

Hypoprothrombinemia After Salicylate Administration in Man and Rabbits.

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During investigations on the effects of large doses of salicylates on the electrolyte structure of the blood, to be reported elsewhere, it was noted that a number of salicylate-intoxicated rabbits died of pericardial hemorrhage following heart puncture, and that their blood sometimes required a long time to clot. Consequently, studies of the prothrombin content of such bloods were undertaken.

Recently Link and his associates reported the finding of hypoprothrombinemia in rats fed salicylates.¹ Earlier, they had found that coumarins induced hypoprothrombinemia in various species of animals,² a finding that gains interest in view of the chemical relationship between the salicylates and the coumarins.

Methods. As a measure of prothrombin, the clotting time of oxalate-plasma recalcified in the presence of an excess of thromboplastin was determined according to the method of Fullerton³ slightly modified, using the venom of the Russel-viper as the thromboplastic agent. By this method the average prothrombin time of normal human plasma, with its standard deviation, was found to be 19.7 ± 1.8 seconds; of dog plasma, 11.3 ± 1.2 seconds; and of rabbit plasma, 11.8 ± 1.2 seconds. Studies were made on bloods of dogs and rabbits given large doses of methyl salicylate, and bloods of rheumatic fever patients (children) who were treated with salicylates.

Results. The dogs showed no change in prothrombin time following intramuscular injections of methyl salicylate in doses, 0.6 cc per kg, which gave rise to signs of severe intoxication (hyperpnea, etc.) and profound

disturbances of the plasma electrolytes.

In rabbits, severe degrees of hypoprothrombinemia were found repeatedly at around 48 hours after the subcutaneous injection of 0.5 cc of methyl salicylate per kg. Several rabbits, however, died within a lesser time without showing such changes. Fig. 1 illustrates typical observations made on 2 rabbits exhibiting severe degrees of hypoprothrombinemia.

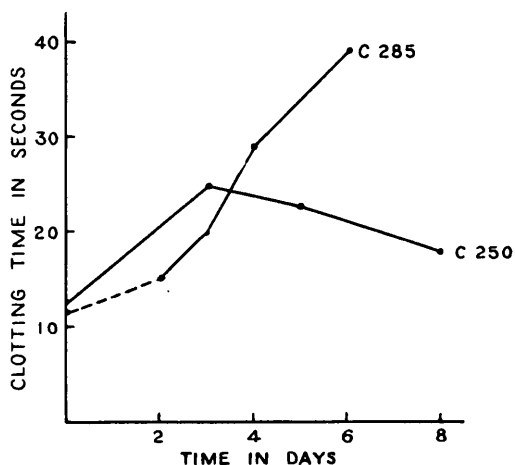


FIG. 1.

Prothrombin time of the blood plasma of 2 rabbits, C 250 and C 285, determined at varying intervals after the subcutaneous injection of 0.5 cc of methyl salicylate per kg.

Studies were made on 15 rheumatic patients, 6 to 14 years of age, during periods of salicylate medication ranging from 2 to 21 days. Thirteen received sodium salicylate and 2 received acetylsalicylic acid, in amounts varying from 1.5 to 8 g daily. Shifts in plasma electrolytes found in these patients will be reported elsewhere; but, suffice to state here, there was no apparent relationship between the chemical changes and changes in the prothrombin time of the blood. Manifestations of salicylism, such as vomiting, earache, diaphoresis, and/or marked hyperpnea, appeared

¹ Link, K. P., Overman, R. S., Sullivan, W. R., Huebner, C. F., and Scheel, L. D., *J. Biol. Chem.*, 1943, **147**, 463.

² Stahlmann, M. A., Huebner, C. F., and Link, K. P., *J. Biol. Chem.*, 1941, **138**, 513.

³ Fullerton, M. W., *Lancet*, 1940, **2**, 195.

TABLE I.
Prothrombin in the Blood Plasma of Rheumatic Patients Receiving Salicylate Medication.

Name	Age, yrs	Dosage, g per day	Time, relative to medication	Prothrombin time, sec	Prothrombin % of normal
A.H.	9	*0	Before	20.2	95
		4	2 days	24.7	65
		4	4 "	22.9	80
		0	1 " after	22.1	85
C.B.	13	*0	Before	20.1	95
		6	2 days	26.6	50
		6	4 "	25.5	55
		6	6 "	26.8	50
		6	8 "	25.8	55
		0	1 " after	23.2	80
H.M.	14	*0	Before	21.0	90
		6	4 days	23.9	70
		6	7 "	23.9	70
		0	5 " after	20.2	95
M.G.	9	*0	Before	20.8	90
		6	4 days	31.1	45
F.F.	12	*0	Before	22.0	85
		8	4 days	22.9	80
		8	21 "	24.9	65
V.P.	12	*0	Before	16.2	—
		6	5 days	24.1	70
		6	8 "	27.5	50
		0	5 " after	19.6	100
		6	5 "	24.8	70
H.V.	12	*0	Before	19.4	100
		6	9 days	21.4	90
L.O.	14	†8	3 "	24.8	65
		8	8 "	35.0	35
		8	9 "	30.2	45
		0	30 " after	19.1	100
		6	4 "	26.9	50

*Sodium salicylate.

†Acetylsalicylic acid.

in three of these patients. Table I presents data on 8 of these patients in whom significant prolongations of prothrombin time were found. The prothrombin values are listed both in seconds clotting time and in percentage of normal, the latter derived from the dilution curve of normal plasma according to Quick.⁴

The results indicate clearly that therapeutic doses of salicylates can lead to a marked prolongation of the prothrombin time of the

blood. The evaluation of the significance of such changes awaits further study. It is conceivable that the hypoprothrombinemia reflects a certain degree of liver damage. A question also arises whether the hemorrhagic tendency occasionally present in rheumatic fever may complicate salicylate therapy or sometimes may be a concomitant effect of such therapy. The possibility of counteracting the effect of salicylate on prothrombin by the administration of vitamin K should be investigated.

⁴ Quick, A. J., *Am. J. Phys.*, 1937, **118**, 260.