NOTE CONCERNING THE LAXATIVE PROPERTIES OF THE TRIBASIC SALTS OF PHENOLPHTHALIC ACID

BY

L. G. ROWNTREE

From the Pharmacological Laboratory of the Johns Hopkins University

REPRINTED FROM

THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

VOL. II, NO. 5. MAY 1911

Reprinted from THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
VOL. II, NO. 5. May, 1911

NOTE CONCERNING THE LAXATIVE PROPERTIES OF THE TRIBASIC SALTS OF PHENOLPHTHALIC ACID

L. G. ROWNTREE

From the Pharmacological Laboratory of the Johns Hopkins University

Received for publication, May 1, 1911

Owing to its efficiency as a laxative, phenolphthalein at present occupies a position of great importance in modern therapeutics. It has attained great popularity with the profession and also with drug firms in general by whom it is exploited alone or in combination with other laxatives under various trade names as Phenolphthaline laxative, Probilin, Prunoids, Laxine, Laxaphen, Exurgine, Phenalein, Phenolax wafers, Thalosen, Laxothalen tablets, Veracolate, etc.

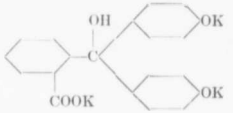
Its pharmacological properties and its efficiency as usually administered by mouth have tempted various workers to utilize it or one of its salts or substitution derivatives as a subcutaneous purgative. Fleig[1] has introduced into medical practice as a hypodermic purgative, a soluble derivative of phenolphthalein which he has called "sodophthalyl." Abel and Rowntree[2] and Rowntree[3] have demonstrated the value of phenolphthalein and more particularly of phenoltetrachlorphthalein in this connection when administered subcutaneously in solution in olive oil. It is established beyond doubt that these preparations possess very valuable laxative properties when so administered, and also that no general undesirable concomitant action is produced elsewhere in the organism. It must be admitted, however, that the bulkiness of injection (20 cc. of the oil solution) stands in the way of

[1] Archives Internat. de Pharmacodyn. et de Thérapie, xviii, 327.
[2] This Journal, vol. i, p. 231
[3] Jour. Amer. Med. Assoc., 1910, vol. liv, p. 344.

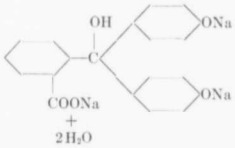
its general adoption, although it does not detract from its efficiency when a subcutaneous laxative is needed.

Through the kindness of Drs. Kober and Marshall of the Research Laboratory of the Roosevelt Hospital, New York, we have lately had the opportunity of investigating the pharmacological properties of potassium phenolphthalate and sodium phenolphthalate. These are the tribasic colorless salts of phenolphthalic acid which have been prepared for the first time by Kober and Marshall.

Potassium phenolphthalate is a light yellowish brown crystalline salt, which turns pink on being exposed to the air for a few hours.



Sodium phenolphthalate is a pinkish yellow crystalline salt, which rapidly becomes strongly pink and finally red on exposure to the air.



Both of these salts readily go into solution in water giving only a faint red color to the solution which has, however, an exceedingly strong alkaline reaction. It became necessary, therefore, to neutralize this solution prior to its subcutaneous administration.

The solution for injection of either of these salts is prepared as follows: To 1 or 2 gm. of the salt in a sterile glass bowl are added 1, 2, or 5 cc. of distilled sterile water, the amount added depending on the dilution desired. The salt readily dissolves, yield-

ing a clear pink or red solution which is strongly alkaline in reaction. To this is added dilute acetic acid[1] (25 per cent) drop by drop; the solution effervesces and becomes deep red in color. The acid it added carefully until the red color entirely disappears, leaving a clear slightly yellow transparent solution which is neutral or even slightly acid to litmus. It is then immediately taken up in a sterile syringe and injected subcutaneously.

By this method a gram of either salt may be obtained in solution in as small a quantity as 1 cc. of fluid. In most of our experiments we prepared the solutions so that 2 gm. would be contained in 5 cc.

This solution must be injected immediately, for if allowed to stand it becomes gradually and progressively alkaline in reaction, so that within one hour it has again taken on a decided red color and a white precipitate has formed. It cannot be heated, for the colorless neutral solution is decomposed even by gentle warming, resulting in an intensely red solution which is strongly alkaline in reaction.

When a dilute solution is desired, water must be added prior to neutralization, or else a weaker solution of acetic acid employed The addition of even a drop of water to the neutral solution causes a white precipitate to be thrown out, which is re-dissolved upon shaking, but if larger amount are added the precipitate is thrown out and is only dissolved in a great excess of water.

Experiments were made to see if these phenolphthalates possess purgative properties. The neutral solution above described was injected into dogs which were kept in separate metabolism cages and whose diet and water had been carefully controlled and the condition of whose stools was known. Only such dogs whose stools were well formed, were hard, dry and friable, were used. The skin was shaved in spots and the drug injected under aseptic conditions and with antiseptic precautions.

The data relating to these experiments are given in Table I.

[1] Acetic acid must be used in this connection as the addition of any of the mineral acids gives a copious white precipitate immediately upon the neutral point being reached.

At first it appeared that no local irritant effect[5] accompanied the subcutaneous administration of these preparations, but in about half of the experiments evidence of local irritant effects did appear, sometimes only as a slight indurated nodule appearing within a week or two after the injection, again as an infiltration involving a considerable area and appearing within two or three days. Undoubtedly these preparations[6] are irritant locally.

These substances are of little or no value as subcutaneous purgatives and do not compare at all favorably with phenolphthalein itself or its tetrachlor derivative. Table II indicates the comparative values as purgatives of phenolphthalein, its tetrachlor derivative and di-sodium phenolphthalein, the data incorporated being obtained from the protocols of dogs, each of which under identical conditions received 0.2 gm. pro kilo of body weight of one or other of these substances.

TABLE I

DRUG AND DOSE	WEIGHT OF DOG IN KG.	DATE	PURGATION	DRUG IN STOOL	DRUG IN URINE	REMARKS
1 gm. potassium phenolphthalate	5.8	11-28				
		11-29	−	−	+	Marked infiltration occurred necessitating several incisions two weeks later.
		11-30	+	+		
		12-1	−	+ trace		
		12-2	−	−		
1 gm. potassium phenolphthalate	7	11-28				
		11-29	+	−		
		11-30	+	+	+	
		12-1	+	−	+	
		12-2	+ very slight	−		
1 gm. potassium phenolphthalate	7	11-30				
		12-1	no feces		+	Slight infiltration occurred at point of injection—a small hard nodule.
		12-2	+	+	+	
		12-3	−		+ trace	
		12-4	−		+	

[5] At this date our results appeared most favorable and we so wrote to Kober and Marshall who unfortunately incorporated this information in their publication.

[6] The addition of acetic acid for purposes of neutralization results in a hypertonic solution of sodium acetate which in itself may be somewhat irritating. Five cc. solution of sodium acetate of equivalent strength however, was injected under the skin in three dogs, but neither inflammation nor sterile infiltration appeared in any instance.

TABLE I (Continued)

DRUG AND DOSE	WEIGHT OF DOG IN KG.	DATE	PURGATION	DRUG IN STOOL	DRUG IN URINE	REMARKS
1 gm. sodium phenolphthalate	7	12-14				
		12-15	+	+	+	
		12-16	+	+	+	
		12-17	+ slight			
		12-18	−			
		12-19	−			
1.5 gm. sodium phenolphthalate	9.7	12-14				
		12-15	+ slight	+	+	
		12-16	−	+	+	
		12-17	−			
		12-18	no feces			
2 gms. sodium phenolphthalate	9.5	12-16				Considerable pain at time of injection. Slight local infiltration.
		12-17	+?very slight	+		
		12-18	+ very slight	+	−	
1.5 gm. sodium phenolphthalate	9.7	1- 7				
		1- 8	no feces		+	
		1- 9	−	−	+	Pain at time of injection. Neck somewhat infiltrated. 1-17-11.
		1-10	+ slight	+	+	
		1-11	−	+ trace		
		1-12	−	+	+ trace	
		1-13	−	−	−	
1.6 gm. sodium phenolphthalate	7	1-9			+	
		1-10	+ slight	+	+	
		1-11	−	+	+	
		1-12	−	−	+	
		1-13	+ slight	+ trace	+ mere trace	
		1-14		−	−	
1.8 gm. sodium phenolphthalate	7	1-10				
		1-11	+ slight	+	+	
		1-12	−	+	+	Some slight infiltration locally at point of injection.
		1-13	+ ? slight	−		
		1-14	+ slight	−	+	
		1-15	−	−	+	
2 gms. sodium phenolphthalate	9.5	1-13				
		1-14	no feces		+	
		1-15	+ slight	+	+	Some slight infiltration at point of injection.
		1-16	+ slight	+	+	
		1-17	−	−	−	

TABLE II

DRUG	WEIGHT IN KG.	DATE	PURGATION	DRUG IN STOOL	DRUG IN URINE	REMARKS
Sodium phenolphtalate 1.94 gm. made up to 5 cc.	9.7	2-7				Only on one day 2-13 was there any suggestion of a laxative effect.
		2-8	–	–	+	
		2-9	–	–	+	
		2-10	–	+	+	
		2-11	–	+		
		2-12	–	+		
		2-13	–	–	–	
Disodium salt of phenolphthalein 1.9 gm. in 60 cc.	9.5	2-7				For three days the stools were unformed and very soft and homogeneous in consistence No local irritation.
		2-8	+ slight	+	+	
		2-9	+	+	+	
		2-10	+	+	+	
		2-11	+	+	+	
		2-12	+	+	+	
		2-13	+ slight	–	+ slight amount	
		2-14	+ slight	–	–	
		2-15	–	–	–	
Disodium salt of phenolphthalein 1.94 gm. in 90 cc.	9.7	2-18				Soft fluctuating swelling on the side 2-19. This partially disappeared in a few days. A definite infiltration present in same area on March 1. Still a trace of drug in stools on March 1.
		2-19	no feces		+	
		2-20	+ slight	+	+	
		2-21	+	+	+	
		2-22	–	+	+	
		2-23	+	+	+	
		2-24	+	+		
		2-25	no feces		–	
Phenoltetrachlorphthalein 1.48 gm. in 90 cc. olive oil	7.4	2-11				Trace of drug in urine but these were not catheter specimens. Stools were formed but soft in consistence and dark in color during most of this period.
		2-12	–	–		
		2-13	+	+	trace	
		2-14	+	+	trace	
		2-15	+ ? slight	+	–	
		2-16	+	+	–	
		2-17	+	+	–	
		2-18	–	+	–	
		2-19	+ slight	+ trace		
		2-20	–	–	–	
Phenoltetrachlorphthalein 1.9 gm. in 120 cc. olive oil.	9.5	2-21				Stools fairly formed except on 2-25. Trace of drug in urine—not catheter sample.
		2-22	+ slight	+	trace	
		2-23	+	+	–	
		2-24	no feces		–	
		2-25	+ semi fluid	+		
		2-26	–	+	–	
		2-27	+	+	trace	
		2-28	+	+	trace	
		3-1	–	trace		

In an earlier communication Abel and Rowntree[7] compared the relative purgative value of phenolphthalein and its tetrachlor derivative and demonstrated that the tetrachlor body exerted a more prolonged action when the two drugs were administered in olive oil in equal amounts pro kilo of body weight—the dose utilized being 23 mg. pro kilo. A study of Table II shows that this does not obtain when larger doses, 200 mg. pro kilo, are utilized, the tetrachlor derivative being administered in olive oil and the phenolphthalein as the disodium salt.

It was not our intention to publish these results except possibly in brief at a later date and only in relation to a further study of members of the phthalein family, but the results of our earlier observations prematurely alluded to in the recent publication by Kober and Marshall[8] has made it incumbent upon us to report in full the actual results obtained in the pharmacological study of these new salts of phenolphthalein.

[7] Loc. cit.

[8] Jour. Amer. Chem. Soc., 1911, vol. xxxiii, p. 59.