ABSORPTION OF DRUGS FROM THE RECTUM

BY

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The administration of drugs by the rectum has been practised from the earliest times. Prescriptions for suppositories were found in the Ebers Papyrus (Bryan, 1930). It would appear that these suppositories were intended for the local treatment of disease of the proctodeum. In more recent years, the idea arose that the rectal route could be used for systematic medication, either as supplementary to the oral route or as an alternative when medicine could not be given by mouth. Cullen appears to have been among the first to realize the wider possibilities of rectal medication (Thomson, 1827). In describing the treatment of tetanus, he wrote that large quantities of opium should be employed before deglutition becomes difficult, 'or that, if this opportunity be lost, the medicine, in sufficient quantity, and with due frequency, should be thrown into the body by clyster; which does not seem to have been hitherto often practised.'

In modern times, although hypodermic, intramuscular and intravenous injections afford a sure means of supplementing or supplanting the oral administration of medicine, the rectal route is still of value. Of the drugs given rectally, clinical evidence of absorption is conclusive in a number of instances, but many drugs which are given per rectum produce no easily recognized effects and clinical evidence of their absorption is equivocal. There are few controlled studies on the rate and completeness of absorption of rectally administered drugs. In the present study absorption of bromide, salicylate and sulphanilamide after rectal administration has been investigated.

Rectal absorption of potassium bromide

It has been stated frequently that bromide is absorbed when administered rectally, but it has

proved impossible to find any records of experimental work substantiating this opinion. It is probable that simple bromide salts are well absorbed, for the more complex substance, tribromethylalcohol (avertin), is definitely absorbed and now holds an established place in the realm of anaesthetics. Previous researches have shown that in the human subject two other halogen salts are well absorbed by the rectum. In an earlier paper (Mackenzie, 1943), Gompertz's (Carpenter, 1925) observation that chloride was well absorbed was confirmed, and Gompertz, Osborne (1922) and Cohn (1932) have shown that iodide is absorbed readily when given in solution.

The present investigation. A one-per-cent. solution of potassium bromide in water was given per rectum to five children. In each the enema was completely retained. The urine was collected for several days and analysed for bromide. The results are shown in table 1.

There was some variation from case to case in the quantities recovered, though the amount excreted in the urine never represented more than a small proportion of the total bromide given. From 7.1 to 11.3 per cent. was recovered in the forty-eight hours after the bromide was given. In 1908, Hales and Fishman gave single doses of sodium bromide by mouth to three students. The bromide excreted in the urine was estimated for several days thereafter. The results obtained by these workers are strikingly similar to these of the present investigation where the bromide was given per rectum. In one case when 1 gm. of sodium bromide was given, Hales and Fishman (1908) found that 8.29 per cent. appeared in the urine in forty-eight hours; in the other two, when 2 gm. of sodium bromide were given, 10.8 per cent. was recovered from one in forty-eight hours and in the second 11.3 per cent. was recovered in fifty-six hours.

The slow excretion of bromide was shown by

TABLE 1

THE EXCRETION OF BROMIDE IN THE URINE AFTER RECTAL ADMINISTRATION

Case	Age in years	KBr given (gm.)	Bromide excreted (as mgm. KBr)				
			Before enema	1st day	2nd day	Total for 48 hours	Per cent. recovered
E. H.	9	1	nil	43.0	28.3	71.3	7.1
S. D.	5	2	nil	80.2	116.2	196.4	9.8
J. R.	8	2	nil	58.3	104.0	162.3	8.1
M. C.	6	2	nil	133.3	45.8	179.1	8.9
E. L.	4	2	nil	95.2	132.0	227.2	11.3

Bill (1869) to be due to the fact that after absorption it displaces some of the chloride of the body fluids. The bromide is only excreted when more chloride is absorbed. So it may be assumed that there is no material difference in the amounts excreted in the urine when the salt is given in solution per rectum from those when a similar dose is given by mouth.

Conclusion. Potassium bromide is absorbed as readily from the rectum as it is when given by the mouth.

Rectal absorption of sodium salicylate

The use of salicylates for the control of pain and temperature in acute rheumatic arthritis is well recognized. With the large doses now commonly employed, toxic manifestations and gastric disturbances have been observed frequently.

In an attempt to minimize these undesirable effects, Heyn (1912) gave sodium salicylate per rectum. He showed that the instillation of 120 to 240 grains of sodium salicylate in 6 oz. of starch water was followed by the relief of the joint pain and a fall in the temperature. Since these therapeutic effects were achieved by rectal salicylate, Heyn (1912) considered the rectal route preferable to the oral one, as thereby gastric disturbances were avoided. Irving (1923) reported similar experiences in children; employing a dosage of 1 to 3 grains per pound of body weight, he noted that older children occasionally complained of headache and tinnitus within fifteen to forty-five minutes of the instillation of the sodium salicylate. Recently Valesquez (1939) obtained satisfactory results with an isotonic solution of sodium salicylate (23.2 gm. per litre.) He has reaffirmed that, since gastric disturbances are thereby avoided, the rectal route is preferable to the oral one.

No controlled study has been reported on the rectal absorption of salicylate in the human subject. In 1933, Blume and Nohara compared the level of salicylate in the blood and the quantity excreted in the urine of rabbits after oral and rectal administration. A slightly higher blood salicylate content was found after rectal administration than when the drug

was given by mouth. Fifty to 80 per cent. of salicylate was recovered in the urine whatever the method of administration. They believed that absorption was more rapid when the drug was given per rectum than by the mouth, as the solution came immediately into contact with a large area of mucosa from which absorption could take place.

The present investigation. One gramme of sodium salicylate and 2.5 gm. of sodium bicarbonate dissolved in 200 c.c. of water were given rectally to ten children. Ten others were given the solution in the same quantities by mouth. The total excretion of salicylate in the urine voided in the thirty-six hours following the administration of the salicylate solution was estimated in each case. Salicylate given by mouth seems to be excreted for a variable time; Hanzlik et al. (1917) gave seventy-eight hours as a median for normal subjects. In the present series most of the salicylate was excreted in twenty-four hours: with two exceptions, only a trace of salicylate was found in the urine excreted from twenty-four to thirty-six hours after administration by mouth or by rectum. Results are given in tables 2 and 3.

The quantities of salicylate recovered in the urine varied considerably in both series. Where the solution was given by mouth, between 10.8 per cent. and 64.9 per cent. were recovered. On the other hand, when it was given per rectum, between 17 per cent. and 52.5 per cent. was recovered. The average recovery was approximately the same in each series, after oral administration 34.4 per cent. and after rectal administration 33.4 per cent.

Most workers agree that salicylate is incompletely excreted, a part being destroyed in the tissues. The amount excreted appears to vary under different conditions, and even under the same conditions there is some variation in the figures given by different workers. When it was given over a period of several days, Hanzlik and Wetzel (1919) found that the total salicylate excreted in the urine varied between 75 per cent. and 80 per cent. On the other hand, Morris and Graham (1931) found that over a period of six days, only 26.0 to 37.6 per cent. of the ingested salicylate was recovered in the urine, but when sodium bicarbonate was given along with the salicylate, the urinary excretion rose to 80 to 91.4 per cent. Apparently the fraction of salicylate

TABLE 2

RECOVERY OF SALICYLATE FROM THE URINE AFTER ORAL ADMINISTRATION OF 1 GM. SODIUM SALICYLATE

Case	Age in years	0-4 hr.		4-24 hr.		24-36 hr.		Total salicylate recovered per cent.
		Vol. c.c.	Sod. Sal. gm.	Vol. c.c.	Sod. Sal. gm.	Vol. c.c.	Sod. Sal. gm.	
D. McQ.	9	350	0.286	700	0.363	210	nil	64.9
M. McE.	8	250	0.106	400	0.156	300	nil	26.2
G. W.	5	400	0.034	300	0.208	900	nil	24.2
J. R.	10	480	0.106	860	0.327	960	nil	45.3
M. C.	6	300	0.131	500	0.040	550	nil	17.1
R. C.	6	300	0.200	100	0.006	500	nil	20.6
S. L.	12	225	trace	260	0.200	80	nil	20.0
H. P.	7	500	0.278	500	0.417	—	nil	69.5
J. R.	10	70	0.064	240	0.044	500	trace	10.8
H. McD.	9	210	0.200	2200	0.275	—	nil	47.5
Average		308.5	0.140	580	0.204			34.4

TABLE 3

RECOVERY OF SALICYLATE FROM THE URINE AFTER RECTAL ADMINISTRATION OF 1 GM. SODIUM SALICYLATE

Case	Age in years	0-4 hr.		4-24 hr.		24-36 hr.		Total salicylate recovered per cent.
		Vol. c.c.	Sod. Sal. gm.	Vol. c.c.	Sod. Sal. gm.	Vol. c.c.	Sod. Sal. gm.	
G. McL.	8	350	0.213	320	0.089	700	nil	30
	8	410	0.096	990	0.421	520	nil	52
J. C.	7	65	0.028	320	0.267	800	0.080	38
A. C.	6	70	0.015	400	0.240	120	nil	25.5
P. S.	5	80	0.027	200	0.159	110	trace	18.4
P. B.	9	325	0.030	700	0.495	250	trace	52.5
M. H.	8	85	0.014	250	0.131	180	0.100	24.5
J. B.	10	410	0.156	480	0.385	320	nil	54.1
H. S.	10	520	0.297	525	0.091	—	nil	39
A. M.	11	150	0.057	535	0.110	—	nil	17
J. B.	5	—	—	—	0.274	—	trace	27.4
Average		247	0.094	475	0.240			33.4

excreted in the urine is much smaller when single small doses are given. Devrient (1921) recovered only from 1.01 to 14.68 per cent. in the urine of patients who each had been given 1 gm. of sodium salicylate in a single dose.

A comparison of the results of the present investigation shows that there is no significant difference in the quantities of salicylate recovered in the urine after oral or rectal administration of sodium salicylate. Thus, it may be assumed that there is no difference in the degree of absorption when the drug is given in solution by either route. A comparison of the rate of excretion of salicylate given by the mouth with the rate when given by the rectum shows that excretion is more rapid after oral administration. The average amount excreted in four hours when the oral route was employed was 0.14 gm., while after rectal injection 0.094 gm. was excreted in the same time. This fact suggests that absorption may be slower when the drug is given per rectum. It is possible that diuresis may also be a factor in determining the rate of excretion. In comparing the two series, it was noticed that where a greater quantity of salicylate was excreted in the first four hours after the salicylate solution was given there was also a greater volume of urine excreted, but that diuresis was greater after the drug was given by the mouth than it was after it was given by the rectum.

Conclusions. Sodium salicylate is readily absorbed from a rectal infusion.

The quantities of salicylate which are excreted after single doses of sodium salicylate given either by mouth or by rectal infusion are variable. Much of the absorbed salicylate is apparently destroyed in the tissues.

Excretion is rapid after both oral and rectal administration, but it is more rapid when given by the mouth than by the rectum.

As a therapeutic measure salicylate enemata can,

if necessary, replace the oral administration of the drug.

Rectal absorption of sulphanilamide

In the administration of sulphanilamide by the mouth nausea and vomiting are frequent accompaniments and the employment of alternative methods may be necessary. Under such conditions, rectal administration as a practical alternative to the painful and sometimes irritating intramuscular injection suggests itself.

That rectal administration of sulphanilamide may be a procedure of practical importance is suggested by the work of Turell, Marino and Nerb (1940). These workers obtained a concentration of 9-15 mgm. per cent. total sulphanilamide in the blood after the rectal instillation of a 1 per cent. solution of the drug over periods of from twenty-four to sixty-five hours. When suppositories were used, the maximum concentration obtained in the blood was 6 mgm. per cent. Wood (1941) reported similar observations with a saturated solution of sulphanilamide. In one case, he obtained a blood sulphanilamide concentration of 12.5 mgm. per cent. after giving 250 grains of sulphanilamide per rectum.

The present investigation. The absorption of the drug when given by the mouth and by the rectum has been compared. The concentration of free sulphanilamide in the blood and the excretion of total sulphanilamide in the urine have been estimated after giving the drug by the mouth in solution and by the rectum when given in solution and in the form of suppositories.

One gramme of sulphanilamide dissolved in 200 c.c. of water was given by mouth to each of ten children. The free sulphanilamide content of specimens of capillary blood taken at one, two, three and five hours after the drug had been given was determined. The total sulphanilamide was estimated in the urine collected for thirty-six hours. A second group of ten children each received 1 gm. of sulphanilamide in 200 c.c. of water per rectum and a third group two suppositories, each containing

0.5 gm. sulphanilamide: specimens of blood and urine were collected and the sulphanilamide content estimated in each case. The results are shown in tables 4, 5 and 6.

Where the sulphanilamide solution was given by mouth, the levels of free sulphanilamide in the blood, after rising to a maximum at one hour, showed a progressive fall, though at five hours there were still considerable quantities of free sulphanilamide in the blood. The recovery in the urine was incomplete, the quantities recovered varying from 76.8 per cent. to 25 per cent. of the amount ingested (average 50.1 per cent.).

Following the rectal infusion of the sulphanilamide solution, the free sulphanilamide content of the blood rose, in some cases, to between 3 and 4 mgm. per cent. The curve was, however, of a different shape, the peak being reached at between two and three hours after the sulphanilamide was given. In all but one case, there was still considerable free sulphanilamide present in the blood at the

end of five hours. The amount recovered from the urine varied from 20.9 to 52.5 per cent. with an average of 42.9 per cent.

Following the administration of the suppositories, in only two cases was there sufficient free sulphanilamide present in the blood in the ensuing five hours for an accurate quantitative estimation to be made. The average amount recovered in the urine was little more than half of that recovered when the drug was given in solution by the rectum (24.5 per cent.).

From a study of the first group, it is evident that both absorption and excretion are rapid when sulphanilamide is given in solution by mouth. The average figure for recovery of total sulphanilamide is similar to that obtained by Scudi and Ratish (1938) in three adult cases. In their investigation the drug continued to be excreted in the urine for fifty hours. In this study upon children, the drug

TABLE 4

ABSORPTION AND EXCRETION OF SULPHANILAMIDE AFTER ORAL ADMINISTRATION OF 1 GM SULPHANILAMIDE

Case	Age in years	Blood Free sulphanilamide mgm. per cent.				Urine Total sulphanilamide	
		1 hr.	2 hr.	3 hr.	5 hr.	Mgm.	Per cent. recovered
G. W.	5	7.0	5.0	5.3	4.6	768	76.8
M. L.	7	—	4.7	4.4	3.7	744	74.4
J. L.	7	5.0	5.0	4.7	3.8	694	69.4
A. R.	9	5.3	4.0	3.0	2.8	500	50.0
J. D.	11	3.2	—	—	—	556	55.6
C. D.	8	5.0	4.0	3.2	2.0	315	31.5
J. L.	8	6.1	4.4	3.8	2.9	250	25.0
E. K.	5	5.7	5.0	4.4	3.6	323	32.3
M. McC.	7	6.3	5.4	4.7	4.0	384	38.4
M. Q.	12	5.3	3.6	3.0	2.9	500	50.0
Mean values		5.4	4.5	4.1	3.4	501	50.1

TABLE 5

ABSORPTION AND EXCRETION OF SULPHANILAMIDE AFTER 1 GM. SULPHANILAMIDE IN 200 C.C. WATER PER RECTUM

Case	Age in years	Blood Free sulphanilamide mgm. per cent.				Urine Total sulphanilamide	
		1 hr.	2 hr.	3 hr.	5 hr.	Mgm.	Per cent. recovered
M. McE.	8	2.2	2.8	3.6	4.2	277	27.7
A. C.	6	2.8	3.9	3.6	2.9	500	50.0
A. B.	12	3.1	3.4	2.5	2.6	209	20.9
G. W.	5	3.2	3.1	3.6	2.2	625	62.5
M. L.	7	2.1	2.9	3.9	3.1	591	59.1
J. L.	7	1.9	2.7	3.1	3.0	236	23.6
A. R.	9	2.5	3.0	2.7	2.5	515	51.5
J. L.	8	1.5	2.0	1.9	1.7	454	45.4
E. K.	5	2.0	2.8	2.2	F. tr.	250	25.0
R. S.	8	2.5	2.7	2.9	2.3	528	52.8
Mean values		2.4	2.9	3.0	2.7	429	42.9

TABLE 6

ABSORPTION AND EXCRETION OF SULPHANILAMIDE AFTER TWO 0.5 GM. SULPHANILAMIDE SUPPOSITORIES

Case	Age in years	Blood Free sulphanilamide mgm. per cent.				Urine Total sulphanilamide	
		1 hr.	2 hr.	3 hr.	5 hr.	Mgm.	Per cent. recovered
G. W.	5	F. Tr.	1.3	1.6	2.0	526	52.6
M. McC.	7	F. tr.	F. tr.	F. tr.	F. tr.	181	18.1
C. R.	9	nil	F. tr.	Tr.	Tr.	111	11.1
J. L.	8	Tr.	Tr.	Tr.	Tr.	95	9.5
A. McD.	8	F. tr.	Tr.	Tr.	—	238	23.8
M. H.	8	F. tr.	Tr.	Tr.	Tr.	357	35.7
M. C.	10	F. tr.	Tr.	Tr.	2.1	436	43.6
E. M.	10	F. tr.	Tr.	Tr.	Tr.	156	15.6
M. S.	11	F. tr.	Tr.	Tr.	Tr.	109	10.9
M. L.	7	F. tr.	Tr.	Tr.	Tr.	157	15.7
Average						245	24.5

could no longer be recovered from the urine after thirty-six hours.

The figures obtained from estimations of sulphanilamide in the blood and in the urine after the rectal injection of a sulphanilamide solution indicate that it is readily absorbed from the enema. A comparison of the composite blood sulphanilamide curves obtained after the oral and the rectal administration of the drug shows that absorption by the rectal route is definitely slower than when it is given by mouth. The fact that smaller quantities of sulphanilamide are recovered in the urine after rectal administration suggests that absorption may not be as complete as when it is given by mouth.

The failure to find more than traces of free sulphanilamide in the blood after the administration of suppositories shows that absorption is much slower when the drug is given rectally in a solid form; for absorption to take place, solution is necessary. In the hind gut, one of the principal functions is the absorption of water, and under normal conditions the contents of the rectum are relatively dry. Unless fluid is supplied, solution and absorption must be slow. That absorption of sulphanilamide from suppositories is less efficient is shown by the small amount recovered in the urine.

In treatment with this drug it is justly held that it is important to attain a high concentration in the blood as soon as possible. The foregoing results suggest that of the methods studied, oral administration attains this object most effectively. In addition to this, estimation of urinary excretion suggests that absorption when the drug is given by the rectum is not as complete as it is when given by the mouth. In the main it appears that oral administration is the method of choice, but on occasion rectal administration of the drug may find a place. Larger

doses should be given when the rectal route is used. The use of suppositories appears to be of little value.

Conclusions. Sulphanilamide, given in solution by mouth, is absorbed with great rapidity. Apparently it is excreted more rapidly in children than in adults.

Sulphanilamide is readily absorbed from the rectum when given in solution, but more slowly and less completely than when given by the mouth. The drug is poorly absorbed from suppositories.

The administration of sulphanilamide in solution per rectum may be of considerable value, especially when there is intolerance to the drug given by the mouth.

General summary

1. The absorption of potassium bromide, sodium salicylate and sulphanilamide given per rectum has been studied.

2. It has been shown that when given in solution, all these substances are readily absorbed from the rectum. Absorption from sulphanilamide suppositories is poor.

3. Rectal absorption of sulphanilamide is slower than when the drug is given orally.

Biochemical methods. The bromide content of the urine was estimated by the method of Behr, Palmer and Clarke (1930). Salicylate was determined by the method of Thoburn and Hanzlik (1915). The free and total sulphanilamide was determined by the method of Bratton and Marshall (1939).

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