Antagonism of Antihypertensive Drug Therapy by Nonsteroidal Anti-Inflammatory Drugs

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SUMMARY Certain nonsteroidal anti-inflammatory drugs antagonize the action of antihypertensive therapy. Indomethacin has been shown to abrogate the antihypertensive effect of β-adrenergic receptor blockers, diuretics, converting enzyme inhibitors, and several antihypertensive drug combinations, and the accumulated evidence on piroxicam indicates that it also raises arterial pressure in treated patients. In contrast, sulindac and aspirin do not reverse the effects of antihypertensive drugs, and currently available data indicate that they are the safest cylooxygenase inhibitors for use in hypertensive patients. In the absence of definitive information on the array of other nonsteroidal anti-inflammatory drugs, they should be considered to pose a risk similar to indomethacin until proved otherwise. The magnitude of the elevation in blood pressure varies between patients, ranging from no effect to dangerous hypertensive responses. Generalized inhibition of the cyclooxygenase enzyme has opposing effects on arterial pressure, lowering renin on one hand and causing sodium retention on the other. Some evidence suggests that cyclooxygenase inhibition causes the greater increments in pressure in patients who initially have low plasma renin activity (often the elderly). The potential for cerebral vascular catastrophes attends these drug interactions in which platelet function also is suppressed by cyclooxygenase inhibition. (Hypertension 11 [Suppl II]: II-4-II-6, 1988)

KEY WORDS • antihypertensive drugs • drug interactions • nonsteroidal anti-inflammatory drugs

THE potential for concurrent administration of drugs that are used in treating arthritis together with antihypertensive agents is considerable. Approximately 30% of the patients with arthritis have hypertension. The potential for catastrophic interaction is illustrated by the consequences of concurrent administration of these drugs in a patient.

A 77-year-old retired minister had a long history of hypertension that had been characterized as low renin essential hypertension based on a plasma renin activity of 1.05 ng/ml/hr measured after administration of furosemide 80 mg and 3 hours of upright posture. His blood pressure had been frequently documented to be under reasonable control with a combination of propranolol 160 mg daily and furosemide 80 mg daily.

His second problem was osteoarthritis involving the hip as well as other joints. This was treated with sulindac 200 mg daily and resulted in fair control except for sporadic flare-ups. Upon reading in the newspaper about a new arthritis drug, piroxicam, he persuaded his local physician to start him on this drug at a dosage of 20 mg daily. Three weeks later, a headache developed that became progressively worse. Fortunately, his wife had been trained to take his blood pressure, which she found to be 230/130 mm Hg. He was immediately hospitalized, during which the severe level of hypertension was confirmed. After the discontinuation of piroxicam, the blood pressure gradually returned to the levels previously observed.

This remarkable hypertensive response to piroxicam pushed the patient to the brink of disaster. It illustrates that some nonsteroidal anti-inflammatory drugs vitiate the action of antihypertensive drugs and that in some patients the hypertensive response may be severe.

Indomethacin is the nonsteroidal drug most extensively evaluated for its potential to antagonize antihypertensive therapy. Indomethacin has been shown to antagonize the antihypertensive effects of β-adrenergic receptor blockers, 1-4 diuretics, 2, 5-7 and converting enzyme inhibitors. 8-11 Indomethacin also elevates arterial pressure in patients receiving diuretics in combination with a number of other antihypertensive agents. 12-14

In contrast to indomethacin, sulindac 400 mg daily does not interfere with the antihypertensive effect of β-adrenergic receptor blockers when given either alone or in conjunction with a diuretic; this dosage of sulindac also did not elevate arterial pressure in a group of patients receiving a variety of antihypertensive drugs.
given in combinations. The lack of a hypertensive response to sulindac in patients on antihypertensive therapy is convincing because in each of these studies there were positive controls in which other nonsteroidal anti-inflammatory drugs caused an elevation in pressure in the same patients. Similar to sulindac, aspirin in dosages of 1.95 g daily and 3.9 g daily did not raise arterial pressure in patients receiving maintenance therapy with combinations of antihypertensive drugs. Although aspirin 5 g daily or in single doses of 1.0–1.5 g antagonized the hypertensive effects of an acute dose of intravenously administered propranolol, the well-known differences between the hemodynamic effects of acute and chronically administered β-adrenergic receptor blockers are such that this observation cannot be extrapolated to any conclusion regarding maintenance therapy.

Information on the vast array of other nonsteroidal anti-inflammatory drugs is only beginning to emerge. The combined evidence on piroxicam indicates that it, like indomethacin, raises arterial pressure in treated hypertensive patients. More information is needed on naproxen, but that currently available suggests that its effect on blood pressure is more like indomethacin than aspirin. It would be prudent to assume that the other nonsteroidal anti-inflammatory drugs will antagonize antihypertensive therapy until appropriate studies prove otherwise. Currently, only sulindac and aspirin may be considered to not abrogate the effects of chronic antihypertensive treatment.

Thus, even though aspirin and sulindac inhibit the cyclooxygenase enzyme in some tissues when administered in vivo, their effects on blood pressure in treated hypertensive patients are completely different from those of the cyclooxygenase inhibitor indomethacin. The reasons for these qualitative differences are not known with certainty, but several possibilities deserve consideration. The disparate effects on blood pressure could reflect differences in the tissue-specific biotransformation of the cyclooxygenase inhibitors. For example, sulindac sulfide, the active metabolite of sulindac, is oxidized back to the inactive prodrug by the kidney, an inactivation mechanism that could protect portions of the nephron from cyclooxygenase inhibition by sulindac sulfide. Metabolism also is important in the pharmacology of aspirin, which is an irreversible inhibitor of the cyclooxygenase enzyme, whereas its metabolite, salicylic acid, is a weak competitive inhibitor. A further possibility is that tissue-selective distribution of drugs could occur. Finally, it is possible that indomethacin and piroxicam antagonize antihypertensive drugs by an action other than cyclooxygenase inhibition.

The mechanism whereby certain nonsteroidal anti-inflammatory drugs antagonize antihypertensive drug action is not known. That such an elevation in blood pressure occurs despite the reduction in renin release known to result from indomethacin emphasizes the complexity of the pathophysiology that results in this effect. Possible explanations include, but are not limited to, retention of sodium, removal of tonic vasodilation produced by prostaglandin, and alteration of adrenergic neurotransmission.

The magnitude of hypertension evoked by indomethacin varies considerably between patients receiving the same antihypertensive drug. For example, the elevation in supine systolic pressure produced by indomethacin in patients receiving thiazide diuretics ranges from no increase to an increase of 44 mm Hg. It is likely that in clinical practice greater elevations in blood pressure would be seen than in carefully monitored trials in which ethical considerations would limit the magnitude to which blood pressure could rise before intervention; the patient presented at the beginning of the report illustrates the potential for an elevation in arterial pressure that is of major clinical importance.

The factors determining which patients are most susceptible to the hypertensive effects of indomethacin and related drugs have not been elucidated, but the possible role of the baseline renin state deserves consideration and further investigation. Indeed, in a highly renin-dependent model of hypertension in the rat, indomethacin actually lowers blood pressure. Furthermore, in rare instances in which hypertension in humans is unusually dependent upon renin secretion, indomethacin has produced a significant reduction in blood pressure. In contrast to the effects in these exceptionally renin-dependent hypertensive patients, inhibition of prostaglandin synthesis with indomethacin or ibuprofen elevated arterial pressure in normal humans with a low renin state that was produced by the administration of fludrocortisone. These opposite effects of indomethacin are observed at the polar extremes of the renin spectrum, and more data are required to ascertain whether patients with low renin essential hypertension might be at greater risk from indomethacin and other cyclooxygenase inhibitors that raise blood pressure in treated patients.

The potential for cerebrovascular catastrophe attends these drug interactions in which platelet function also is suppressed by cyclooxygenase inhibition. With the possibility of multiple physicians participating in the care of patients who have hypertension and arthritis and because of the over-the-counter availability of nonsteroidal anti-inflammatory drugs, the education of patients regarding these interactions will minimize their risk.

Considerable further research is required to characterize the pharmacological agents that evoke this interaction, to elucidate its mechanism, and to provide a basis upon which the individuals most susceptible to the hypertensive effects of the nonsteroidal anti-inflammatory drugs can be identified. It is probable that new fundamental insights regarding cardiovascular control should emerge from an understanding of the mechanism of this drug interaction.

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