SULFAPYRIDINE AND VOMITING

An Experimental Study of the Mechanism in the Dog*

JOSEPH F. SADUSK JR., JOHN W. HIRSHFELD, AND ANNE SEYMOUR

It is generally conceded that nausea with vomiting is the most common toxic manifestation of sulfapyridine therapy and may appear in approximately 60 to 70 per cent of cases treated with the drug. Occasionally the vomiting is so severe as to make necessary the cessation of therapy.

Explanations proposed for the mechanism of this vomiting fall into two groups, namely, a local effect upon the gastro-intestinal tract and a central effect upon the vomiting center. The latter view is supported by the work of Marshall and Long,[5] who have observed that vomiting is produced both in dogs and man when sodium sulfapyridine is given intravenously. That this explanation may not be entirely correct, however, has been suggested by Haviland and Blake,[8] who found that the sulfapyridine concentration in vomitus of patients receiving sulfapyridine by a parenteral route only may be considerably higher than that in the blood.

In addition, we have observed that sulfapyridine is excreted into the stomach of the dog with surprising rapidity following the intravenous injection of sodium sulfapyridine. In Table 1 are summarized the results of ten experiments in which a 5 per cent solution of sodium sulfapyridine was injected intravenously into dogs until vomiting was produced. As soon as possible after the act of vomiting, a specimen of blood was taken from the dog. In both this and the vomitus the concentration of non-acetylated sulfapyridine was determined by the method of Marshall and Litchfield.[4] The time at which emesis occurred after beginning the injection of sulfapyridine is also recorded. The results show that within 4 to 52 minutes after beginning the injection of the drug, sulfapyridine was frequently present in the vomitus in a concentration nearly as high as

* From the Departments of Internal Medicine and of Surgery, Yale University School of Medicine. The expense of this study was defrayed by the Clinical Research and Teaching Fund of the Yale University School of Medicine. The material of this paper was presented in abstract form before the American Society for Clinical Investigation in May, 1940.

TABLE 1

THE RAPID EXCRETION OF SULFAPYRIDINE INTO THE STOMACH AFTER INTRAVENOUS ADMINISTRATION OF SODIUM SULFAPYRIDINE TO DOGS

Dog No.	*Weight kg.*	*Time after beginning injection of sod. sulfapyridine minutes*	*5% sodium sulfapyridine injected cc.*	*Sulfapyridine conc. Blood mg. %*	*Vomitus mg. %*
7	12.1	38	65.0	23.0	21.5
8	10.3	44	60.0	23.0	3.4
10	6.5	13	35.0	26.5	24.0
10	6.5	8	30.0	21.5	3.0
11	19.0	4	45.0	17.0	9.5
12	11.2	31	70.0	21.5	23.0
15	17.4	52	110.0	29.0	23.5
16	6.4	9	35.0	32.0	24.0
18	8.8	24	60.0	30.0	24.4
19	12.4	13	65.0	32.0	11.2

that in the blood. These observations, then, would leave open the question as to whether the excretion of sulfapyridine into the gastric juice might not play some part in the mechanism of nausea and vomiting.

We have, therefore, systematically studied the problem in the dog, which is an excellent animal to use in an experimental study of this nature, since it exhibits definite signs of nausea, as evidenced by salivation, licking, chewing, and apprehension, and vomits readily and with satisfactory consistency under treatment with sulfapyridine. Experiments dealing with (1) the relation between blood concentration of sulfapyridine and emesis in normal dogs, (2) the effect of total gastrectomy and complete gastro-intestinal evisceration on the emetic action of sulfapyridine, and (3) the response of the vomiting center to the direct application of sulfapyridine, are recorded in this paper.

In these studies dogs were selected which consistently vomited when given sulfapyridine, since one may occasionally find dogs in which the emetic action of the drugs is absent or not manifest until toxic cerebral symptoms are produced.

Experimental

Relation of blood concentration of sulfapyridine to emesis in dogs

In order to establish the range of blood concentration of sulfapyridine within which intact dogs vomit, experiments were carried

out in which a 5 per cent solution of sodium sulfapyridine* was injected intravenously in increments of from 5 to 20 cc. (depending upon the size of the dog) and at intervals of from 3 to 10 minutes. A typical experiment is illustrated in the following protocol.

Protocol 1. Intravenous injection of 5% sodium sulfapyridine in a normal dog.

Dog No. 1, female, mongrel terrier, weight 8.5 kg.

January 9:

2:46 P. M.—5.0 cc. of 5% sodium sulfapyridine solution intravenously.
2:51 P. M.—5.0 cc. of 5% sodium sulfapyridine solution intravenously.
2:55 P. M.—Sulfapyridine blood concentration 6.8 mg.%.
2:56 P. M.—5.0 cc. of 5% sodium sulfapyridine solution intravenously.
3:01 P. M.—5.0 cc. of 5% sodium sulfapyridine solution intravenously.
3:05 P. M.—Sulfapyridine blood concentration 15.8 mg.%.
3:06 P. M.—5.0 cc. of 5% sodium sulfapyridine solution intravenously.
3:11 P. M.—5.0 cc. of 5% sodium sulfapyridine solution intravenously.
3:16 P. M.—Sulfapyridine blood concentration 22.8 mg.%.
3:17 P. M.—5.0 cc. of 5% sodium sulfapyridine solution intravenously.
3:21 P. M.—5.0 cc. of 5% sodium sulfapyridine solution intravenously.
3:22 P. M.—Slight licking, apprehensive.
3:24 P. M.—Moderate licking, followed shortly after by an abdominal contraction.
3:26 P. M.—Sulfapyridine blood concentration 28.8 mg.%.
3:27 P. M.—5.0 cc. of 5% sodium sulfapyridine solution intravenously.
3:29 P. M.—Vomited.
3:31 P. M.—Sulfapyridine blood concentration 30.6 mg.%.
3:34 P. M.—Vomited again.

In Table 2 are summarized the results of 29 such experiments upon 16 normal and intact dogs. Of these 16 dogs, 13 vomited at a sulfapyridine concentration in the blood of from 17 to 36.5 mg. per cent. The remaining three dogs, Nos. 13, 14, and 17, did not vomit before symptoms of central nervous system intoxication became evident, at which time the injections were terminated. The sulfapyridine blood concentration in these three dogs ranged from 33 to 41 mg. per cent at this time.

Of the 13 dogs that vomited, two (Nos. 6 and 20), in the initial test, failed to vomit prior to the onset of convulsions but did vomit in subsequent experiments before intoxication of the central nervous

* The sodium sulfapyridine used in this investigation was supplied by Merck & Co., Inc., through the courtesy of Dr. D. F. Robertson.

TABLE 2

RELATION OF SULFAPYRIDINE CONCENTRATION IN THE BLOOD TO VOMITING IN DOGS FOLLOWING THE INTRAVENOUS ADMINISTRATION OF SODIUM SULFAPYRIDINE

Dog No.	*Weight kg.*	*5% Sod. sulfapyridine injected cc.*	*Sulfapyridine conc. in blood* mg. %*	*Emesis*
1	8.5	40.0	29.6	+
1	8.5	35.0	25.8**	+
1	8.5	45.0	30.6	+
1	8.5	45.0	29.5***	+
5	11.0	45.0	21.5	+
6	9.1	70.0†	30.0	—
6	9.1	75.0	33.0	+
7	12.1	65.0	23.0	+
8	10.3	60.0	23.0	+
10	6.5	35.0	26.5	+
10	6.5	30.0	21.5	+
11	19.0	45.0	17.0	+
12	11.2	70.0	21.5	+
13	6.5	35.0†	33.0	—
14	6.6	55.0†		—
14	6.6	55.0†	41.0	—
15	17.4	110.0	29.0	+
15	17.4	120.0	29.0	+
16	6.4	35.0	36.5	+
16	6.4	35.0	32.0	+
16	6.4	30.0	30.0	+
17	4.0	35.0†	37.0	—
17	4.0	35.0†	40.0	—
18	8.8	60.0	30.0	+
18	8.8	40.0	20.5	+
19	12.4	65.0	32.0	+
20	3.8	40.0†	29.0	—
20	3.8	30.0	18.0	+
20	3.8	25.0	23.0	+

* Blood sample taken either at time of emesis or at onset of convulsions if vomiting did not occur.

** 100 cc. of 20 mg. % sulfapyridine put into stomach by tube before starting experiment.

*** Suspension of 1.0 gm. sulfapyridine in 100 cc. of water put into stomach by tube before starting experiment.

† Convulsions, experiment terminated.

system became manifest. It should be mentioned, perhaps, that both these dogs and the other three which failed to vomit, appeared to be of nervous temperament and rather high-strung.

Experiments carried out on one dog (No. 1) revealed that the onset of vomiting and its relation to blood concentration of sulfapyridine was not materially changed by the prior instillation into the stomach of a solution or suspension containing up to as much as 1 per cent of sulfapyridine in water. These experiments are presented in Table 2.

Experiments on gastrectomized and eviscerated dogs

In order to exclude the possible local effect of sulfapyridine on the stomach as part of the mechanism involved in the vomiting caused by this drug, five similar experiments were carried out on three gastrectomized dogs.

These dogs were subjected to total gastrectomy, and, 3 to 12 weeks later, intravenous injection of sodium sulfapyridine was carried out by the same procedure as that used in the normal dogs. All three dogs vomited within the range of blood concentrations found to cause emesis in normal dogs. The data are shown in Table 3. The protocol of a representative experiment follows:

Protocol 2. Intravenous injection of 5% sodium sulfapyridine in a gastrectomized dog.

Dog No. 2, female, mongrel beagle, weight 11.0 kg. (prior to operation).
October 27:
Total gastrectomy under intravenous nembutal anesthesia.
December 18:
1:50 P. M.—10.0 cc. of 5% sodium sulfapyridine solution intravenously.
1:52 P. M.—Sulfapyridine blood concentration 2.8 mg.%.
1:55 P. M.—5.0 cc. of 5% sodium sulfapyridine solution intravenously.
1:58 P. M.—Sulfapyridine blood concentration 10.5 mg.%.
2:03 P. M.—5.0 cc. of 5% sodium sulfapyridine solution intravenously.
2:15 P. M.—Sulfapyridine blood concentration 19.3 mg.%.
2:15 P. M.—5.0 cc. of sodium sulfapyridine solution intravenously.
2:19 P. M.—Moderate licking and salivation. Sulfapyridine blood concentration 25.6 mg.%.
2:20 P. M.—5.0 cc. of sodium sulfapyridine solution injected intravenously, followed by marked licking, salivation, yawning, and apprehension.
2:25 P. M.—5.0 cc. of sodium sulfapyridine solution intravenously.
2:26 P. M.—Dog presented typical actions of vomiting, producing 5 to 10 cc. of yellow mucus, which contained no sulfapyridine on analysis.
2:30 P. M.—Actions of vomiting repeated. Sulfapyridine blood concentration 34.0 mg.%.

Further experiments of this type, of necessity acute, were performed in five dogs following removal of the entire gastro-intestinal tract. The operative technic in general was that described by Eggleston and Hatcher.[1] In this procedure the entire stomach, large and small intestine, spleen, and most of the pancreas were removed.

TABLE 3

VOMITING IN DOGS GIVEN SODIUM SULFAPYRIDINE INTRAVENOUSLY FOLLOWING TOTAL GASTRECTOMY

Dog No.	*Weight of dog* kg.*	*5% Sod. sulfapyridine injected cc.*	*Emesis*	*Sulfapyridine conc. in blood at emesis mg. %*
2	11.0	30.0	+	22.4
2	11.0	35.0	+	34.0
2	11.0	31.0	+	23.1
3	9.3	40.0	+	29.6
4	10.8	40.0	+	24.3

* Weight of dogs prior to gastrectomy, following which they lost considerable weight.

Chloroform was employed as the anesthetic. Results essentially similar to those recorded above were obtained (Table 4). The protocol of a typical experiment is outlined below.

Protocol 3. Intravenous injection of 5% sodium sulfapyridine in an eviscerated dog.

Dog No. 19, female, white spitz, weight 12.4 kg.

April 22:

1:38–1:51 P. M.: Dog vomited at sulfapyridine blood concentration of 32.0 mg.%, following the intravenous injection of a total of 65.0 cc. of 5% sodium sulfapyridine.

April 24:

1:47–2:28 P. M.: Under light chloroform anesthesia, the gastro-intestinal tract from rectum to esophagus, including the spleen, and the greater part of the pancreas, was removed.

2:38 P. M.—Dog walking about.

2:42 P. M.—20.0 cc. of 5% sodium sulfapyridine solution intravenously.

2:45 P. M.—20.0 cc. of 5% sodium sulfapyridine solution intravenously.

2:48 P. M.—10.0 cc. of 5% sodium sulfapyridine solution intravenously.

2:50 P. M.—Dog apprehensive, licking, retched.

2:51 P. M.—10.0 cc. of 5% sodium sulfapyridine solution intravenously.

2:54 P. M.—Dog apprehensive, licking, retched.

2:56 P. M.—10.0 cc. of 5% sodium sulfapyridine solution intravenously.

2:58½ P. M.—Vomiting movements.

2:59 P. M.—Sulfapyridine blood level 21.5 mg.%. Animal sacrificed.

In these experiments, two of the five dogs did not vomit. One dog (No. 12) fell into shock during operation and remained so depressed after operation that failure to vomit is not surprising. The

TABLE 4

VOMITING IN DOGS GIVEN SODIUM SULFAPYRIDINE INTRAVENOUSLY FOLLOWING TOTAL REMOVAL OF GASTRO-INTESTINAL TRACT

Dog No.	Wt. of dog kg.	Before evisceration			After evisceration		
		5% Sod. sulfapyridine injected cc.	Emesis	Sulfapyridine conc. in blood mg. %	5% Sod. sulfapyridine injected cc.	Emesis	Sulfapyridine conc. in blood mg. %
5	11.0	45.0	+	21.5	40.0	+	23.0
9	18.5	(a)	(a)	(a)	140.0	—	51.0*
12	11.2	70.0	+	21.5	95.0	—†	40.0*
15	17.4	110.0	+	29.0	100.0	+	31.5
19	12.4	65.0	+	32.0	70.0	+	21.5

(a) Not tested for vomiting before evisceration.
* Blood sample taken after end of intravenous injection, at which time there were generalized convulsions.
† Dog in shock during the experiment and very depressed.

other dog (No. 9) had not been tested for vomiting with sulfapyridine before operation and it seems possible that it would fall into the small group of dogs that fail to vomit with the drug prior to the onset of convulsions. It may also be observed that there is no essential difference in the blood concentration of sulfapyridine at the time of emesis in the dogs either prior to or after evisceration.

Results of these experiments, then, would certainly indicate that vomiting caused by sulfapyridine is not dependent upon the presence of sulfapyridine in the gastro-intestinal tract, whether ingested or excreted into the stomach.

Experiments on the vomiting center

A study of the possible direct action of sulfapyridine upon the vomiting center was then undertaken. In 1891 Thumas[6] described an area situated in the floor of the fourth ventricle in the region of the dorsal nucleus of the vagus nerve which he called the vomiting center. More specifically, this is a physiological area in the midline of the floor of the fourth ventricle measuring about 5 mm. in length and 2 mm. in width and extending to a point about 2 mm. posterior to the calamus scriptorius. He found that destruction of this area caused inhibition of vomiting and that the local application of minute quantities of apomorphine to this point caused prompt emesis in dogs. This center may be exposed with moderate difficulty in the

living dog in a two-stage operation as originally described by Hatcher and Weiss.[2]

Our procedure was, briefly, as follows: A dog of suitable size and disposition was trained for several weeks to lie quietly in the prone position with head extended between the fore legs. Under sterile precautions and deep nembutal anesthesia, an incision in the midline was made extending from the nuchal crest to the level of the third cervical vertebra and carried down to the skull. Following initial trephine, the bone over the inferior portion of the cerebellum was now rongeured away so that an opening of from 1.5 to 2 cm. was made. The wound was then closed with interrupted silk sutures, taking special precautions to secure perfect hemostasis.

Twenty-four hours later with the dog in prone position, the wound was opened, under local novocaine anesthesia, exposing the dura. This and the arachnoid were opened exposing the cerebellum which could be gently lifted up, thus bringing into view the floor of the fourth ventricle.

Various concentrations of sulfapyridine in normal saline, ranging from 10 to 100 mg. per cent, were now dropped in turn from a micro-pipette on to the vomiting center. Following this, solutions of apomorphine in normal saline, beginning with a concentration as low as 0.0001 mg. of apomorphine per 1.0 cc. of solution were applied to the vomiting center in a similar manner. When emesis had been produced, the operative wound was closed and sodium sulfapyridine was then administered intravenously to the point of vomiting.

The protocol of a typical experiment is given below:

Protocol 4. Direct application of sulfapyridine to the vomiting center. Dog No. 7, female, white spitz, weight 12.1 kg.

March 6:

2:26–3:04 P. M.—Dog vomited at sulfapyridine blood concentration of 23.0 mg.%, following the intravenous administration of 65.0 cc. of 5% sodium sulfapyridine.

March 11:

3:00 P. M.—Under intravenous nembutal anesthesia, trephine of skull with exposure of the dura. Wound sutured.

March 12:

1:35–2:14 P. M.—Under local infiltration novocaine anesthesia, the floor of the fourth ventricle was exposed.

2:15 P. M.—Vomiting center mechanically stimulated with a foreign object. Dog vomited.

2:18 P. M.—Saline washed over vomiting center. No effect.
2:20 P. M.—10 mg.% sulfapyridine applied. Repeated. No effect.
2:26 P. M.—30 mg.% sulfapyridine applied. Repeated. No effect.
2:33 P. M.—50 mg.% sulfapyridine applied. Repeated. No effect.
2:37 P. M.—100 mg.% sulfapyridine applied. Repeated. No effect.
2:45 P. M.—0.00005 mg. (0.5 cc. solution) apomorphine applied.
2:47 P. M.—0.00004 mg. (0.4 cc. solution) apomorphine applied.
2:51 P. M.—Dog retched.
2:51 P. M.—0.0002 mg. (0.2 cc. solution) apomorphine applied.
2:52 P. M.—0.0003 mg. (0.3 cc. solution) apomorphine applied.
2:52½ P. M.—Dog vomited vigorously.
2:55 P. M.—Operative wound closed.
3:50–4:17 P. M.—Intravenous injection of 60.0 cc. of 5% sodium sulfapyridine solution. Dog vomited at 4:18 P. M., sulfapyridine blood level 30.0 mg.%.

The results of three such experiments are summarized in Table 5. It may be observed that none of these dogs vomited with the local application of sulfapyridine. Two of the dogs vomited following the local application of apomorphine in quantities of 0.0005 (0.0002 and 0.0003) and 0.007 mg., respectively. The failure of the remaining dog to vomit we believe to be due to a web of fibrin over the medulla which was impossible to remove. All three dogs vomited promptly upon the intravenous administration of sodium sulfapyridine.

These experiments would suggest that sulfapyridine vomiting is not due to a direct action upon the vomiting center. This statement, of course, assumes that sulfapyridine will penetrate to the vomiting center as rapidly as apomorphine, but direct proof of this is lacking.

Discussion

The present explanation is that the act of vomiting, in general, is dependent upon three factors: (1) coordinated actions of the muscles of the stomach, esophagus, and abdominal wall; (2) a center[6] in the medulla, which discharges impulses along efferent fibers in the phrenic, sympathetic, and cranial nerves; and (3) the stimulation of this vomiting center by afferent impulses arising in any of the viscera or even in other cerebral centers. This vomiting center may also be stimulated directly by certain agents, carried to it in the blood stream, such as apomorphine, emetine, and picrotoxin.

In regard to the mechanism of vomiting due specifically to sulfa-

TABLE 5

DIRECT APPLICATION OF SULFAPYRIDINE AND APOMORPHINE TO THE VOMITING CENTER

Dog No.	Wt. kg.	Injection of 5% Sod. sulfapyridine solution intravenously prior to exp. on vomiting center*			Application to vomiting center				Injection of 5% Sod. sulfapyridine solution intravenously immediately following exp. on vomiting center		
					Sulfapyridine		Apomorphine				
		Volume injected cc.	Emesis	Blood conc. mg. %	Highest conc. mg. %	Emesis	Amount mg.	Emesis	Volume injected cc.	Emesis	Blood conc. mg. %
7	12.1	65.0	+	23.0	100	—	0.0005	+	60.0	+	30.0
8	10.3	60.0	+	23.0	100	—	0.04	—†	50.0	+	34.0
10	6.5	35.0	+	26.5	100	—	0.007	+	45.0	+‡	37.5
		30.0	+	21.5							

* Experiment carried out at least 72 hours prior to the first stage of operation exposing the vomiting center.

† Web of fibrin over floor of fourth ventricle.

‡ Dog also showed signs of central nervous system intoxication.

pyridine, it would appear, with the experimental evidence offered above, that it is dependent upon an indirect stimulation of the vomiting center, mediated either through reflexes arising from some organ other than the gastro-intestinal tract or through action of the drug on other cerebral centers. This interpretation obviously depends upon the assumption that sulfapyridine directly applied to the vomiting center actually penetrates as does apomorphine.

The fact that both man and dog vomit following the intravenous administration of the drug is not sufficient evidence for assuming that sulfapyridine acts directly upon the vomiting center.

The exact site of origin of the reflex stimulation by sulfapyridine on the vomiting center is not clear at the present time and further investigation of this problem is in progress.

Summary and conclusions

1. Following the intravenous injection of a 5 per cent solution of sodium sulfapyridine, dogs were found to vomit at a sulfapyridine concentration in the blood of from 17 to 36.5 mg. per cent. Occasionally, dogs were found that did not vomit, but exhibited signs of central nervous system intoxication when the blood sulfapyridine reached a sufficiently high level.

2. Sulfapyridine is readily excreted into the stomach after the intravenous injection of a 5 per cent solution of sodium sulfapyridine.

3. Removal of the stomach, and even of the entire gastro-intestinal tract including the spleen and the greater part of the pancreas, does not inhibit the act of vomiting when sodium sulfapyridine is given intravenously in dogs.

4. Direct application of sulfapyridine, in a concentration as high as 100 mg. per cent, to the vomiting center does not cause vomiting, whereas similar application of apomorphine to the vomiting center does cause emesis.

5. The above facts indicate that sulfapyridine vomiting in dogs is not due either to local action in the stomach or to direct action upon the vomiting center. They further suggest that the vomiting is mediated through a reflex stimulation of the vomiting center, which certainly is not exclusively from the gastro-intestinal tract but may arise from some other site or sites.

References

1 Eggleston, C., and Hatcher, R. A.: The seat of the emetic action of apomorphine. J. Pharmacol. & Exper. Therap., 1911/12, *3*, 551.

2 Hatcher, R. A., and Weiss, S.: The seat of the emetic action of digitalis bodies. Arch. Int. Med., 1922, *29*, 690.
3 Haviland, J. W., and Blake, F. G.: Parenteral administration of sulfapyridine. Am. J. Med. Sci., 1940, *199*, 385.
4 Marshall, E. K. Jr., and Litchfield, J. T.: The determination of sulfanilamide. Science, 1938, *88*, 85.
5 Marshall, E. K. Jr., and Long, P. H.: The intravenous use of sodium sulfapyridine. J. Am. Med. Asso., 1939, *112*, 1671.
6 Thumas, L. J.: Ueber das Brechcentrum und über die Wirkung einiger pharmakologischer Mittel auf dasselbe. Virchows Arch. f. path. Anat., 1891, *123*, 44.

The authors wish to express their appreciation to Dr. Max Taffel of the Department of Surgery, Yale University School of Medicine, for his aid in the neurosurgical aspects of the experiments upon the vomiting center.