jections of Nembutal, the susceptibility of the animals to this drug gradually increases. This increase appears to be associated with an increase in the weight of the animals.

4. The sex of the guinea pig did not appear to alter the sleeping time following single injections of Nembutal.

The author wishes to express his appreciation to Dr. Charles F. Kutscher through whose liberal support this study was made possible.

REFERENCES

(1) Kinsey, V. E.: *Jour. A. Ph. A.*, 29 (1940), 292.

(2) Carmichael, E. B., and Posey, L. C., *Proc. Soc. Exptl. Biol. Med.*, 32 (1933), 1329.

(3) Carmichael, E. B., and Posey, L. C., *Anesthesia and Analgesia*, 16 (1937), 156.

(4) Sherman, H. C., La Mer, V. K., and Campbell, H. L., *J. Am. Chem. Soc.*, 44 (1922), 165.

(5) Moore, B., *Biochem. J.*, 4 (1909), 323.

Potassium Bismuth Saccharate. II. Toxicity, Absorption and Distribution of Bismuth Following Intramuscular Injection*

By C. W. Sondern, A. E. Pugh, F. V. Kalich, George Lann and C. J. W. Wiegand

The preparation and chemical properties of a water-soluble potassium bismuthyl saccharate have been given in a previous report from this laboratory (1). This paper presents a study of the absorption, distribution, excretion and toxicity of a preparation containing this compound.[1]

EXPERIMENTAL

The absorption, distribution and excretion in rabbits was determined after a single intragluteal injection of doses equivalent to 5 mg. and 3 mg. of bismuth per Kg. body weight into two groups of six animals each. These doses were as small as the precision of the analytical method would permit for subsequent determination of the distribution of the bismuth in the various organs. One, three and five days after the injection, two animals in each group were sacrificed by exsanguination and the organs immediately removed for assay. The excretion was determined by collecting the urine and feces separately after each twenty-four-hour interval.

Quantitative determinations of the bismuth content of the biological material were made by the iodide method for amounts of the metal in excess of fifty micrograms (2), and by the dithizone method for smaller concentrations (3).

Table I presents the data on total excretion of bismuth in terms of the per cent of the amount injected.

Table I.—Excretion in Per Cent of Amount of Bismuth Injected

Dose, mg./Kg.	Rabbit No.	Excretion Time, Days	Urine	Feces	Total
5	1	1	6.0	0.7	6.7
	2		0.8	0.1	0.9
	3	3	1.2	0.5	1.7
	4		8.1	4.7	12.8
	5	5	11.6	3.7	15.3
	6		17.4	6.5	23.9
3	7	1	1.2	0.1	1.3
	8		0.3	0.1	0.4
	9	3	13.1	0.2	15.1
	10		15.6	2.0	17.6
	11	5	16.1	2.6	18.7
	12		23.3	4.1	27.4

It is seen that with the larger dose of bismuth about one-fifth of the amount injected is excreted within the five-day period with the peak of the excretion occurring after the first three days. With the smaller dose a disproportionately smaller amount was found in the excreta. The daily variation in the amount found was roughly proportional to the quantity of excreta but individual animals showed no constant relationship between the amount of bismuth excreted and the time after injection.

Table II shows the distribution of the bismuth in the organs of the injected animals. In addition the last column gives the total recovery of bismuth in terms of the per cent of the injected quantity.

The toxicity of potassium bismuthyl saccharate for white rats by both intravenous and intramuscular injection is shown in Table III.

Sections of the kidneys of the animals receiving a fatal dose of the bismuth compound showed widespread pathology. The rapidly fatal doses produced desquamation of the epithelium of the convoluted tubules, dilatation of the tubules and abundant albuminous casts. Animals living longer than one week but subsequently succumbing to the metal showed, in addition to the above changes, focal areas of necrosis of the kidney parenchyma and more or less extensive calcification of the tubular epithelium. The animals receiving a sub-lethal dose showed, after three weeks' observation, cloudy swelling and some desquamation of the tubular epithelium.

* From the Research Laboratories of George A. Breon & Co.

[1] Sacbimuth—a solution containing 50 mg. potassium bismuthyl saccharate per cc. (equivalent to 25 mg. bismuth), 25 per cent sucrose and 2 per cent benzyl alcohol.

Table II.—Distribution of Bismuth in the Organs

(Mg. of Bi/100 Gm. of Organs)

No.	Time, Days	Kidney	Liver	Colon	Muscle	Heart	Spleen	Central Nervous System	Blood Cells	Blood Serum	Inj. Leg	% Recovery
		Dose—5 mg. of Bi per Kg.										
1	1	2.25	0.37	0.38	0.06	0.003	0.02	0.001	0.001	0.003	8.42	93
2	1	1.83	0.30	0.40	0.05	0.003	0.04	0.003	0.001	0.002	7.87	88
3	3	2.80	0.13	0.31	0.06	0.003	0.02	0.002	0.001	0.004	4.73	77
4	3	1.60	0.20	0.06	..	0.012	0.05	0.004	0.001	0.006	2.83	67
5	5	2.00	0.10	0.06	0.02	0.006	0.02	0.004	0.002	0.002	5.09	54
6	5	3.11	0.15	0.06	..	0.003	0.02	0.003	0.001	0.005	8.09	87
		Dose—3 mg. of Bi per Kg.										
									Total Blood			
7	1	0.90	0.25	0.10	0.03	0.008	0.04	0.002	0.002		3.50	92
8	1	1.50	0.41	0.13	0.02	0.004	0.02	0.004	0.001		3.28	90
9	5	3.00	0.11	0.06	0.06	0.012	0.05	0.003	0.003		2.40	84
10	5	2.20	0.08	0.03	0.05	0.006	0.03	0.003	0.004		2.45	83

Table III.—Toxicity of Potassium Bismuthyl Saccharate

Intravenous

Dose mg. of Bi per Kg.	No. of Animals	Per Cent Deaths	L. D.50
7.0	9	0	10.41 mg. of Bi/Kg.
8.0	9	0	
9.0	16	0	
9.5	10	30	
10.0	20	35	
11.0	5	100	
12.0	3	100	

Intramuscular

Dose mg. of Bi per Kg.	No. of Animals	Per Cent Deaths	L. D.50
75.0	3	0	172.1 mg. of Bi/Kg.
100.0	5	0	
120.0	10	0	
140.0	10	10	
150.0	10	10	
170.0	14	50	
200.0	6	100	
250.0	3	100	

SUMMARY

1. Excretion in Rabbits.—(*a*) With a single dose of 5 mg. Bi/Kg. 15–24% of the injected bismuth is excreted within five days. With the smaller dose of 3 mg. Bi/Kg. 19–27% of the injected bismuth is excreted in the same period of time.

(*b*) The ratio of the bismuth excreted in the urine to that excreted in the feces is 3:1 with the larger dose and about 6:1 with the smaller.

(*c*) The peak of excretion lies between the third and fifth days.

The excretion of bismuth after intramuscular injection of potassium bismuthyl saccharate solution is somewhat slower than has been reported for other water-soluble preparations (4).

2. Absorption.—(*a*) The absorption from the site of injection appeared to be gradual but somewhat variable within individual animals. With the larger dosage, 26% was absorbed on the first day, 60% within three to five days. On the smaller dosage, 63% was absorbed the first day and 70% within five days.

The absorption of the potassium bismuthyl saccharate is somewhat slower than the generally reported absorption of other water-soluble bismuth preparations (4).

3. Distribution.—(*a*) The kidney shows the greatest concentration of the bismuth (1.00–3.11 mg./100 Gm.).

(*b*) The liver is next in bismuth content varying from 0.08 to 0.41 mg./100 Gm.

(*c*) The bismuth content of the colon varies with the quantity of fecal contents.

(*d*) Heart—3–12 micrograms in heart muscle.

(*e*) Spleen—20–50 micrograms.

(*f*) Central nervous system—1–4 micrograms.

(*g*) Blood cells—1–2 micrograms; blood serum—1–6 micrograms.

4. Toxicity.—Intravenous—10.41 mg./Kg.; intramuscularly—172.0 mg./Kg.

The intravenous and intramuscular toxicities of the potassium bismuthyl saccharate are comparable to those reported for the tartrate (4).

CONCLUSIONS

Intramuscular injections of potassium bismuthyl saccharate are gradually absorbed and excreted. Bismuth is present in all the organs and tissue fluids within 24 hours resulting in fairly uniform blood bismuth levels for 5 days.

REFERENCES

(1) Doak, G. O., *Jour. A. Ph. A.*, 29 (1940), 108.
(2) Method to be published elsewhere.
(3) Hubbard, Donald M., *Ind. Eng. Chem., Anal. Ed.*, 2 (1939), 343.
(4) Von Oettingen, W. F., *Physiol. Rev.*, 10 (1930), 221.
(5) Hanzlik, P. J., Lehman, A. J., and Richardson, O. P., *J. Pharmacol.*, 62 (1938), 404.

Effect of Fresh *Alœ Vera* Jell in the Treatment of Third-Degree Roentgen Reactions on White Rats*

A Preliminary Report

By Tom D. Rowe†

So far as is known, there is no proven curative treatment for third-degree roentgen reactions. In March 1935, Drs. C. E. and Creston Collins called attention to an apparently successful treatment of X-ray reactions by the use of fresh *Alœ vera* leaf (1). Since that time various medical journals have carried articles by physicians reporting the effectiveness of this leaf in treating such burns (2, 3, 4, 5, 6, 7, 8, 9, 10). These reports have been sufficiently promising to indicate that this leaf possesses curative properties. However, all of the work has been done on individual cases, and no reports have been made on experimental work in which controls were used. It appeared, therefore, that before *Alœ vera* could be given full credit for beneficial effects, controlled experimental work should be done.

With this in mind, Dr. C. A. Pohle, professor of radiology, University of Wisconsin, was consulted as to the animals to use and what section of the animals was best suited for the study of irradiation reactions. He suggested the skin of the back of white rats. The first few months of work were entirely experimental, and were directed toward determining what technique and dosage of roentgen rays to use. Twenty-four rats were used for this purpose. At the conclusion of this work, the actual problem was begun.

EXPERIMENTAL

Dr. F. B. Mandeville, professor of radiology at the Medical College of Virginia, coöperated in all X-ray treatments and supervised their administration. In carrying out this problem, the following procedure was employed: First, the rats were anesthetized by intraperitoneal injection of pentobarbital. The hair on the back was then removed with scissors and the rats irradiated individually. During irradiation, each rat was entirely covered with lead foil except for two areas on the back. These areas were 2 cm. square and approximately $2^1/_2$ cm. apart. The rats were given a total of 4000 r., using no filter with 100 kilovolts, 5 milliamperes at a distance of 22.5 cm. They were given the 4000 r. in two doses, 2000 r. one week and 2000 r. a week later. Administration of 4000 r. in a single dose frequently caused death. Using the above factors, 300 r. is the dose which will produce threshold erythema on the average human adult.

Treatment was administered to the rats in groups of eight. Three weeks after the first 2000 r. had been given, each rat showed severe, third-degree X-ray reactions on each of the exposed areas. Photographs were taken at this time and treatment with *Alœ vera* was begun (Fig. 1).

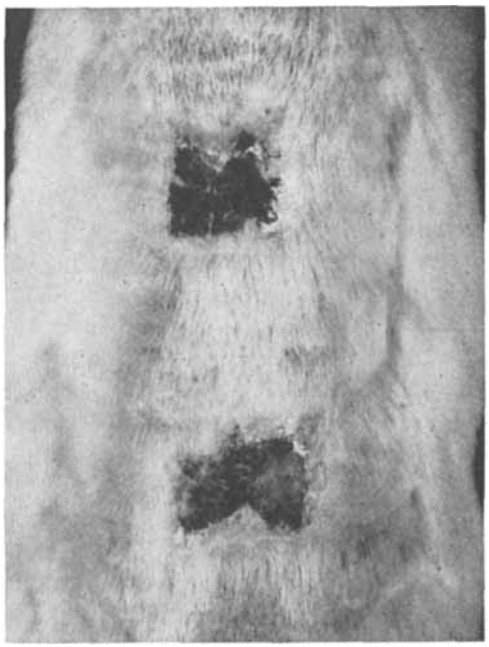

Fig. 1.—Typical Irradiated Areas at Beginning of Treatment.

One irradiated area was used as a control, receiving no treatment other than two applications daily of cotton packs saturated with normal saline

* Presented before the Scientific Section, AMERICAN PHARMACEUTICAL ASSOCIATION, Richmond meeting, 1940.

The work reported on in this paper was partly financed by grants from the Virginia Academy of Science and the Medical College of Virginia Research Fund.

† Assistant Professor of Pharmacy, School of Pharmacy, Medical College of Virginia, Richmond, Virginia.