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Hemodynamic Changes during Acute Salicylate Intoxication in Conscious Dogs (40091)

BIN C. WANG, NANCY J. MUETING, AND KENNETH L. GOETZ

Division of Experimental Medicine, St. Luke's Hospital and St. Luke's Foundation, Kansas City, Missouri 64111

Although salicylate intoxication continues to be a common clinical problem, especially in pediatrics, relatively few studies have been carried out on the cardiovascular effects of salicylates. A report of Tenney and Miller (1) is perhaps the most cited reference that deals with the circulatory effects of salicylates, yet that work was performed before beta adrenergic blocking agents were available. Tenney and Miller (1) concluded that salicylates have a direct stimulating action on cardiac muscle which probably is independent of autonomic nervous activity. For the most part the cardiovascular effects of salicylates have been studied in the anesthetized dog (1, 2); there is growing evidence, however, that the conscious dog responds to certain physiological and pharmacological stimuli in a manner quite different from that of the anesthetized dog (3). For the above reasons, we have examined in detail the cardiovascular and acid-base responses that are elicited by the intravenous infusion of large doses of sodium salicylate into the conscious dog.

Methods. Experiments were performed on conscious mongrel dogs weighing an average of 13 kg. Each dog was prepared for the experiments during a preliminary operation under anesthesia with sodium pentobarbital (25 mg/kg body weight with supplements as required). The chest was entered aseptically on the left side, and a flow probe was placed around the ascending aorta. Vinyl catheters were placed in the descending aorta, pulmonary artery, and superior vena cava by the technique of Herd and Barger (4). In addition, a catheter was inserted into the left atrium through a small tributary of a pulmonary vein. The proximal ends of the catheters and flow probe cable emerged from the skin adjacent to the spinal column and were embedded in a styrofoam block. The wound was closed with sutures and sealed with a spray dressing. During the operation each animal received 500 ml of 5% dextrose in water iv; this solution also contained one million units of aqueous penicillin G. Postoperatively, the animals received 300,000 U of procaine penicillin G im daily for 5 days. All catheters were flushed with saline three times each week and filled with a solution of sodium heparin in saline (1000 U/ml). A nylon jacket protected the catheters and flow probe.

Each dog was allowed to recover from the operation for at least 1 week and was trained to rest quietly in an animal stand. During each experiment pressures in the aorta, pulmonary artery, left atrium, and superior vena cava were monitored continuously using Statham P23Db transducers. Cardiac output was measured with an electromagnetic flowmeter and a circuit that automatically zeroed the baseline of aortic flow on a beat-to-beat basis (5). All pressures and flow signals were recorded on an oscillographic recorder. Data were analyzed by an automatic data averager that accurately computed the time-integrated mean value of up to seven inputs and printed a copy of the results (6). Total peripheral vascular resistance and pulmonary vascular resistance were calculated by standard methods (7).

Sodium salicylate was dissolved in distilled water to produce an isotonic solution (24 mg/ml) which was infused intravenously at a rate of 20 mg/kg/min. Three different doses of sodium salicylate were infused into each dog according to the following sequence: day 1, 100 mg/kg; day 2, recovery period; day 3, 200 mg/kg; day 4 and day 5, recovery period; day 6, 200 mg/kg after pretreatment with propranolol (2 mg/kg); day 7 and day 8, recovery period; day 9, 300 mg/kg. In addition, isotonic saline in a volume comparable to each of the three salicylate doses was given to some animals at the same rate to examine the effect of the volume load itself on the cardiovascular system. The recovery periods were adequate to allow dissipation of the

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effects of the previous dose of salicylate as evidenced by a normal acid-base status and undetectable levels of plasma salicylate in all control periods.

Rectal temperature of the animal was continuously monitored with a thermistor probe. Arterial blood samples were drawn anaerobically. Plasma pH, PO_2, and PCO_2 were measured with appropriate electrodes maintained at 37°. Appropriate coefficients were used for temperature correction for pH (8), PO_2, and PCO_2 (9). Plasma bicarbonate values were calculated from pH and PCO_2 using the Henderson–Hasselbalch equation. Plasma salicylate concentration was determined according to the method of Trinder (10).

The data in the table and figures are expressed as the mean ± SE. The paired t test was used to determine whether the changes induced by salicylate infusion were significantly different from control values. The analysis of variance (F test) and a sequential variant of the Q method (11), originally designed by Newman and Keuls, were used to determine whether the peak changes induced by a given dose of salicylate differed significantly from the response at other dose levels. All P values of greater than 0.05 were considered to be statistically insignificant.

Results. The mean hemodynamic responses of 11 conscious dogs to the intravenous infusion of sodium salicylate (200 mg/kg) are summarized in Fig. 1. Heart rate, cardiac output, and pulmonary arterial pressure increased following salicylate infusion while total peripheral resistance decreased. The maximum changes in these variables occurred at the end of the 10-min infusion period, but the values remained significantly different from their respective control measurements throughout the entire experiment. The increase in cardiac output was caused almost entirely by an increase in heart rate; stroke volume remained essentially unchanged with the exception of a slight increase that occurred 5 min after the infusion began. Aortic pressure increased initially and then gradually decreased to below control measurements approximately 1 hour after the onset of the infusion. Both central venous pressure and left atrial pressure gradually decreased with time. Pulmonary vascular resistance was not altered significantly by salicylate infusion. Infusion of a volume of saline equal to that of the salicylate infusion failed to produce any significant cardiovascular changes in the five dogs tested (not shown), thus indicating that the changes observed after salicylate infusion were caused by the substance itself, and not by the volume of fluid added. Figure 1 also illustrates the effect of sodium salicylate after beta adrenergic

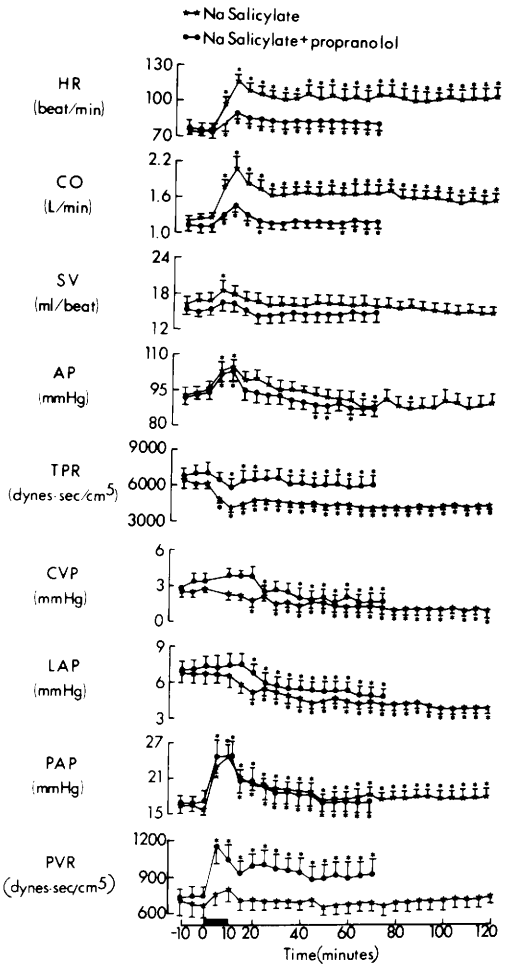

FIG. 1. Time course of the mean cardiovascular responses following the intravenous infusion of sodium salicylate (200 mg/kg) with and without pretreatment with propranolol (2 mg/kg). The 10-min infusion period is denoted by the bold horizontal line. Abbreviations used are: HR, heart rate; CO, cardiac output; SV, stroke volume; AP, aortic pressure; TPR, total peripheral resistance; CVP, central venous pressure; PAP, pulmonary arterial pressure; LAP, left atrial pressure; and PVR, pulmonary vascular resistance. An asterisk indicates values that are significantly different from control measurements ($P < 0.05$ by paired t test, $n = 11$).

blockade (propranolol, 2 mg/kg). The maximum increases in heart rate and cardiac output elicited by salicylate were attenuated by approximately 60% after pretreatment with propranolol, whereas the decrease in total peripheral resistance was attenuated by approximately 35%. Pretreatment with propranolol also altered the response of the pulmonary vasculature to the salicylate infusion as evidenced by the significant increase in pulmonary vascular resistance induced by salicylate after propranolol was given. Other cardiovascular responses elicited by salicylate were relatively unaffected by pretreatment with propranolol.

The peak hemodynamic changes elicited by three doses of sodium salicylate are shown in Fig. 2. Salicylate produced significant increases in heart rate, cardiac output, aortic pressure, and pulmonary arterial pressure, and significant decreases in total peripheral resistance, left atrial pressure, and central venous pressure. Pulmonary vascular resistance increased slightly after each of the three doses of salicylate, but the increases did not differ significantly from control values ($P > 0.05$). Although all cardiovascular changes appeared to have a dose-dependent tendency, an analysis of variance indicated that only four variables, ΔHR, ΔCO, ΔTPR, and ΔPAP showed significant dose-dependent changes ($P < 0.05$). The maximal response of these four variables to a dose of 200 mg/kg was significantly greater than the response to 100 mg/kg ($P < 0.05$). On the other hand, the responses to a dose of 300 mg/kg were slightly less than the responses to a dose of 200 mg/kg, but the differences did not reach statistical significance ($P > 0.05$).

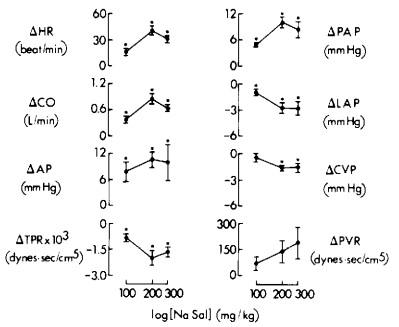

FIG. 2. Peak cardiovascular changes produced by the intravenous infusion of three doses of sodium salicylate. An asterisk indicates values that are significantly different from their respective control measurements ($P < 0.05$ by paired t test). The number of animals studied was 13, 11, and 9 for doses of 100, 200, and 300 mg/kg, respectively. Abbreviations used are the same as those in Fig. 1.

Data of plasma salicylate concentration, body temperature, and arterial plasma pH, PCO_2, $\{HCO_3^-\}$, and PO_2 are shown in Table I. The concentrations of salicylate in plasma at 15 min after infusion were 24 ± 1, 42 ± 1, and 60 ± 2 mg/100 ml of plasma for doses of 100, 200, and 300 mg/kg, respectively. Plasma salicylate concentration then decreased with time as shown in Table I. The mean control body temperature of the dog ranged from 39.3 to 39.6°; it was not significantly altered by any of the three doses of salicylate. Arterial plasma pH and PO_2 increased following salicylate administration while PCO_2 decreased and $\{HCO_3^-\}$ decreased slightly or did not change. We regularly observed an increase in the respiratory rate after salicylate was given. Pretreatment with propranolol did not alter the acid-base and PO_2 changes elicited by salicylate (not shown in Table I). The emetic threshold of our conscious dog, at a comparable infusion rate, was about equal to that reported in the conscious cat (12); vomiting occurred in all dogs during the 10-min infusion of salicylate at doses of 200 mg/kg or higher.

Discussion. In conscious dogs, sodium salicylate produced an increase in cardiac output, a decrease in total peripheral resistance, and a biphasic response in aortic pressure (an initial increase followed by a decrease to below control values). These hemodynamic changes are generally comparable to those reported in the anesthetized dogs (1). They differ, however, in that the cardiac output of our conscious dogs was increased by an increase in heart rate whereas this was accomplished by an increase in stroke volume in the anesthetized dogs (1). In conscious dogs, sodium salicylate also produced an increase in pulmonary arterial pressure and decreases in left atrial pressure and central venous pressure. The increase in pulmonary arterial pressure was largely attributable to an increase in pulmonary blood flow under normal conditions. The decreases in left atrial pressure and central venous pressure were probably due to vasodilation of the peripheral vasculature. These hemodynamic changes elicited by sa-

TABLE I. PLASMA SALICYLATE CONCENTRATION, BODY TEMPERATURE, AND ARTERIAL pH AND BLOOD GASES AFTER iv Na SALICYLATE.

	Dose (mg/kg)	*n*	Control	60 min	120 min
{Sal} pl[a] (mg%)	100	13	0	21 ± 1	19 ± 1
	200	12	0	39 ± 1	36 ± 1
	300	9	0	55 ± 3	50 ± 2
Body temp. (°C)	100	12	39.4 ± 0.2	39.5 ± 0.1	39.2 ± 0.2
	200	11	39.5 ± 0.3	39.5 ± 0.2	39.3 ± 0.2
	300	6	39.3 ± 0.3	39.3 ± 0.2	38.9 ± 0.1
pH	100	12	7.42 ± 0.01	7.45 ± 0.01*	7.45 ± 0.01
	200	10	7.42 ± 0.01	7.45 ± 0.01*	7.48 ± 0.01*
	300	6	7.40 ± 0.01	7.49 ± 0.02*	7.49 ± 0.02*
PCO_2 (mmHg)	100	12	35.2 ± 1.1	31.2 ± 0.8*	31.1 ± 0.7
	200	11	36.1 ± 1.1	32.1 ± 0.7*	29.8 ± 0.8*
	300	6	35.0 ± 0.2	28.3 ± 1.1*	28.3 ± 0.7*
$\{HCO_3^-\}$ (m*M*)	100	12	22.8 ± 0.7	21.2 ± 0.5*	20.7 ± 0.5
	200	10	22.4 ± 0.5	21.8 ± 0.4	21.2 ± 0.9
	300	6	21.9 ± 0.5	21.4 ± 0.7	21.1 ± 1.0
PO_2 (mmHg)	100	12	90.2 ± 1.7	93.6 ± 1.3*	95.0 ± 2.3
	200	11	91.9 ± 1.7	95.9 ± 1.2*	96.3 ± 1.2*
	300	6	88.1 ± 2.3	96.5 ± 1.8*	92.5 ± 3.5

[a] Plasma salicylate concentration.
* Significantly different from control ($P < 0.05$).

licylate were dose-dependent and a maximum response was obtained at a dose of 200 mg/kg.

The mechanism of the hemodynamic changes elicited by salicylate is not entirely clear. Tenney and Miller (1) proposed that the increase in cardiac output elicited by salicylate is independent of any nervous influence and is mediated through a direct stimulation of the salicylate ion on the myocardium. Their conclusion was based upon data indicating that the alpha adrenergic antagonist, phenoxybenzamine, and the ganglionic blocker, tetraethyl ammonium chloride, did not prevent the initial pressure increase elicited by salicylate. Supporting evidence was provided by others who found that intravenous infusion of salicylate caused a typical positive inotropic response after procaine had been infused epidurally to produce sympathetic block (2). In addition, low concentrations of salicylate have been reported to increase contractility of the isolated heart (13). These results along with our data indicating that propranolol did not completely abolish the salicylate-induced increases in heart rate and cardiac output support the hypothesis that salicylate does exert a positive inotropic effect directly on the myocardium. On the other hand, since beta adrenergic blockade with propranolol significantly attenuated the increases in heart rate and cardiac output caused by salicylate, our results provide some evidence that these responses may be attributed partly to the activation of beta adrenergic receptors. This view is consistent with the observation that large doses of salicylate activate central sympathetic centers (13). Our results also suggest that salicylate may activate the beta adrenergic receptors in the peripheral vasculature because pretreatment with propranolol attenuated the decrease in total peripheral resistance elicited by salicylate. Moreover, the increase in pulmonary vascular resistance induced by salicylate after pretreatment with propranolol may imply that salicylate normally activates both vasodilator (beta) and vasoconstrictor mechanisms. That is, the beta receptor blockade may have eliminated the vasodilation and thus unmasked the vasoconstriction. It should be kept in mind, however, that propranolol may exert its effect through nonspecific membrane actions or through effects on the central nervous system. Therefore the question regarding the effect of salicylate on the activation of beta adrenergic receptors is not completely settled.

Sodium salicylate did not alter the body temperature of our conscious dogs even though comparable doses of salicylate produce hyperthermia in the anesthetized dog

(14). Salicylate increases heat production by uncoupling oxidative phosphorylation in mitochondria (15) with a consequent increase in oxygen consumption (14), but it also increases heat dissipation through peripheral vasodilation. The net effect on body temperature thus depends on the balance of these two opposing changes, and it appears that this balance is altered by anesthesia.

Salicylate produces respiratory alkalosis in the conscious dogs as evidenced by an increase in arterial plasma pH, a decrease in PCO_2, and no significant change in bicarbonate concentration. Thus the respiratory response of these animals is similar to that of normal human subjects given comparable doses of salicylate (16). Since CO_2 production is increased following salicylate administration (1, 14), the observed decrease in arterial PCO_2 suggests that the salicylate infusion increased alveolar ventilation. Salicylate also produces hypocapnea in anesthetized dogs, but a mild bicarbonate deficit is superimposed on the respiratory alkalosis (14). The absence of the bicarbonate deficit in our experiments may be attributable to the vomiting which occurred consistently when doses of 200 mg/kg or higher were given.

Summary. The hemodynamic changes following intravenous infusions of sodium salicylate were measured in conscious dogs. The sodium salicylate produced dose-dependent increases in heart rate, cardiac output, and pulmonary arterial pressure, and a dose-dependent decrease in total peripheral resistance with maximum responses being obtained at the dose of 200 mg/kg. Sodium salicylate also produced decreases in left atrial pressure and central venous pressure and a biphasic response in aortic pressure. Pretreatment with propranolol significantly attenuated the increases in heart rate and cardiac output, as well as the decrease in total peripheral resistance elicited by salicylate, thus implying that the salicylate-induced cardiovascular responses are mediated partly through the activation of beta adrenergic receptors.

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