REBOUND RISE IN RENIN CONCENTRATIONS AFTER CESSION OF SALICYLATES

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Salicylates are widely used in the treatment of rheumatic disorders, and they have been shown to induce minor changes in renal function. One of the major mechanisms of action of salicylates is the suppression of prostaglandin synthetase activity, and in animal models renal prostaglandin production is closely related to renin release and the regulation of renal blood flow. Indomethacin has been shown to decrease the glomerular filtration rate and to lower plasma renin activity in human beings, and to reduce the antihypertensive effectiveness of certain beta-adrenoreceptor-blocking agents. We therefore studied the effects of aspirin, another commonly prescribed non-steroidal anti-inflammatory agent, on plasma renin concentration, both during administration and after withdrawal.

METHODS

Two studies of the effect of salicylate on plasma renin concentration were performed. The first was carried out in conjunction with a study of the effect of five weeks of salicylate ingestion on renal function in nine normal volunteers. Subjects were given 3.9 g of salicylate per day as a sustained-release preparation (Bonis SRA) in two divided doses. The subjects were kept on a constant diet containing no added salt throughout both studies. Twenty-four-hour urinary collections were made before salicylate administration at weekly intervals for the five weeks of treatment, and, in six volunteers, two weeks after the treatment ceased. Blood was collected at the same time of day during each 24-hour urine collection; estimations of serum and urine electrolytes and creatinine concentrations were performed on a Technicon AutoAnalyzer. Blood was also collected for estimation of plasma renin concentration on Day 0, one and four weeks after salicylate administration began, and two and five weeks after it ceased. All blood samples were taken with the volunteers in the supine position for at least five minutes. Blood for the plasma renin estimation was collected in heparin and centrifuged immediately; plasma was stored at -20°C until assay. In the initial study (Study 1), plasma renin assays were carried out as the study progressed. In the second study (Study 2), six of the original volunteers were given the same dose of salicylate for a two-week period, and blood was taken for estimation of plasma renin concentration before the commencement of the study, at three-day intervals during salicylate treatment, and three, seven, 14, and 21 days after the treatment ended. On this occasion the frozen plasma samples from any one subject were assayed together at the end of the study, to avoid the possibility of any influence from interassay variability. Plasma renin concentration was estimated in both studies by the method described by Boyd. Renal function and changes in plasma renin concentration, urea, and electrolytes were analyzed statistically by Student's t-test for paired variables.
RESULTS

The changes in plasma renin concentration during Study 1 are shown in Figure 1. There was a significant decrease (P<0.01) from a mean of 2.94 ng per milliliter per hour to a mean of 1.41 ng per milliliter per hour when salicylate treatment was started. Plasma renin concentrations remained low during treatment but rose again after treatment, to a mean of 7.75 ng per milliliter per hour - significantly higher than pre-treatment levels (P<0.005). Plasma renin concentrations returned to pre-treatment levels by 10 weeks.

Plasma renin concentrations in Study 2 are shown in Figure 2; renin levels again fell significantly (P<0.05) and rose significantly above pre-treatment levels (P<0.001) when treatment ceased. During the second study, supine blood pressure was measured, and the patient was weighed whenever blood was withdrawn for renin estimation. No significant changes in blood pressure or weight occurred either during treatment or afterward.
In Study 1 serum potassium increased slightly but significantly during salicylate treatment, from a mean of 3.7 mmol per liter to a mean of 4.2 mmol per liter (P<0.0005). There was no change in serum sodium or urinary electrolytes during the study. Serum creatinine rose significantly during the initial phase of the study (P<0.001) but then fell while the volunteers were still taking salicylates. This pattern was reflected by a similar initial reduction in creatinine clearance and a return to pretreatment levels while salicylate treatment was continued.\textsuperscript{10}

DISCUSSION

Rebound vascular phenomena, such as angina\textsuperscript{12} and hypertension, \textsuperscript{13} have been described after the withdrawal of propranolol and clonidine. We describe here a rebound in plasma renin concentration after it was suppressed for some weeks by salicylate administration. Plasma renin concentration fell significantly when aspirin treatment began and remained low for the duration of the treatment. When salicylate administration ceased, plasma renin concentrations rose significantly above pretreatment levels before returning to normal.

Renin is found predominantly in the kidney and is secreted by the juxtaglomerular cells in response to a number of factors.\textsuperscript{14} The transient decrease in creatinine clearance noted during administration of salicylate may reflect changes in
renal blood flow that resulted in a reduction in renin release secondary to relative arteriolar constriction. The striking observation of a rebound rise in plasma renin after withdrawal of salicylate cannot be explained by the changes in serum potassium, which rose slightly during salicylate administration and then returned to the control level. The rebound effect was most probably associated with the removal of suppression of prostaglandin production. During the suppressed period, receptor sensitivity to prostaglandin action at the afferent arteriole may become enhanced in a manner analogous to denervation hypersensitivity; if after any such increase, receptor sensitivity was slow to revert to normal after cessation of treatment and the return of prostaglandin secretion, an increased prostaglandin effect might ensue. This, in turn, might lead to an unusual dilatation of the afferent arteriole, with a resulting increase in renin secretion above control values.

Whatever the mechanism of the rebound rise, this phenomenon may be clinically important; if a rebound renin release is common after suppression by prostaglandin inhibitors, it may be important in patients who take the drug intermittently. We did not observe any increase in blood pressure during the phase of increased renin concentration after salicylate withdrawal, but it is possible that increased renin release resulted in a redistribution of the blood flow in various organs.

REFERENCES