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THE EFFECT OF SALICYLATES ON THE ELECTROLYTE STRUCTURE OF THE BLOOD PLASMA.¹ II. THE ACTION OF THERAPEUTIC DOSES OF SODIUM SALICYLATE AND OF ACETYLSALICYLIC ACID IN MAN

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While hyperpnea and reduction of the CO₂ content of the blood are generally recognized findings of salicylate intoxication, little is known concerning the effect of therapeutic doses of salicylates. The prevailing impression (1) appears to be that such doses have no effect on the respiration. Investigations dealing with this question in experiments of a few hours duration showed small decreases of the CO₂ tension after single doses of salicylate (2, 3).

As part of an inquiry into the physiologic actions of salicylates, a study was undertaken on the changes in the electrolyte equilibrium of the blood of patients receiving therapeutic doses of salicylates.

METHODS

With precautions to avoid stasis, venous blood samples were drawn by means of a tightly-fitting syringe and needle and were delivered under paraffin oil. Determinations of serum pH, CO₂, chloride, and sodium were carried out by methods previously described (4).

RESULTS

In Table I are presented the data on the electrolyte equilibrium of 21 rheumatic patients, 3 to 15 years old, and weighing 15 to 65 kgm., who had received sodium salicylate or acetylsalicylic acid orally in amounts ranging from 0.07 to 0.28 gram per kgm. body weight daily. The period of medication varied from 1 to 28 days. Fourteen of the patients developed one or more of the manifestations of salicylism. These varied in severity from a simple hyperpnea, the mildest symptom, to intense vomiting with hematemesis, which was observed in 2 of the patients. A relationship between dosage and symptoms is clearly indicated:

¹ A preliminary report was presented before the American Pediatric Society, May 1, 1942 (*Am. J. Dis. Child.*, 1942, 64, 200).

only 2 of 8 patients who received salicylates in doses of 0.15 gram per kgm. or less developed the signs of salicylism that appeared in 12 of 13 patients who received higher doses, a statistically highly significant difference. The pH values in the control sample of blood, *i.e.*, samples that were taken either before the start of the treatment or several days after its discontinuance, ranged from 7.37 to 7.52, average 7.43. During the period of treatment, most patients showed small variations, mostly increases, in the pH of their blood, the highest value observed being 7.57. The CO₂ content, averaging 26.2 m.eq. per liter for the control samples, decreased in every instance and reached values of less than 20 m.eq. per liter in 14, and of less than 15 m.eq. per liter in 3 of the patients. The CO₂ tension, at a mean value of 42 mm. Hg in the control samples, also fell during each period of medication. In 13 of the patients, the tension reached values of below 30 mm. Hg and in 3, values of below 20 mm. Hg. The serum chloride averaged 102 m.eq. per liter in the control samples. It was below 100 m.eq. per liter before treatment started in 3 patients with cardiac decompensation. On 2 of these, the sodium also was determined and found to be 135 and 136 m.eq. per liter. In 18 of the patients the chloride increased, the maximum increase being 16 m.eq. per liter. The serum sodium, 140 m.eq. per liter in the control samples, during the period of medication deviated from the normal by less than 4 m.eq. per liter in 8 patients, decreased by as much as 9 m.eq. per liter in 4, and increased in 1 patient. This increase occurred in 1 of the patients with cardiac decompensation in whom a low serum sodium and chloride had been found in the preliminary blood sample.

In Figures 1 to 3 are portrayed different patterns of change in the electrolyte equilibrium of the plasma, representing diverse types of adjust-

TABLE I—Continued

Case number	Age	Weight	Period of medication*	Salicyl dosage	pH	CO ₂	pCO ₂	Chloride	Sodium	Symptoms of salicylism
				grams per kgm. per day						
12	3	15	2	S 0.27	7.52	14.6	18	114	138	Hyperpneic
			3 after	0	7.44	26.6	40	108	138	
13	9	21	before	0		26.5		97		Vomiting
			4	S 0.28	7.52	18.1	22	98		
14	12	33	before	0	7.45	27.2	40	102		None Vomiting, irritable
			2	A 0.12	7.40	23.4	38	104		
			4	A 0.12	7.41	19.7	30	109		
15	13	52	before	0	7.42	27.0	42	102		Listless, ringing in ears Listless, ringing in ears
			2	A 0.12	7.42	17.4	27	110		
			4	A 0.12	7.46	22.3	31	106		
			3 after	0	7.40	25.4	42	105		
16	14	41	6	A 0.18	7.41	19.7	31	106	135	Hyperpneic Vomiting, hematemesis
			12	A 0.18	7.49	21.0	27	102	134	
			20 after	0	7.44	25.8	38	105	140	
17	13	32	2	A 0.19	7.49	25.2	34	105	135	None Vomiting
			4	A 0.19	7.43	22.3	33	104	135	
18	6	21	before	0	7.37	24.9	42	109	140	None Vomiting, lethargic
			2	A 0.20	7.46	17.2	24	112	142	
			4	A 0.20	7.44	12.6	18	112	139	
19	13	30	5	A 0.20	7.50	20.1	25	110	134	Hyperpneic Hyperpneic
			7	A 0.20	7.48	16.4	21	110	134	
			3 after	0	7.38	26.0	44	106	143	
20	12	31	before	0	7.42	29.6	47	104	143	None Vomiting
			3	A 0.20	7.45	19.5	28	111	141	
			5	A 0.20	7.46	19.4	27	114	146	
			1 after	0	7.40	20.2	32	112		
			2 after	0	7.44	25.8	38	108	141	
			4 after	0	7.51	29.1	38	104		
21	6	24	3	A 0.21	7.38	15.3	24	112		Dyspneic, irritable
			3 after	0	7.37	26.6	47	105		

S Sodium salicylate.

A Acetylsalicylic acid.

* Samples designated "before" were taken before salicylate administration was begun. The figures followed by "after" indicate the period after medication had been stopped.

ride, not shown, changed little. In 11 of 13 patients, on whom repeat-samples of blood were obtained during periods of salicylate medication, further decreases of the CO₂ tension, accompanied by diminished CO₂ content, were observed. The mean difference between the CO₂ tensions of the first and the second samples during periods of medication, statistically highly significant, was 3.6 mm. Hg with a S.E. of 0.9 mm. Hg. This indicates a cumulative effect of the drug.

No marked difference was observed between the effect of sodium salicylate and of acetylsalicylic acid; however, the data are insufficient for a detailed comparison.

In Figure 4 is presented a scatter diagram and

the calculated regression line depicting the relationship between the CO₂ tension and the daily dosage of salicylate. All CO₂ tension data listed in Table I are plotted, with the exception of that of case 10 which was obtained within 1 day of the start of medication. The relationship between salicylate dosage and CO₂ tension, evident to cursory inspection, is highly significant. It is of interest to note that the regression line cuts the ordinate at a CO₂ tension value of 40.4 mm. Hg, close to the mean value of 42 mm. Hg of the control samples. The equation for the regression line is:

$$y = 40.4 + (-72.3) x_1$$

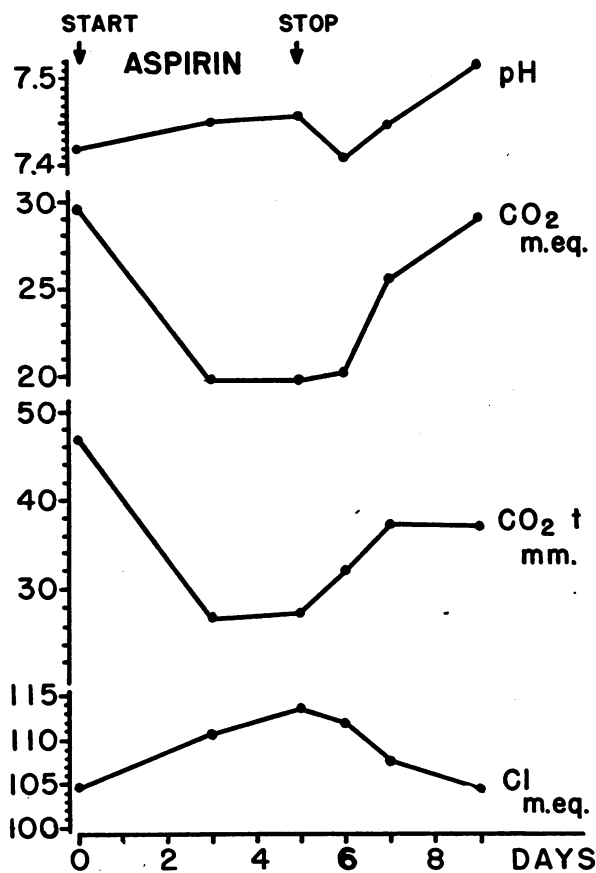


FIG. 1. DATA FOR THE BLOOD OF F. S.

where y indicates the CO₂ tension in mm. Hg, and x_1 the daily dose of salicylate in grams per kgm. bodyweight.

If the period of medication is taken into account, a closer fitting regression equation is obtained:

$$y = 42.2 + (-73.7) x_1 + (-0.27) x_2$$

where y and x_1 have the same meaning as above, and x_2 indicates the period of medication in days. Both regression coefficients are significant as tested by the t test, t_1 being 6.06, and t_2 being 2.09.

This result, based on all observations, reinforces the conclusion reached from the analysis of the repeat-samples alone and indicates that the effect of salicylate increases with the period of medication.

DISCUSSION

Strict comparison of the data of the present study, obtained on venous blood, with the results

on arterial plasma of the preceding investigation cannot be undertaken owing to variations of the average arterio-venous difference and of the composition of the blood in different veins. On the average, the pH of venous plasma is about 0.03 units lower, and the CO₂ content and tension about 2 m.eq. per liter and 5 mm. Hg higher, respectively, than are the corresponding values for arterial plasma. Estimates of the composition of arterial plasma by the use of such correction factors are subject to errors in opposite directions; veno-stasis would tend to increase the arterio-venous differences, while increased cardiac output would lead to an approach of arterial and venous values. Under the conditions of the present study, in all likelihood the first influence predominated, leading to an underestimate of the effect of salicylates on the electrolyte equilibrium of the blood.

The data on human subjects tend to bear out the conclusions reached from animal experiments; namely, that salicylates produce a primary hyperventilation with consequent decrease of the CO₂ tension and a tendency toward increased pH values. In the human subjects, who received

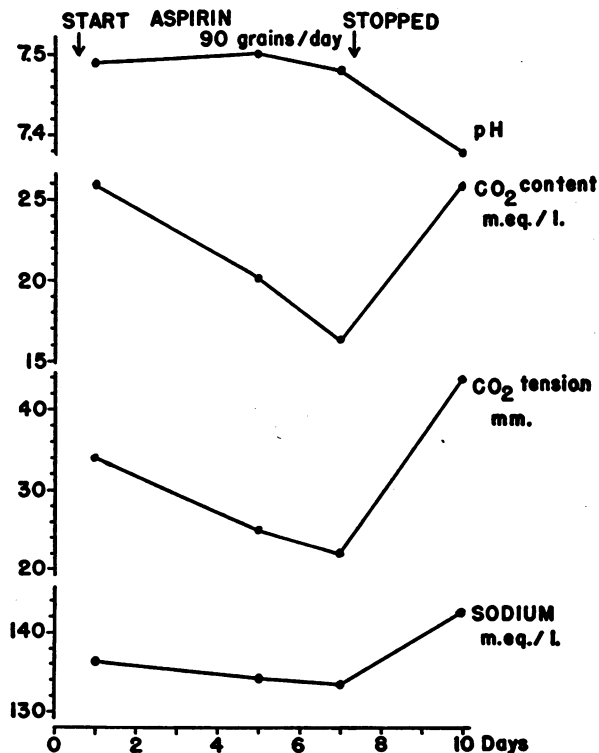


FIG. 2. FINDINGS ON THE BLOOD OF A. D.

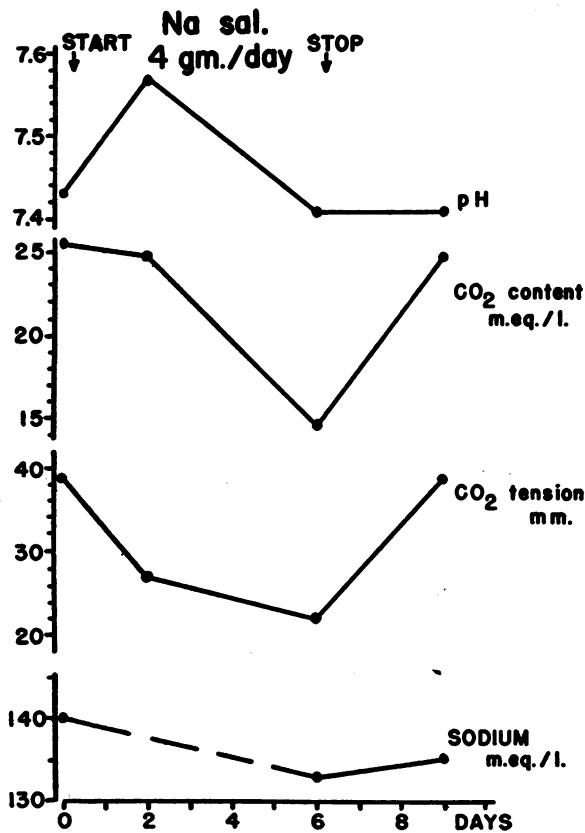


FIG. 3. DIFFERENT PATTERNS OF CHANGE IN THE ELECTROLYTE EQUILIBRIUM OF THE PLASMA

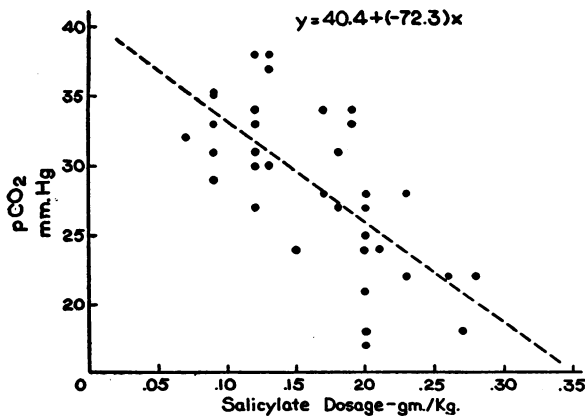


FIG. 4. RELATIONSHIP BETWEEN THE CO₂ TENSION AND THE DAILY DOSAGE OF SALICYLATE

smaller doses than the experimental animals, pH change was usually slight, indicating successful compensation. The compensatory decrease of the bicarbonate concentration in most cases was offset

by a commensurate increase of chloride so that the total electrolyte concentration of the plasma was maintained. In 4 of the patients, however, decreases of the serum sodium were seen such as were commonly observed in dogs with salicyl poisoning.

A decreased CO₂ tension, found in every patient studied, may be taken as *prima facie* evidence of increased pulmonary ventilation; however, hyperpnea was not always noticed. This may have been because salicylates at first affect the amplitude, rather than the frequency of the respirations.

The fact that small doses of salicylates cause chemical changes of the blood in the same direction as those observed in severe poisoning, may indicate that, in these respects at least, the normal pharmacologic and toxic effects of salicylates differ in degree only.

SUMMARY

In the plasma of patients receiving therapeutic doses of sodium salicylate or of acetylsalicylic acid, decreased tension and content of CO₂, and small changes of pH were found. The plasma chloride was usually elevated, and the sodium was occasionally decreased. The effect of salicylate appeared to be proportional to the dose administered and to increase with the period of medication. The results indicate that salicylates produce primary hyperpnea with consequent decrease of CO₂ tension. Various types of adjustment of the electrolyte equilibrium to the hyperventilation were observed.

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