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THE EFFECT OF SALICYLATE ADMINISTRATION ON THE ACETONE BODY CONTENT OF THE BLOOD

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The symptoms of acidosis are stressed in the reports of cases of poisoning following the taking of salicylates, either accidentally in toxic doses or from their prolonged administration.

Langmede reporting in the Lancet (1), calls attention to the acidosis occurring in children under salicylate treatment. These children were ill in hospitals suffering from acute rheumatic fever. Constipation was a constant symptom according to the report.

More recently J. G. M. Olmstead and C. A. Aldrich (2) report their observations and cite references in the literature of such cases.

The following series of experiments were carried out by us to determine if the symptoms of salicylate poisoning were due to an increased acetone body content in the circulation.

PURPOSE AND PLAN OF INVESTIGATION

The following experiments were planned with the idea of determining whether or not the salicylates in full therapeutic doses influence the blood content of acetone bodies. Vigorous adult rabbits were used in our first series of experiments. They were narcotized by administering urethane 25 per cent solution and chloretone saturated solution by stomach tube. Then under local anesthesia (cocaine) the trachea was cannulized and attached to a Dresser respiratory apparatus; one of the carotids was cannulized and connected to a mercury manometer in order to observe any fluctuations in blood pressure. In none of the experiments did the blood pressure fall below 75 mm. of mercury.

The temperature of the animals was carefully noted by thermometers, and was maintained by means of artificial heat from an electrical plate.

The sodium salicylate was given intravenously in the first series of experiments with the exception of the last animal which received 2 grams sodium salicylate per stomach tube. Two cubic

TABLE 1

Minute volume of expired air

EXPERIMENT NUMBER	NORMAL	TIME AFTER RECEIVING DRUG									
		15 minutes	30 minutes	1:00	1:30	2:00	3:00	4:00	4:30	5:00	5:30
	cc.										
1	680				690		760				
2	740		1,212	1,152		1,180	968				
3	640		1,180	980							
4	980		920	1,060	1,160						
5							900	920	980	765	699
6						1,035	786	918	877		850

Experiment 6 received 2 grams of sodium salicylate per stomach tube instead of intravenous administration.

TABLE 2

Rate of respiration per minute

EXPERIMENT NUMBER	NORMAL	TIME AFTER RECEIVING DRUG								
		15 minutes	30 minutes	1:00	1:30	2:00	3:00	4:00	4:30	5:00
1	40				68		56			
2	52		108	116		116	124			
3	56	88	56	60						
4	48		52	56	64	68				
5							48	52	48	39

centimeters of 8 per cent aqueous solution were given in the first experiment, 6 cc. in the second, and 8 cc. in the remaining experiments.

The minute volume of respired air was noted from time to time and recorded in the table.

A sample of blood of about 5 grams weight was drawn into

tarred flasks, weighed and analyzed for their preformed acetone and beta-oxybutric acid content according to Marriot's modification of Scott-Wilson's method (3). The nephelometer method of estimation was used.

After comparing the figures in tables 1 and 2 it does not appear that salicylates affect the respiratory rate or blood pressure to

TABLE 3

Blood acetone content of rabbit in salicylate dyspnea

Milligrams of acetone per gram of blood

EXPERIMENT NUMBER	NORMAL	TIME AFTER RECEIVING DRUG									
		5 minutes	10 minutes	15 minutes	30 minutes	1:00	1:30	2:00	3:00	4:00	4:30	5:30
2	0.02308	0.01967			0.0254		0.02183		0.02026			
3	0.0329		0.02802		0.0214	0.0301						
4	0.03204			0.0702		0.0366		0.0401				
5	0.0224								0.0194	0.0283	0.027	0.0183
6*	0.00862							0.0262	0.03614		0.02978	

* The animal in experiment 6 received its salicylate per stomach tube. The blood sample withdrawn for estimation of normal was taken before the administration of the narcotic. In the preceding experiments the samples for estimation of normals were withdrawn after the animals were narcotized. The lower normal in experiment 6 may be accounted for by the time of withdrawal in relation to the action of the anesthetic.

TABLE 4

Blood beta-oxybutyric acid content in salicylate dyspnea

Milligrams per cubic centimeter

EXPERIMENT NUMBER	NORMAL	TIME					
		10 minutes	15 minutes	30 minutes	1:00	2:00	3:00
3	0.0336	0.0334		0.0464	0.0395		
4	0.0531		0.068			0.0658	
6	0.0179						0.0434

any appreciable extent within the time above recorded. There is an increase in the minute volume of expired air, but not so great or constant as would be looked for in specific drug action.

Comparison of the figures in tables 3 and 4 reveals no apparent increase in the blood content of acetone or beta-oxybutyric acid following the drug administration.

The normal figure for beta-oxybutyric acid in experiment 6 is

considerably less than the normals in the preceding experiments. It compares favorably however with later experiments, i.e., experiments 11, 13, 14, 15, and 16. The high normal values of experiments 3, 4, and 5 are probably due to the action of the narcotic used in these experiments, in which the blood samples for normal estimation were drawn after the animals were fully narcotized. Blood for normal in experiment 6 and later experiments were drawn before the anesthetic was given under local anesthesia.

In the cases of poisoning cited above the symptoms of acidosis came on after twenty-four hours from the time the salicylate was taken.

With the idea in view that the drug might affect the general metabolism so that a condition of acidosis would result after a longer time, we began a second series of experiments in which the salicylate was given in toxic amount over longer periods of time.

THE EFFECTS OF EXTENDED SALICYLATE ADMINISTRATION ON THE ACETONE BODY CONTENT OF THE BLOOD

In the experiments the blood samples were drawn under cocaine anesthesia. After the normals were taken a large initial dose of the drug was given, followed at frequent intervals by small amounts over periods of twenty-four to forty-eight hours. The animals were kept saturated up to their lethal limit. We found 0.8 gram sodium salicylate by mouth per kilogram to be the minimum lethal initial dose. Four of the animals succumbed during the course of the administration. The drug was given per stomach tube supplemented by hypodermic injection, whenever there appeared to be much gastric irritation following the use of the stomach tube.

All of these animals became very dyspneic; the breathing was first exaggerated, panting, as though after a severe exertion within two and a half to three hours after the initial dose. As the toxicity increased the respirations became slower and deeper; the animal fighting for air; irregular and gasping before death. Convulsions usually preceded death. The rabbit in the thirteenth experiment died forty-two hours and twenty minutes after receiving the initial dose of 0.8 gram per kilogram. He had received all told by hypo and stomach tube at time of death 3.3 grams per kilogram.

TABLE 5

Milligrams preformed acetone per cubic centimeter blood after extended and toxic dosage of sodium salicylate

EXPERIMENT NUMBER	NORMAL	TIME AFTER TAKING DRUG					
		2:00	3:25	5:50	6:00	19:30	28:15
7	0.0096	0.0145					
8	0.0157					0.0136	
11	0.0103				0.0119		
13	0.0089						0.0136
14	0.0180		0.0101	0.0128			

TABLE 6

Milligrams beta-oxybutyric acid per cubic centimeter blood after extended and toxic dosage of sodium salicylate

EXPERIMENT NUMBER	NORMAL	TIME AFTER TAKING DRUG				
		3:25	5:50	6:00	28:15	30:25
11	0.0248			0.02604		
13	0.0182				0.01603	0.0222
14*	0.0237	0.0237	0.0182			

* Experiment 14 are the figures from cat's blood.

TABLE 7

Rate of respiration after extended and toxic salicylate dosages

EXPERIMENT NUMBER	NORMAL	TIME AFTER TAKING DRUG					
		1:00	3:00	3:30	4:00	6:00	7:00
11	300	320	220	200	160	120	128
13	144				118		
14	86		112		280	200	116

Samples of blood were drawn under cocaine anesthesia as soon as marked symptoms of respiratory distress and toxicity appeared, and analyzed for their acetone body content as in the previous experiments.

Examination of the results in tables 5, 6, and 7 reveal no alteration of blood acetone body content to a degree that would produce symptoms of acidosis. The salicylate was given over a period of time long enough in this last series of experiments to determine whether or not any metabolic change produced by it was responsible for an increase in the acetone body content as noted by Langemede (1) and in the poison case reports.

A change in the respiratory rate was brought about in all cases, which was evidently due to the central action of the drug. The low acetone body content of the blood as shown by the accompanying tables would occlude any change from possible acidosis.

TABLE 8

Human blood acetone content after salicylate administration

EXPERIMENT NUMBER	NORMAL	24 HOURS
15*	0.0062	0.00861
16	0.0048	0.00409
	Beta-oxybutyric acid	
15*	0.00114	0.0189
16	0.01714	0.01343

* Nine-year-old child.

A cat was used in experiment 14 on the possible assumption that a carnivorous animal might respond differently than a herbivorous one. The salicylate proved to be more highly toxic to the cat than the rabbit, but the analytical results revealed no change in the acetone body content of the blood.

THE EFFECT OF SALICYLATE ADMINISTRATION ON THE ACETONE BODY CONTENT OF THE HUMAN BLOOD

The effect of salicylate medication on the acetone body content of the blood in man was studied in one child requiring salicylates and one adult in health. The child, aged nine, was given $\frac{1}{3}$ gram sodium salicylate hourly for twenty-four hours. The adult weighing 175 pounds took 1 gram of sodium salicylate

each hour for seventeen doses. An insignificant increase occurred in the acetone and beta-oxybutyric acid content of the child's blood, but no increase occurred in the blood of the adult. Cinchonism was caused by the salicylate in both cases.

It might be remarked that the blood of the child showed a tendency to increase the acetone and beta-oxybutyric acid in content. Possibly this may be accentuated in some cases.

CONCLUSION

Salicylate circulating in full therapeutic or toxic doses in the blood does not alter the acetone, diacetic acid or oxybutyric acid content of the blood in man or rabbit.

REFERENCES

(1) LANGEMEDE: Lancet, 1906, i, 1822.
(2) OLMSTED, J. G. M., AND ALDRICH, C. A.: Acidosis in methyl salicylate poisoning. Jour. Amer. Med. Assoc., May 5, 1928, xc, 1438.
(3) MARRIOT: Jour. Biol. Chem., xvi, 1913, p. 293.