihypertensive medication. The study was single (patient)-blind. The patients were given indomethacin 50 mg b.i.d. and seen 2 and 4 weeks later. They were then given placebo and seen 2 weeks later.

The second study[9] involved patients who had their blood pressure controlled on either amlodipine (5 or 10 mg/day) or enalapril (20 or 40 mg/day) as monotherapy. Patients stayed on the same dose of their antihypertensive medication throughout the study. After a 2-week indomethacin placebo run-in period, patients who had a clinic blood pressure of <160/90 mm Hg and whose supine diastolic blood pressure did not differ by more than 5 mm Hg were randomized to the study. This was a double-blind, crossover study comparing indomethacin 50 mg b.i.d. and placebo. Each period was 3 weeks and the patients were seen at week 2 and week 3. At week 3, blood pressure was measured with an ambulatory blood pressure monitor (A&D TIM2421, A&D Company, Ltd., Tokyo, Japan) for 26–27 hours at 15-minute intervals. The change in blood pressure between the placebo and indomethacin period on enalapril was compared with the change on amlodipine.

In the above studies, the statistical comparisons used were one- and two-way analysis of variance and paired *t* tests where appropriate. The studies were approved by the Ethics Committee of the Austin and Repatriation Medical Centre.

## RESULTS

### Study 1

Twenty-seven patients, 12 on felodipine and 15 on enalapril, completed the study.[8] In the patients on felodipine, there were no significant alterations in blood pressure throughout the study (Figure 1). In patients on enalapril, the blood pressure rose significantly within 2 weeks of starting indomethacin and stayed at a similar level for the next 2 weeks. The blood pressure returned to its baseline level within 2 weeks (Figure 1). In both groups, there were significant weight gains with indomethacin, but these did not differ (Table I). Plasma renin fell with indomethacin in both groups (Table I). Plasma $K^+$ rose in the patients on enalapril and felodipine, and the rise in $K^+$ was greater in patients on enalapril. There were small changes in plasma creatinine.[8]

### Study 2

Twenty-four of 33 patients on enalapril and 26 of 32 patients on amlodipine completed the study[9]

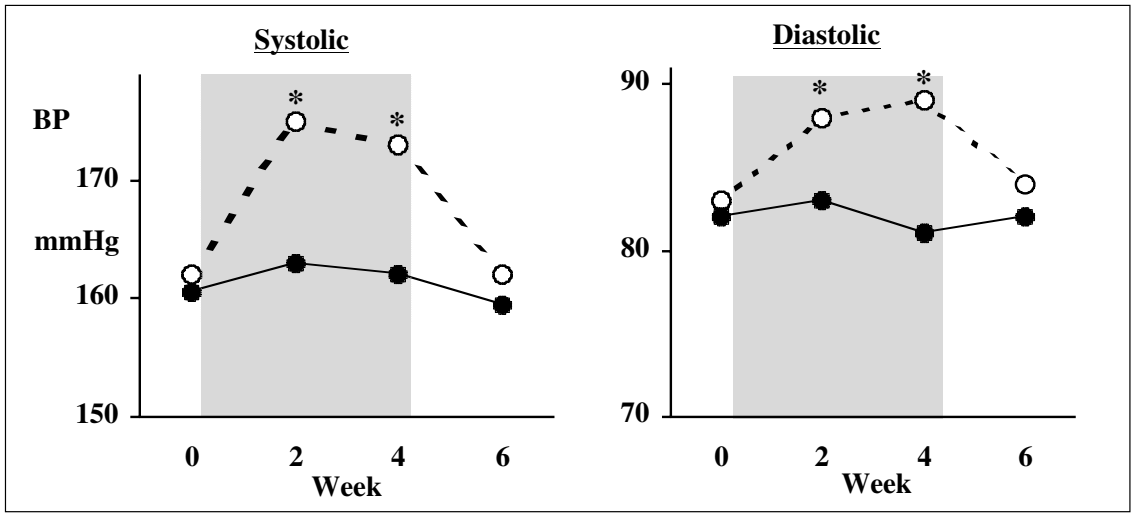


*Figure 1. Effect of indomethacin on systolic and diastolic blood pressure (BP) in patients on felodipine (filled circles) or enalapril (open circles) monotherapy. Indomethacin was taken between week 0 and week 4 (stippled area).* *p<*0.01 compared to week 0 and week 6 and* p<*0.05 compared with blood pressure on felodipine*

**Table I.** Effect of Indomethacine on Weight, Plasma $K^+$, and Plasma Renin Activity in Patients on Enalapril or Felodipine

| | ENALAPRIL | FELODIPINE | *P* VALUE FELODIPINE VS. ENALAPRIL |
|---|---|---|---|
| Change in weight (kg) | 0.8±0.3* | 0.4±0.2 | 0.15 |
| Change in creatinine (mmol/L) | 0.03±0.01* | 0.02±0.01 | 0.6 |
| Change in $K^+$ (mmol/L) | 0.24±0.04* | 0.12±0.04* | 0.04 |
| Change in plasma renin activity (pmol angiotensin I/mL/h) | –3.7†±1.1* | –0.36†±0.11* | <0.05 |
| Percent fall in plasma renin activity | 33 | 22 | 0.3 |

Values are means±SEM. *$p<0.05$; †initial values were E=11.1 and F=1.64 pmol angiotensin I/mL/h

and had clinic blood pressure measurements. Satisfactory ambulatory blood pressure measurement on both occasions was obtained in 18 patients on enalapril and in 23 on amlodipine. The patients had a mean age of 72 years (enalapril) and 69 (amlodipine), with a range of 44–88 years. The male:female ratio was 4:1. The data are presented from the patients who had satisfactory ambulatory blood pressure measurement.[9]

In the patients on enalapril, the 24-hour mean blood pressure rose by 11.7±2.9/5.1±1.6 mm Hg ($p$=0.002) (Figure 2) and the pulse rate fell by 6.0±1.0 beats/min. In patients on amlodipine, there were no significant changes in blood pressure (1.1±1.9/0.4±1.2 mm Hg) (Figure 2). The rise in blood pressure with indomethacin in people on enalapril was greater than that in the people on amlodipine ($p$=0.017). Similar results were obtained for both daytime and nighttime blood pressure. In 15 of the 18 patients on enalapril, the blood pressure on indomethacin was higher, while in the 23 patients on amlodipine, 12 values were higher and 11 values were lower.

In both groups of patients, there were similar weight gains and significant falls in plasma renin activity (Table II). Plasma $K^+$ and creatinine were not significantly altered.

## DISCUSSION

The studies reported have demonstrated that indomethacin raises blood pressure in elderly patients whose blood pressure had been controlled on an angiotensin-converting enzyme (ACE) inhibitor, but has little or no effect on blood pressure in patients controlled on a dihydropyridine calcium blocking drug (amlodipine or felodipine).

There are no good comparative studies of the effect of NSAIDs on blood pressure when people are treated with diuretics or β blocking drugs. In the meta-analysis undertaken by Johnson et al.,[7] it appeared that NSAIDs, as a group, elevated systolic blood pressure by 5.0 mm Hg and that the effect was greater in people on β blocking drugs than in those on diuretics or vasodilators. In the studies reported,[7] there were apparently no people on ACE inhibitors or calcium blocking drugs, which are now the most commonly used agents.

An important question is whether there are differences between the various NSAIDs. It has been claimed that some nonsteroidal drugs may have a lesser effect on blood pressure than other agents, and that some (sulindac) may even lower blood pressure.[7,10–14] This conclusion is based on relatively weak evidence, and sulindac does not reduce blood pressure, as has been claimed.[7,10] When the different drugs have been compared with each other and with placebo, the doses have frequently been in the lower range of the recommended dose[11,12] and the patients studied have been relatively young, with few studies in people older than 60 years. Also, it is uncertain, when drugs are compared, if the same magnitude of pain relief was achieved. The drug that we used in our studies (indomethacin) has been shown to increase blood pressure in most studies,[15–17] and we used it in rela-

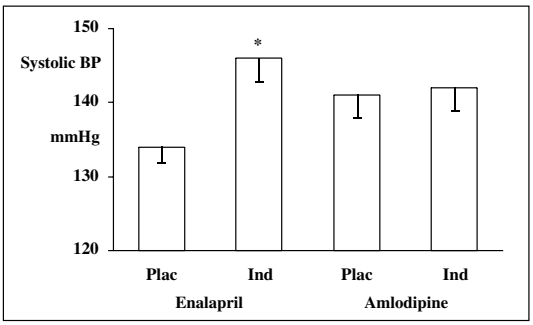


*Figure 2. Systolic blood pressure (BP) in patients on enalapril or amlodipine when given indomethacin (Ind)* *p<*0.01 with placebo (Plac)*

**Table II.** Effect of Indomethacin on Weight, Plasma $K^+$, Creatinine, Plasma Renin Activity, and Aldosterone in Patients Taking Enalapril or Amlodipine

| | Enalapril | Amlodipine | *P* Value Enalapril vs. Amlodipine |
|---|---|---|---|
| Wt (kg) | 0.9±0.4* | 0.9±0.3* | 0.9 |
| $K^+$ (mmol/L) | 0.09±0.08 | 0.19±0.05* | 0.4 |
| Creatinine (mmol/L) | 0.00±0.01 | 0.00±0.01 | 0.9 |
| Change in plasma renin activity (pmol angiotensin I/mL/h) | –3.7±1.1* | –0.29±0.09* | <0.05 |
| Percent fall in plasma renin activity | –56% | –15% | <0.05 |
| Aldosterone (pmol/L) | 70±26* | 2±35 | 0.1 |

Values are means±SEM. *$p<0.05$

tively high doses (50 mg b.i.d.). This dose usually gives effective pain relief but is associated with considerable side effects. Houston et al.[18] undertook a study in which people controlled on verapamil were given ibuprofen, naproxen, or placebo in a parallel-design study. There was no significant rise in blood pressure and they concluded that verapamil may have advantages in people receiving NSAIDs. This conclusion is probably correct, but there was no evidence presented that the dose of ibuprofen or naproxen used increased blood pressure in either untreated or treated (with other drugs) hypertensive patients.

The COX-2 inhibitors appear to raise blood pressure in treated hypertensive patients, a conclusion based on clinical observation and adverse drug reports. There is a suggestion that roficoxil and celecoxil may have different effects. The apparent different effects of NSAIDs on blood pressure may not represent a fundamental difference but perhaps reflects the magnitude of COX inhibition. When medications were developed after the introduction of indomethacin, the aim was to have drugs that had less effect on the gastric mucosa and would cause less blood loss. It is likely that to achieve this, lower doses were used, which had an anti-inflammatory effect that may not have been as complete as with indomethacin. With the development of the COX-2 inhibitors,[19–21] there was little concern related to gastric bleeding and thus more effective inhibition of COX was achieved with greater analgesic effect, but also a greater effect on renal function. This may result in sodium retention and an increase in blood pressure. While we postulate that most NSAIDs, given in sufficient dose, would cause blood pressure elevation in sensitive subjects, this does not apply to the dose of aspirin used prophylactically.[22]

The mechanism by which blood pressure rises with NSAIDs is not certain. We believe that it is due to sodium retention due to changes in renal blood flow and the glomerular filtration rate. When sodium is retained or when people have a high salt intake, not all people have a rise in blood pressure.[23] Some individuals are salt sensitive and others are relatively salt insensitive. In salt insensitive people, blood pressure may not be expected to rise with NSAIDs, and this may explain the failure of the meta-analysis by Johnson et al.[7] to show clinical effects in many of the studies, particularly in young volunteers, many of whom are salt insensitive. In a group of elderly, normotensive people, Mulkerrin et al.[24] showed that ibuprofen elevated blood pressure, while it had no effect in a young group.

Lowering of blood pressure by most antihypertensive agents is usually accompanied by sodium retention, which prevents some of the blood pressure-lowering effect. Thus, sodium restriction or diuretics have an additive effect when given to people on β blockers, ACE inhibitors, and vasodilators.[25,26] In contrast, in persons whose blood pressure is controlled with dihydropyridine calcium blocking drugs, sodium restriction and/or diuretics have little further effect on blood pressure.[25,26] The addition of a diuretic in patients unresponsive to a nondihydropyridine does, however, augment the blood pressure response.[27]

We postulate that all of the NSAIDs, if given in doses that have equivalent antianalgesic effect, would alter renal function and cause sodium retention. The blood pressure response will depend on whether or not patients are salt sensitive. If they are salt sensitive, the blood pressure will rise.

In most people, blood pressure will not be adequately controlled on monotherapy,[9] and fewer than 30% of unselected elderly hypertensive patients achieve a systolic blood pressure <140 mm Hg on sequential monotherapy. Thus, dual therapy will be

required in most patients. If NSAIDs primarily cause a rise in blood pressure due to sodium retention, it would seem appropriate that calcium channel blocking drugs and/or diuretics should be a critical part of such combination.

Patients at particular risk of a rise in blood pressure with NSAID therapy are the elderly, individuals with impaired renal function, and diabetics, even when not on other treatment. If such persons are on treatment with drugs whose effectiveness is improved by diuretics or salt restriction, the risk is increased. Those drugs include ACE inhibitors, angiotensin I receptor blocking drugs, β blockers, α blockers, vasodilators, and, paradoxically, diuretics (the response to a diuretic depends on sodium intake).[28] Thus, if blood pressure needs to be controlled in such patients and they also require analgesic relief, dihydropyridine calcium blocking drugs will provide more consistent blood pressure control.

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