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THE EFFECT OF SALICYLATES ON THE ELECTROLYTE STRUCTURE OF THE BLOOD PLASMA. I. RESPIRATORY ALKALOSIS IN MONKEYS AND DOGS AFTER SODIUM AND METHYL SALICYLATE; THE INFLUENCE OF HYPNOTIC DRUGS AND OF SODIUM BICARBONATE ON SALICYLATE POISONING

S. Rapoport, George M. Guest

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Research Article

THE EFFECT OF SALICYLATES ON THE ELECTROLYTE STRUCTURE OF THE BLOOD PLASMA.[1] I. RESPIRATORY ALKALOSIS IN MONKEYS AND DOGS AFTER SODIUM AND METHYL SALICYLATE; THE INFLUENCE OF HYPNOTIC DRUGS AND OF SODIUM BICARBONATE ON SALICYLATE POISONING

By S. RAPOPORT and GEORGE M. GUEST

(From the Children's Hospital Research Foundation and the Department of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati)

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The clinical picture typical of salicylate poisoning has often been described: hyperpnea appears to be the most prominent symptom; other symptoms are vomiting, thirst, sweating, diuresis, fever, and various signs of irritation of the central nervous system, including convulsions followed by depression and coma. Albumen, casts, and red and white cells are often found in the urine. The physiologic mechanism underlying the hyperpnea of salicylism has been the subject of much discussion. As the dyspnea of salicylate poisoning was noted to resemble the Kussmaul type of breathing of diabetic coma, ketone bodies were suggested as a common cause for the acidosis and hyperventilation in both conditions (1). This hypothesis was not borne out in later studies, which did not reveal increased ketonemia in man or rabbits receiving large doses of salicylates (2). In more recent times the theory of a primary metabolic acidosis, accepted by many clinical observers, appeared to be supported by the finding of a decreased bicarbonate content of the blood, but the origin of this presumed acidosis has remained obscure (3 to 5). Increased amounts of lactate found in the blood of rabbits following sodium salicylate administration were thought to be partly responsible for the presumed acidosis (6). The significance of this observation appears uncertain, since the increases varied widely, and the muscular effort involved in hyperventilation may have accounted for them. A renal mechanism for the metabolic acidosis has been suggested (7, 8) but the rapidity of the onset of the hyperpnea and the inconstancy and mildness of the renal changes appear difficult to reconcile with such an hypothesis. Another group of observers has favored the view that the hyperpnea is of central origin and that changes in the blood are secondary. In a study of salicylate poisoning in man the finding of insignificant changes in the blood pH in the presence of lowered concentrations of bicarbonate suggested that the hyperpnea must result from central stimulation by the drug (9). Others (10, 11) came to the same conclusion on the basis of short-time experiments with small doses of sodium salicylate in man, in which lowered CO_2 tensions and alkaline urines were observed coincidentally with unchanged values for the alkali reserve of the blood. A critical evaluation of the literature led to the conclusion that the cause of the hyperpnea was both central and metabolic (12). In a recent study dealing experimentally with the effects of toxic doses on the composition of the blood of dogs (13), a pH of 7.61 concomitant with a CO_2 content of 13 m.eq. per liter was reported in 1 dog and mention was made of unpublished experiments, which also indicated the presence of at least transient alkalosis following the administration of salicylates. In this study, changes in the heat regulation were stressed as an explanation for the hyperpnea of salicylism. In all, it would appear that the data available at present are insufficient to permit a satisfactory description of the electrolyte structure of the blood in salicylate poisoning.

The observation of a case of aspirin poisoning in a 3-year-old child, with the plasma pH elevated and the CO_2 content and tension decreased, led us to investigate the effects of salicylates in monkeys and dogs. Sodium and methyl salicylate were administered to the animals by parenteral routes and blood analyses were performed for pH, CO_2, chloride, sodium, and potassium. The serum protein and the distribution of the acid-soluble phosphorus in the blood of several ani-

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

mals were determined. The effects of several hypnotic drugs and of sodium bicarbonate on the hyperpnea of salicylism were also studied.

METHODS

Rhesus monkeys weighing 3 to 5 kgm., and male mongrel dogs weighing 14 to 20 kgm. were used. The animals were fasted 24 hours before and during the experimental periods but were allowed free access to water at all times. Weight, temperature, and respiratory rate were recorded in all, and urinary output in some of the dogs. The dogs lost on the average 1.5 kgm. of weight during the experiments. The respirations of all animals increased greatly in frequency and depth following the administration of salicylates. Two types of hyperventilation were observed occurring in the same animals alternately within short periods of time: (*1*) deep labored breathing reaching frequencies as high as 150 per minute; and (*2*) panting, much more shallow in character, at rates of 250 or more respirations per minute. During the later stages of fatal intoxication or under the influence of hypnotic drugs, the first type of breathing predominated and panting was observed only occasionally. The temperature of the animals rose in a few instances to values as high as 41° C., but often remained at 39° C. The urinary output was greatly increased in the beginning of the intoxication, and diminished during the later stages.

Blood samples from the femoral artery were drawn with a tightly-fitting syringe and needle and were delivered under paraffin oil. The serum pH values were determined with a glass electrode at 38° C. with precautions against exposure to air. Serum CO_2, chloride, phosphorus, and protein values were determined by methods previously described (14), sodium by the method of Leva (15), and potassium according to the slightly-modified method of Consolazio and Talbott (16). The CO_2 tension was calculated from the values for pH and bicarbonate. Data on the hemoglobin, the red count, and the packed volume of red cells of several animals did not reveal any significant change, and, therefore, are not reported here.

EXPERIMENTATION WITH SODIUM SALICYLATE

In Table I are shown representative experiments on the effect of sodium salicylate on monkeys and dogs:

Rhesus monkey number 400, weighing 3.6 kgm., received repeated intravenous injections of sodium salicylate. The animal presented signs of poisoning closely resembling those seen in man, including hyperpnea, flushing of the face, weakness, and profuse diuresis. The chemical data on the blood taken 1 hour after the last dose of sodium salicylate, when the animal appeared very weak, showed an extraordinarily elevated pH, a moderately reduced CO_2 content, and a greatly decreased tension of CO_2.

Dog S1 received a total of 1.0 gram per kgm. of sodium salicylate intraperitoneally in divided doses over a period of 24 hours. Extreme hyperpnea developed shortly after the first dose of 0.2 gram per kgm. had been administered and continued until the dog died. Diuresis, great weakness, and hyper-reflexia were noticed among the signs of intoxication.

The dogs 839 and 840 were studied with the purpose of following the effect of single intravenous doses of sodium salicylate on the electrolyte equilibrium. Dog 840

TABLE I

Effect of sodium salicylate on the ionic equilibrium of blood plasma

Animal	Number	pH	CO_2	pCO_2	Chloride	Comment
			m. eq. per liter	*mm. Hg*	*m. eq. per liter*	
Monkey	400	7.85	16.5	9	97.3	Received 1.1 grams per kgm. intravenously in 5 divided doses over a period of 30 hours. Sample 1 hour after last dose. Panting, flushed face, weak. Sacrificed.
Dog	S1	7.44	25.7	38	102.2	Preliminary sample, followed by intraperitoneal injections of 0.2 gram doses of sodium salicylate. Wt. 14 kgm.
		7.49	24.2	32	105.3	4 hours later; total dose 0.4 gram per kgm.; breathing fast.
		7.66	23.1	20	110.9	24 hours later; total dose 1.0 gram per kgm.; panting hard, weak. Died 1 hour after sample.
Dog	840	7.42	20.5	31	112.9	Preliminary sample, followed by intravenous injection of sodium salicylate, 0.6 gram per kgm. Weight 17 kgm.
		7.62	17.9	17	111.3	45 minutes later; panting hard.
		7.50	19.2	24	108.4	3 hours later; very weak; died ½ hour later.
Dog	839	7.48	22.3	30	113.4	Preliminary sample, followed by intravenous injection of sodium salicylate, 0.3 gram per kgm. Weight 15 kgm.
		7.49	22.2	29	109.2	20 minutes later; breathing rapidly.
		7.58	22.5	24	109.6	1.5 hours later; panting.
		7.54	22.9	27	107.2	5 hours later; hyperpnea diminished.
		7.43	22.0	33	103.9	23 hours later; appears normal.

TABLE II

Effects of methyl salicylate on plasma electrolytes

Dog	pH	CO_2	pCO_2	Chloride	Sodium	Comment
		m. eq. per liter	*mm. Hg*	*m. eq. per liter*	*m. eq. per liter*	
Pr.	7.42	25.4	40	111.4	150.3	Preliminary sample, followed by intramuscular injection of 2 ml. doses of methyl salicylate. Weight 15 kgm.
	7.41	18.6	28	106.6		30 hours later; total dose 14 ml.
	7.41	12.9	19	102.6	129.6	53 hours later; total dose 18 ml.; panting, weak; died 8 hours later.
Pa.	7.48	22.7	32	118.1	148.7	Preliminary sample, followed by intramuscular injection of 2 ml. doses of methyl salicylate. Weight 31 kgm.
	7.49	13.7	17	113.4	141.8	44 hours later; total dose 16 ml.; hyperpnea intense.
	7.49	12.8	16	106.9	137.5	68 hours later; total dose 23 ml.; seems very weak, died ½ hour later.

received what turned out to be a lethal dose, 0.6 gram per kgm. Within 20 minutes of the injection, the animal was breathing very deeply and continued to do so until its death 3½ hours later. The sample taken 45 minutes after the injection showed marked elevation of the pH, a slight drop in the content of CO_2, and a marked drop in the tension of the CO_2. The 3-hour sample showed less deviation from the normal in values for pH and CO_2, but the animal at that time appeared very weak and was breathing less forcefully. Dog 839 received only 0.3 gram per kgm. of sodium salicylate and tolerated the drug well. The rise in pH and fall in CO_2 tension were at their height 1½ hours after the injection. After 5 hours, hyperventilation was present to a moderate extent, and when the last blood sample was taken 23 hours after the injection, the respiration had returned to normal. The CO_2 content of the serum changed little during the experiment.

The serum chloride of these animals did not exhibit marked deviations from the normal.

THE EFFECT OF METHYL SALICYLATE

Methyl salicylate was substituted for sodium salicylate in the later experiments in order to avoid the complicating effect of sodium ions. The drug was always administered intramuscularly.

Table II presents data on the changes of the serum electrolytes in 2 dogs that received repeated injections of methyl salicylate totaling 18 and 23 ml. respectively. The serum pH of these animals changed little, but both CO_2 content and CO_2 tension of the serum were markedly lowered. The chloride and the sodium levels also decreased. In Figure 1 are presented data on a third animal which received repeated injections of the drug in increasing amounts over a period of 4 days. The serum pH of this dog reached a peak of 7.64 and when the animal developed what were thought to be tetanic convulsions dropped rather sharply. The content and tension of CO_2 in the serum of this dog decreased to levels of 10.7 m.eq. per liter, and 12 mm. Hg, respectively, the sodium to a level of 124 m.eq. per liter and with it the chloride (not shown) to 94 m.eq. per liter. The effect of a single

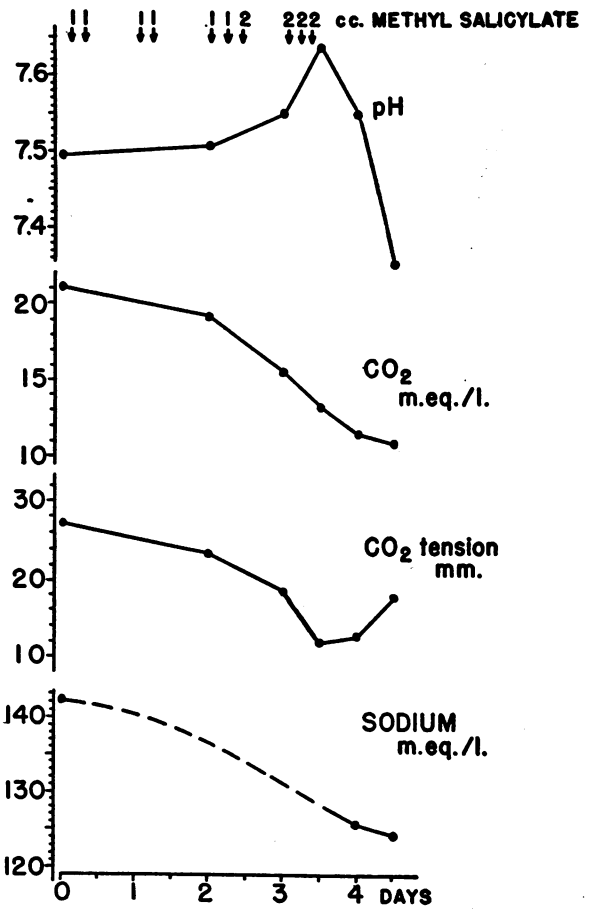

FIG. 1. THE EFFECT OF REPEATED DOSES OF METHYL SALICYLATE

Dog weighing 14 kgm., received intramuscularly the amounts of methyl salicylate indicated in the figure. The animal began to hyperventilate vigorously on the third day. On the fourth day, the animal was weak and showed hyper-reflexia and muscular twitchings. It was moribund when the last blood sample was taken.

large non-fatal dose of methyl salicylate on pH and CO_2 of the serum of another dog, who received 10 ml. of the drug, is shown in Figure 2. The greatest change took place after about 24 hours, with a slow return to normal values over a period of 4 days.

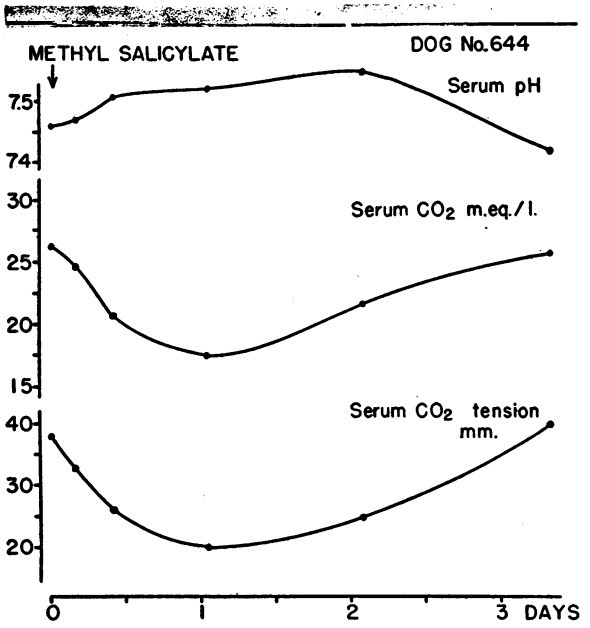

FIG. 2. THE EFFECT OF A SINGLE DOSE OF METHYL SALICYLATE

Dog 644, weighing 15 kgm., received 10 ml. of methyl salicylate intramuscularly. Within a few hours the respirations increased, to reach a maximum about 24 hours after the injection, and decreased after 48 hours.

In Table III are presented data on the sodium, potassium, and chloride content of the sera of 9 dogs all of whom developed the typical signs and chemical changes of salicylism, after having received 10 ml. of methyl salicylate. The sodium was decreased in 5, and little changed in the sera of 3 of the animals. In 3 animals both serum chloride and sodium were diminished significantly; in 2 the sodium alone, and in 1 the chloride alone was decreased; the concentration of potassium in the serum fell in every instance.

TABLE III

Sodium, chloride, and potassium in the plasma of dogs 24 hours following methyl salicylate administration

Dog number	Before			After		
	Sodium	Chloride	Potassium	Sodium	Chloride	Potassium
	m. eq. per liter	*m. eq. per liter*	*m. eq. per liter*	*m. eq. per liter*	*m. eq. per liter*	*m. eq. per liter*
645	150	117	6.2	143	112	3.4
932	141	104	5.0	134	103	4.6
933	145	108	4.2	128	96	2.7
937	149	119	6.8	134	108	2.9
938	148	117	5.1	142	115	4.0
936	141	108	4.5	139	101	2.6
940	139	110	4.0	144	119	3.0
941	146	112	4.4	145	110	2.9
Sp.	142	110		146	112	

The distribution of the acid-soluble phosphorus in the blood was determined in several animals. The inorganic phosphorus was regularly decreased, but little change was found in the organic acid-soluble phosphorus content of the erythrocytes. The serum proteins were not significantly altered.

RESULTS

The results of the foregoing experiments may be summarized briefly as follows. In all experiments, reduced tensions of CO_2 in the serum were found. Significant elevation of the serum pH occurred in most instances, but occasionally change of pH was absent. The serum bicarbonate concentration was lowered in all experiments of longer duration, but such change was absent in the animals receiving sodium salicylate intravenously. The serum sodium concentration was lowered in the majority, and the chloride in about half of the dogs. Potassium values were regularly decreased.

The evidence would appear to indicate that salicylates cause primary hyperventilation. The resultant lowering of the CO_2 tension leads to an alkalotic tendency in the blood. The lowering of the bicarbonate concentration may be interpreted as a secondary compensatory change tending to maintain the usual ratio between carbonic acid and bicarbonate, and resulting in a smaller shift of pH than would otherwise occur. The adjustments in the bicarbonate content are comparatively slow, since they are apparently accomplished by a renal mechanism. This point is illustrated in the experiments on the effects of intravenous administration of sodium salicylate, in which pH and CO_2 tension were markedly altered within a short time, without much change in the total CO_2 content of the serum. Several mechanisms appear possible for the compensatory decrease of bicarbonate. The most efficient and successful compensation (17) would be a reciprocal increase in the concentration of chloride to make up for the lowering of the bicarbonate, thus maintaining the total ionic concentration. Such substitution of chloride for bicarbonate ions, observed repeatedly in man under various conditions, occurred only rarely in the dogs. The removal of bicarbonate, unaccompanied by corresponding increases in other anions,

resulted in lowered total ionic concentrations as indicated by the diminished concentration of sodium and potassium in the blood. In several of the experiments, a diminution of the serum chloride occurred, which was usually accompanied by a marked decrease in the total ionic concentration (sodium + potassium). This decrease was particularly pronounced in animals that had received repeated doses of salicylate, and had been for several days in the state of salicylism. A reduction of the ionic concentration could conceivably occur by way of increased retention of water with consequent dilution of the electrolytes. Actually all animals lost weight and had profuse diuresis. It would appear, therefore, that the animals lost large amounts of sodium, thus offsetting the loss of carbonic acid in the blood by a direct removal of bicarbonate in the urine. Instead of tending to maintain the total electrolyte concentration, such shifts in the electrolyte structure result in cumulative deviations from the normal. The explanation of their mechanism appears difficult. Perhaps the salicylates have an independent action on the kidney which results in impairment of its defense of the osmolarity of the body fluids. The marked diuresis and the albuminuria may be other manifestations of the reno-toxic effect of the salicylates.

The lowered potassium concentration in the serum of the dogs suggests impairment of renal control. The possibility, however, of disturbance of the equilibrium between extra- and intracellular potassium concentrations must be considered. Unpublished data obtained in this laboratory suggest that alkalosis *per se* might exert this effect and also explain lowered concentrations of inorganic phosphorus.

THE EFFECT OF HYPNOTICS ON SALICYLISM

It seems reasonable to assume that the central stimulation caused by the salicylates can be counteracted by hypnotic drugs. In order to test this assumption, experiments were carried out in dogs on the effect of sodium pentobarbital, sodium barbital, paraldehyde, and morphine on the salicylism induced by methyl salicylate. The interaction of sodium barbital and of sodium salicylate was also investigated.

Pentobarbital sodium. In Figure 3 are portrayed the effects of pentobarbital sodium on the pH, the content and tension of CO_2, and the rate of respiration of a dog which had received in a single dose enough methyl salicylate to produce severe, but not usually fatal, intoxication. On the day following the injection, 2 samples of blood drawn 4 hours apart showed by the progressive alterations of pH and CO_2 that the intoxication was progressing rapidly. Ten minutes after the injection of pentobarbital sodium, the respirations decreased to the normal rate of 20 per minute, and coincidentally the pH fell to a normal value, the serum CO_2 content increased somewhat, and as a result the CO_2 tension rose. A sample of blood taken 50 minutes later showed normal values for all constituents. Two hours after this sample was taken, the respiratory rate had again doubled, the pH had increased to 7.52, the content of CO_2 had dropped to 22.5 m.eq. per liter, and its tension to 28 mm. Hg. Subsequent samples showed decreasing content and tension of the CO_2. Unlike the animals that received similar doses of salicylates alone, this dog remained in a comatose condition, breathing laboriously, and died 20 hours after the injection of pentobarbital sodium.

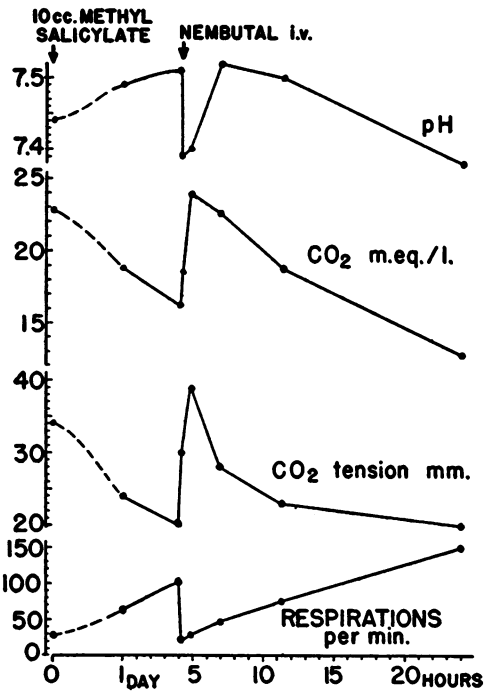

FIG. 3. THE EFFECT OF PENTOBARBITAL SODIUM

Dog, weighing 18 kgm., received 10 ml. of methyl salicylate on the day preceding the intravenous injection of 29 mgm. per kgm. of pentobarbital sodium (nembutal).

In Figure 4 are presented data on the effect of pentobarbital sodium on pH, CO_2, and sodium of the serum of a dog that received a smaller dose of methyl salicylate. This animal showed only mild intoxication, with a respiratory rate of 66 per minute, and there were moderate alterations in the electrolyte structure of the blood. Ten minutes after the injection of pentobarbital sodium, the CO_2 tension had risen to 37 mm. Hg with corresponding changes of pH and CO_2 content. Forty-five minutes later, the values approached normal even closer. During the following hours of observation the respiratory depressant effect of pentobarbital sodium proved to be transient, and the respirations again increased in magnitude. Concomitantly, the CO_2 tension fell again, and the pH rose somewhat. Twenty-four hours later, the animal appeared to have recovered from all ill effects and presented normal values for all constituents of the plasma (not shown). The dog appeared to be narcotized, or perhaps comatose, for 12 hours after the injection of the pentobarbital sodium. This is noteworthy since the usual duration of the narcosis produced by such doses of pentobarbital sodium rarely exceeds 4 hours.

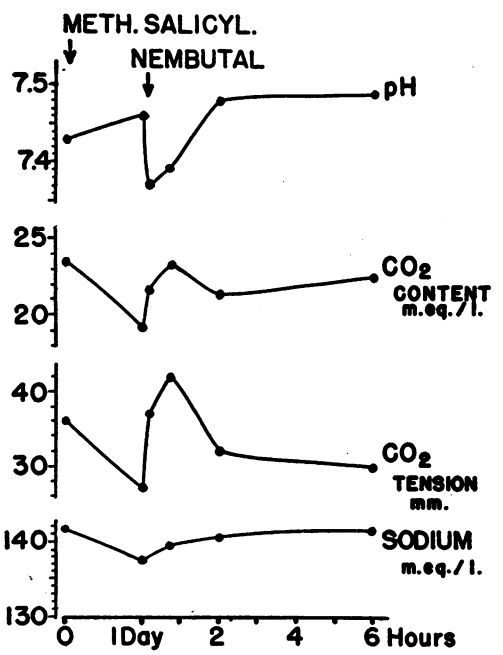

FIG. 4. THE EFFECT OF PENTOBARBITAL SODIUM

Dog 645, weighing 18 kgm., received 7 ml. of methyl salicylate on the day preceding the injection of 29 mgm. per kgm. of pentobarbital sodium (nembutal).

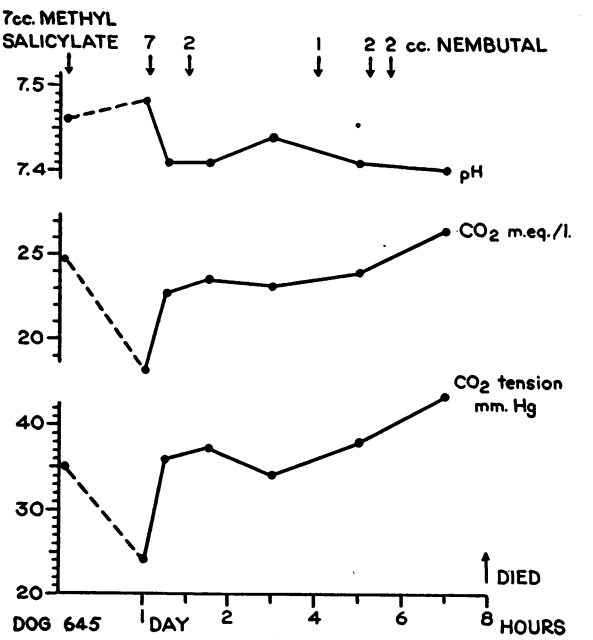

FIG. 5. THE EFFECT OF REPEATED INJECTIONS OF PENTOBARBITAL SODIUM

Dog 645, weighing 19 kgm., received 7 ml. of methyl salicylate on the day preceding the injections of pentobarbital sodium at intervals indicated.

In Figure 5 are shown data of an experiment designed to keep the respirations and the CO_2 tension of a dog with salicylism as nearly normal as possible by repeated injections of pentobarbital sodium. Dog 645 received 7 ml. of methyl salicylate, an amount usually producing only moderate intoxication. On the next day, a blood sample showed moderately reduced tension and content of CO_2. At that time the respirations were fairly deep at a rate of about 40 per minute, and the hyperpnea appeared to be increasing. After the injection of the hypnotic drug, the respirations immediately slowed to 23 per minute. The blood sample drawn 30 minutes afterwards showed a return to normal values for pH and CO_2. A short time later the respirations increased again, and 2 ml. of pentobarbital sodium were given, resulting in a diminution of the hyperpnea. Samples 1½ and 3 hours after the first injection indicated that a normal CO_2 tension was being maintained. After the fourth hour, the respirations of the dog increased again in frequency, but became much shallower. More pentobarbital sodium was given without any noticeable effect on the respirations which remained at a rate of about 60 per minute.

Bloods drawn at that time showed slowly-rising CO_2 tension. The animal became increasingly comatose and died after 7½ hours.

In Figure 6 are presented 2 experiments on the antagonistic effects of pentobarbital sodium and of sodium salicylate on dogs 839 and 841. The respiratory rate of both animals fell immediately after the injection of the hypnotic drug and the blood samples drawn 5 minutes later showed slight increases in the CO_2 tension. Then, the animals received 0.3 gram per kgm. of body weight of sodium salicylate slowly by vein. Half an hour later, the respiratory rate of dog 839 had increased greatly, and a blood sample after 1 hour showed elevation of the pH with corresponding reduction of the CO_2 tension. Repeated injections of pentobarbital sodium did not reduce the respiratory rate, but the sample drawn 3 hours after the injection of salicylate showed a less marked deviation from the normal than the 1-hour sample. The animal was growing weaker and more comatose at that time and died 15 minutes after the last sample of blood was drawn. Dog 841 showed the suppressive effects of the hypnotic drug on the hyperpnea more clearly, the respirations remaining at a low frequency for more than ½ hour following the injection of the sodium salicylate. This animal recovered from the effects of both drugs.

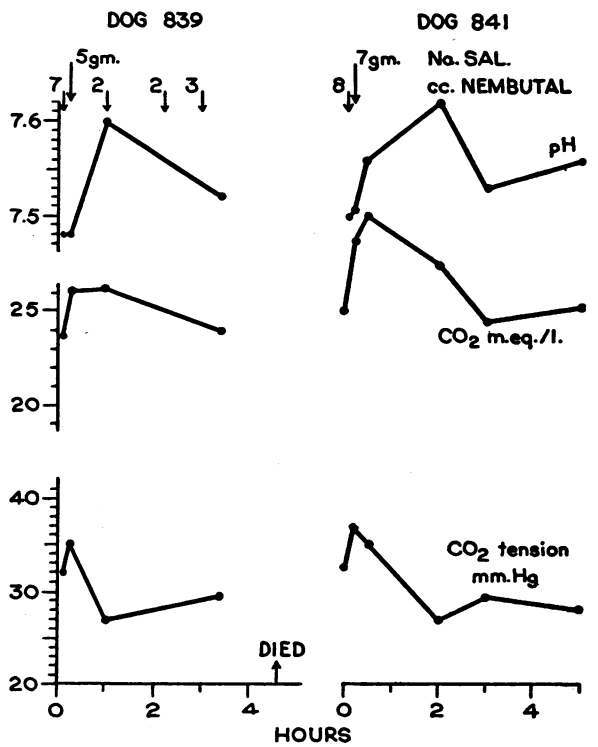

FIG. 6. THE EFFECTS OF SODIUM SALICYLATE AND OF PENTOBARBITAL SODIUM

Dog 839, weighing 16 kgm., received 7 ml. of the hypnotic drug. The respiratory rate fell from 24 to 14 per minute. The animal then received 5 grams of sodium salicylate in 25 per cent solution slowly by vein. The respiratory rate increased to 64 per minute and remained elevated throughout the experiment. Dog 841, weighing 19.5 kgm., received 8 ml. of pentobarbital sodium by vein. His respirations promptly decreased from 20 to 8 per minute. Seven ml. of sodium salicylate were then injected by vein. The respiratory rate remained constant for ½ hour, then increased to values of 72 per minute after 2 hours. After 7 hours, the rate had fallen again to 25 per minute. The animal remained comatose 9 hours.

Sodium barbital. One experiment was performed to test the effect of sodium barbital on the hyperpnea of salicylism. One dog received 0.1 gram per kgm. of the drug intraperitoneally on the day after the administration of 10 ml. of methyl salicylate. The respirations slowed progressively during the next 2 hours to a level of 40 per minute when the animal died.

The experiments with pentobarbital sodium offer support for the assumption of a primary effect of salicylates on the respiratory center. If salicylism were characterized by a metabolic acidosis, the hyperventilation would constitute a compensatory mechanism tending to lessen the fall in pH by reduction of the carbonic acid of the blood. Suppression of an hyperpnea of such origin would lead rapidly to low pH values and elevated tensions of CO_2. Actually, in the foregoing experiments the pH and CO_2 tension returned immediately to normal values with abolition of the hyperpnea and did not drift into the acidotic range. The corrective effect of single injections of pentobarbital sodium on the ionic equilibrium was transient, but normal values of pH and CO_2 could be maintained by repeated doses. It appears that salicylate and pentobarbital sodium, while exhibiting antagonistic effects on the ventilation of the dogs, had synergistic depressant and toxic actions on their central nervous systems. The animals lapsed into a deeply comatose state and died after the combined administration of both drugs in doses that were easily tolerated singly.

Paraldehyde. In order to explore further the effects of hypnotic drugs on salicylism, 2 experi-

TABLE IV

Salicylism in dogs: effect of paraldehyde and of morphine

Dog number	Drug	pH	CO_2	pCO_2	Respiratory rate	Comment
		m. eq. per liter	*m. eq. per liter*	*mm. Hg*	*per minute*	
940	Paraldehyde	7.46	24.9	35	20	Preliminary sample, followed by intraperitoneal injection of 10 ml. methyl salicylate. Weight 18 kgm.
		7.46	16.1	22	100	After 23 hours; respiration moderately increased. 10 ml. paraldehyde injected after sample.
		7.48	17.0	22	70	½ hour later; deep respirations. 10 ml. paraldehyde injected after sample.
		7.47	11.0	14	160	2 hours later; died after 2 more hours.
941	Paraldehyde	7.40	22.1	36	20	Preliminary sample, followed by intraperitoneal injection of 10 ml. methyl salicylate.
		7.48	18.1	25	130	After 23 hours; panting intermittently. 10 ml. paraldehyde injected after sample.
		7.40	17.6	27	60	10 minutes later.
		7.52	12.8	15	250	1 hour later; panting, comatose.
		7.54	10.0	11	250	4 hours later; comatose, labored breathing; died ½ hour after sample.
Sp.	Morphine	7.46	14.5	19	200	16 hours after 10 ml. methyl salicylate. 135 mgm. morphine injected intramuscularly, in divided doses, over period of 2½ hours.
		7.57	12.0	13	180	3 hours after start of morphine injections; twitching of extremities every 3 to 4 minutes, generalized convulsions immediately after sample; died 2 hours later.

ments were carried out with paraldehyde. This drug was chosen because of its low toxicity and because it has little, if any, effect on the respiration. In Table IV are presented data on 2 dogs, each of which was injected with paraldehyde on the day following the administration of 10 ml. of methyl salicylate. Dog 940 received 20 ml. and dog 941 received 10 ml. of paraldehyde intraperitoneally. The data listed in the table demonstrate the absence of any depressant effect of paraldehyde on either hyperpnea or alkalosis. Actually, the impression was gained that the hyperpnea was intensified following the administration of the hypnotic drug. Both animals died about 4 hours after receiving doses of paraldehyde far below those tolerated by normal dogs. It would appear, therefore, that paraldehyde, as well as the barbiturates, potentiate the toxic effect of salicylates.

Morphine. In view of the pronounced depressant influence of morphine on the respiration of normal animals, it appeared of interest to study its effect on the hyperpnea of salicylism. The data of 1 experiment are presented in Table IV. Morphine did not produce significant reduction in either depth or rate of the respirations. Its outstanding pharmacologic effect was a further increase of the hyper-reflexia, leading to generalized tetanic convulsions. In 2 other dogs, similar observations were obtained.

It is known that morphine has both narcotic and convulsant effects. This experiment suggests that salicylates have the property of reinforcing the convulsant and suppressing the hypnotic action of morphine.

The experiments with the several hypnotic and respiratory depressant drugs may indicate that salicylates increase the susceptibility of the central nervous system to the toxic effects of hypnotic drugs. The results suggest that the administration of any hypnotic drug in the treatment of salicylism in man is inadvisable.

EFFECT OF SODIUM BICARBONATE IN SALICYLISM

Since sodium bicarbonate has been thought to ameliorate the toxic effects of salicylates (8, 12, 18), it appeared of interest to study its effect on the ionic structure of the blood in salicylism. In Figure 7 are presented the data on 1 dog who received 0.6 gram per kgm. of sodium bicarbonate intravenously 1 day after the administration of 10 ml. of methyl salicylate. Two preliminary samples of blood drawn 4 hours apart indicated that the animal was in a state of moderate salicylism. Ten

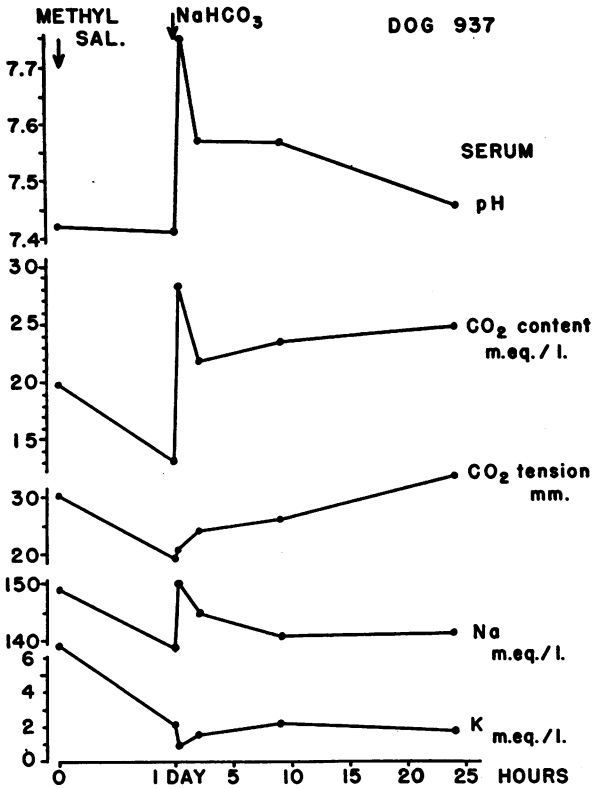

FIG. 7. THE EFFECT OF SODIUM BICARBONATE ON SALICYLISM

Dog 937, weighing 17 kgm., received 10 ml. of methyl salicylate intramuscularly on the day preceding the intravenous injection of 10 grams of sodium bicarbonate in 5 per cent solution. The animal appeared unaffected by the injection.

minutes after the injection of the sodium bicarbonate, the plasma pH was found to be 7.73, and the CO_2 content had increased by 15 m.eq. per liter, while the CO_2 tension had remained unchanged. The serum sodium, which was below the normal level before the injection, rose, while the potassium decreased even further. Blood samples 2 and 9 hours later showed that the pH had decreased and the CO_2 tension had risen slowly. Twenty-four hours after the injection of the sodium bicarbonate, the animal appeared to be entirely normal and showed no sign of intoxication. In Figure 8 are portrayed the changes in dog 938, which received identical experimental treatment. Five minutes after the injection of sodium bicarbonate, the blood pH rose to 7.68 and the CO_2 content to 31 m.eq. per liter. For 9 hours after the injection, a state of severe alkalosis persisted, but 24 hours later the animal appeared to be in good condition. Of the several more experiments with similar results, one deserves special mention. Shortly after the administration of sodium bicarbonate the animal developed convulsions, apparently tetanic in nature, and died.

Sodium bicarbonate does not appear to have a primary effect on the disturbance of the electrolyte equilibrium in salicylism. Neither the hyperpnea nor the CO_2 tension were immediately changed. The bicarbonate content was increased. The pH changed in proportion to the varying ratio between bicarbonate and carbonic acid, a result similar to that obtained by two investigators (19) in

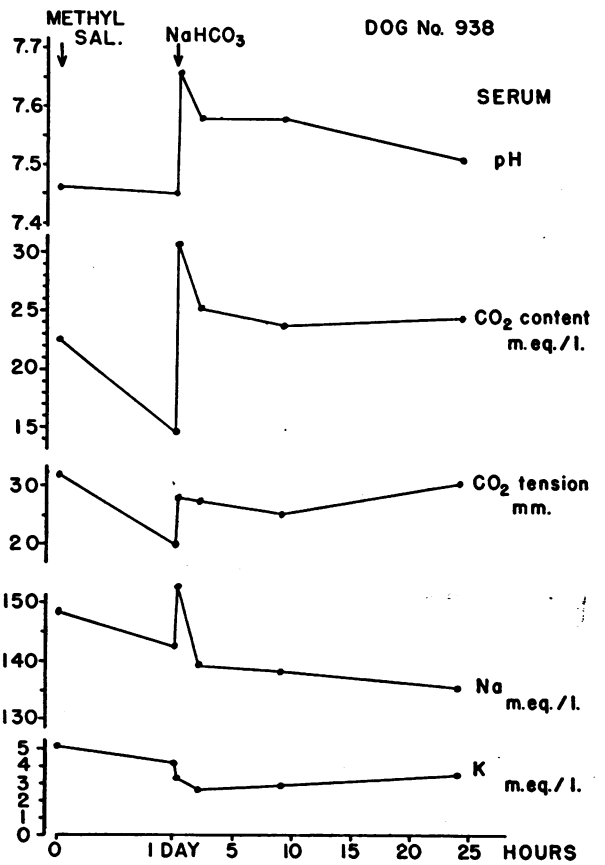

FIG. 8. THE EFFECT OF SODIUM BICARBONATE ON SALICYLISM

Dog 938, weighing 17 kgm., received 10 ml. of methyl salicylate. Twenty-four hours later, when hyperpnea led to lowered CO_2 content and tension of the blood, 10 grams of sodium bicarbonate were injected intravenously. The animal's respirations appeared unaffected. Panting continued the rest of the day, but the dog appeared normal in all respects 24 hours after the injection of the sodium bicarbonate.

normal human subjects. These findings also support the theory that salicylates exert their effect centrally and that a state of respiratory alkalosis characterizes salicylism. Sodium bicarbonate appeared to hasten the recovery from the intoxication, the dogs appearing normal within 24 hours after the administration of salicylates while untreated control animals appeared ill for 2 additional days. Sodium bicarbonate may exert its beneficial effect on the duration of the intoxication by causing increased urinary elimination of salicylate (8). The occurrence of tetany after the injection of sodium bicarbonate appears hardly surprising in view of the extent of the elevation of the pH produced. The possibility of tetany should be considered when the administration of sodium bicarbonate is contemplated in the treatment of salicylism in man.

DISCUSSION

The finding that salicylates cause a respiratory alkalosis does not in itself imply that these drugs exert their effect directly on the respiratory center. The possibility of a reflex mechanism for the hyperpnea by way of stimulation of the chemoreceptors in the carotid bodies must be considered. The evidence for the site of action is meager at the present time. Results have been obtained in 1 cat (20) which appeared to indicate that sodium salicylate exerted mainly a central effect, but a reflex component in the causation of the hyperpnea could not be excluded. The fact that the hyperventilation in the experiments here reported could be abolished, at least transiently by barbiturates, would also appear to indicate a direct action of salicylates on the respiratory center. As further indirect evidence of a direct influence on the brain may be cited the presence of other symptoms of irritation of the central nervous system, as well as the pathologic findings of congestion and petechial hemorrhages in the brain tissue.

The findings here reported deal only with humoral phases of the varied and widespread effects of salicylates. These drugs appear to act on the liver in a specific manner, affecting its content of glycogen and glutathione (21) and influencing the production of prothrombin (22, 23) and of fibrinogen (unpublished data). The effect of salicylates on the kidneys has been mentioned earlier. Alterations in the function of these organs may in turn affect the electrolyte balance of the blood, modifying the usual picture of respiratory alkalosis.

Salicylates influence the intermediary metabolism in a variety of ways, affecting the excretion of nitrogen and of uric acid and inhibiting the activity of several oxidative enzyme systems (21). Their effect on the intermediary metabolism of the cells may underlie their physiologic actions; *e.g.*, the stimulation of respiration may result from an altered metabolism of the cells of the respiratory center.

CONCLUSIONS

1. The administration of methyl and sodium salicylates to monkeys and dogs causes primary hyperventilation with lowering of the CO_2 tension in the blood, leading to an alkalotic tendency, which may or may not be accompanied by decreases of bicarbonate. Frequently, lowered total electrolyte concentrations were observed. Low concentrations of inorganic phosphorus and of potassium were found.

2. The effect of pentobarbital sodium, barbital sodium, paraldehyde and morphine on the hyperpnea of salicylism were studied in dogs. Hyperventilation could be suppressed and normal values for pH and CO_2 restored by the administration of pentobarbital sodium. All hypnotic drugs studied appeared to increase the toxicity of the salicylates. Morphine was found to exert a convulsant action without notable decrease of the hyperpnea.

3. The effect of sodium bicarbonate on the electrolyte structure of the blood in salicylism in dogs was to increase pH and bicarbonate content without affecting the tension of CO_2. The administration of sodium bicarbonate appeared generally to shorten the duration of the salicylate intoxication, but in 1 animal fatal tetany occurred.

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