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The Influence of Aloe and Podophyllum on the Flow of Hepatic Bile in the Dog*

By Lloyd W. Hazleton†

Recent investigations (1, 2) indicate that acute fistula methods for studying the flow of hepatic bile give reliable results if conditions are properly controlled. The work of Kocour and Ivy (3) establishes the uniform production of bile by the liver in dogs with chronic biliary fistulas in which the gall bladder is excluded and the bile collected under suction at all times.

The following investigations on the choleretic properties of Extract of Aloe (N. F. VI) and of Resin of Podophyllum (U. S. P. XI) employ the acute technique of Co Tui (2) with certain modifications.

Table I.—The Effect of Extract of Aloe and Resin of Podophyllum on the Flow of Hepatic Bile and Blood Pressure of Dogs

Dog No.	Drug[a]	Choleretic Dose, Mg.	Route	Bile, Average per Period, Cc. Control	Bile, Average per Period, Cc. Exptl.	Blood Pressure, Mm. Hg Control	Blood Pressure, Mm. Hg Exptl.
3	C	...	..	0.7	0.5[b]	...	...
4	C	...	..	1.5	1.5	...	...
13	C	...	..	1.0	1.4	80–166	68–104
24	C	...	..	0.8	1.4	96–137	146
32	C	...	..	1.8	2.8	108–160	108–116
		Total					
2	P	100	Tube	0.7	1.2	...	...
5	P	100	Tube	1.0	1.1	...	...
6	P	100	Tube	1.7	1.4	...	...
7	P	100	Tube	2.0	2.2	...	...
26	P + A	50 Each	Tube	1.4	0.8	140–174	112–160
28	P + A	50 Each	Tube	1.7	2.7	106–135	110–124
		per Kg.					
9	A	5	Vein	0.7	1.4	...	...
11	A	5	Vein	1.5	2.0	138	138–150
14	A	5	Vein	0.6	0.9	160	150
15	A	5	Vein	2.1	2.4	160–170	160–172
18	P	5	Vein	1.0	2.0	144–188	140–166
20	P	5	Vein	1.2	2.2	148–166	150–200
34	P	2	Vein	3.5	5.5	98–114	108–138
36	P	2	Vein	1.6	3.2	148	156–165
38	P	2	Vein	1.6	3.2	132–154	134–164
62	R	2	Vein	1.6	1.8	130	135
68	R	5	Vein	1.3	1.6	145	158

[a] C = control, no drug; P = resin of podophyllum; A = extract of aloe; R = rosin.
[b] Experimental interval in control animals corresponds to interval following administration of drug to treated animals.

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EXPERIMENTAL

Adult dogs, fasted over night and anesthetized with 30 mg. per Kg. of sodium pentobarbital administered intravenously, were used in these ex-

periments. The number of male and female animals was approximately equal and no distinction was made between the two. A midline incision was made and the cystic duct tied or clamped to eliminate bladder bile, and the common duct was cannulated with a glass cannula connected to gum tubing. The tubing was exteriorized through the incision and the opening adjusted to the level of the common duct to eliminate hydrostatic pressure.

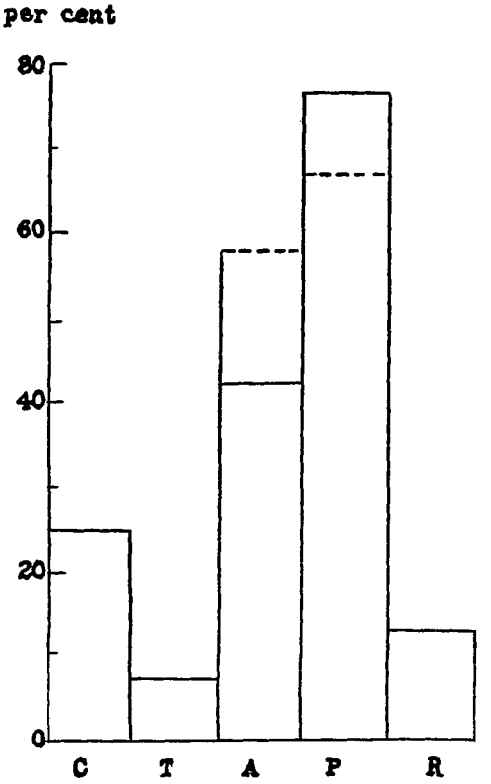

Fig. 1.—The Per Cent of Increase in Biliary Flow Following the Administration of Drugs, and During a Comparable Interval in Control Animals.

C = control, no drug, 5 dogs; T = resin of podophyllum alone or with extract of aloe given by intestinal tube, 6 dogs; A = extract of aloe intravenously, 4 dogs; P = resin of podophyllum intravenously, 5 dogs; R = rosin intravenously, 2 dogs. Dotted line indicates value when additional periods are included.

Tracheal cannulas were routinely inserted and the femoral vein exposed for injection. In all but the earlier experiments blood pressure tracings were made from the cannulated carotid artery and respiratory tracings were taken from the tracheal cannula. Additional sodium pentobarbital was administered as needed to maintain uniform anesthesia. The bile was collected in graduated tubes and measured at the end of each 30-minute period.

Controls.—To establish the rate of biliary flow throughout the duration of the experiments (about four hours), five dogs which received no drug other than the anesthetic were used as controls. The averages of the first four and of the second four periods in the individual animals are recorded in Table I. These correspond, respectively, to the control and experimental intervals described below. The percentage increase in biliary flow for the second interval is shown in Fig. 1. Three of these experiments were continued through additional periods, but there was no change in the average figures.

Due to individual variation in the above animals, the rate of flow was established for each dog over a period of four 30-minute periods prior to the administration of the drug. The values given in Table I are the averages for the first four periods (control interval) and the four periods (experimental interval) immediately following the administration of aloe, podophyllum or rosin. Percentage changes from the average control values are recorded in Fig. 1.

Duodenal Administration.—In six of the dogs drugs were administered into the duodenum by means of a catheter inserted through a stab wound in the pylorus. Each of four dogs received 100 mg. of resin of podophyllum (total). The remaining two received 50 mg. of resin of podophyllum plus 50 mg. of extract of aloe. The results are shown in Table I and the average percentage changes in Fig. 1.

Intravenous Administration.—Four dogs were given intravenous injections of 5 mg. per Kg. of extract of aloe in aqueous solution. The results are given in Table I and Fig. 1. Three experiments were conducted for additional periods and the dotted area of Fig. 1 shows the effect of including these additional periods.

Two dogs received 5 mg. per Kg. of resin of podophyllum which was dissolved by the addition of a sufficient quantity of $0.5N$ potassium hydroxide and diluted to 5 cc. Three additional animals received 2 mg. per Kg. of resin of podophyllum dissolved in alcohol and diluted to 40% alcoholic concentration by the addition of $0.2M$ sodium phosphate. The results are given in Table I and Fig. 1.

One dog was given 2 mg. and another 5 mg. per Kg. of Rosin (U. S. P. XI) intravenously. The rosin was boiled in distilled water for one-half hour, dried, weighed, dissolved in alcohol and the solution diluted to 40% alcoholic concentration by the addition of $0.1M$ sodium phosphate. The results are given in Table I and Fig. 1.

Effect of Blood Pressure.—In the course of the experiments four dogs developed blood pressures of below 60 mm. of mercury after an initial level of 100 mm. or above. These were allowed to remain uncorrected and the flow of bile observed. Following the drop in pressure the biliary flow decreased to such an extent that the average for the four animals was only 0.4 cc. per period. In one animal with a mean pressure of 58 mm. of mercury induced by hyper-ventilation there was a cessation of biliary flow for one period (30 minutes). Upon elevation of

the mean pressure to 84 mm. by additional anesthetic, the flow increased to above 2.0 cc. per period and remained at this level for the duration of the experiment. The results from these animals were deleted from the series and do not appear in the table or figure.

DISCUSSION

Although Co Tui (2) found that under conditions similar to the above the flow of bile in dogs reached a constant level or decreased during the control period, and Halpert (4) reported similar results in rabbits, the results presented above indicate that in dogs there is a tendency toward an increase in volume during the later periods. This phenomenon must be taken into consideration when evaluating the choleretic properties of a drug, as three of the five control dogs in this series showed an increase, the average being 25%. Markowitz (5), using ether anesthesia, observed a marked decrease or cessation of biliary flow for 24 hours after the operation, but Coffey, *et al.* (6), could detect no reduction in biliary flow following the intravenous administration of sodium amytal to a chronic fistula dog.

The administration of resin of podophyllum alone or in combination with extract of aloe by duodenal tube resulted in values which were too irregular to interpret accurately, probably due in part to variability in absorption during anesthesia and the limited period of the experiments. In two of the six experiments the flow was decreased, while the average increase in volume for the group was approximately 7%.

The intravenous injection of extract of aloe was followed by a 42% increase in the average bile production within the experimental interval of four 30-minute periods. In the three experiments which were prolonged for three or four 30-minute periods beyond the usual experimental interval the rate of biliary flow continued to increase or remained at a high level. Inclusion of these results brings the average increase over the control value to 58%, as indicated by the dotted line in Fig. 1. The inclusion of additional periods in the control animals did not change the per cent of increase. From these observations it is apparent that the choleretic action of extract of aloe is comparatively slow in onset and of long duration. In contrast to the above two groups there was no incidence of decrease in bile production and the smallest increase was 14%. The injections were followed by a slight increase in blood pressure with no untoward effects.

Intravenous injection of resin of podophyllum produced a 77% increase in the average bile production. The smallest individual increase was 57%. Inclusion of results from the two experiments which were continued for additional periods gives an average increase of 67%, indicating that the maximum action was reached within the four 30-minute periods of the standard experimental interval. The rate of flow during the control interval (four 30-minute periods) does not seem to be a factor in this choleretic effect (see dog No. 34, Table I). The injections were followed by a gradual increase in blood pressure accompanied by strong pulsations and an occasional extra systole. The condition receded and usually disappeared within about one hour. Since the increase in blood pressure is not proportional to the increase in bile, and there is no other apparent correlation between these two factors except in cases of extremely low pressure, it is apparent that the increased choleresis is not a result of the increase in blood pressure. Stewart and Ryan (7) observed in clinical cholecystographic studies that four hours after the administration of podophyllin (Resin of Podophyllum) the gall bladder was very much more distended with bile than before the drug was given.

Since intravenous injection of rosin increases the flow of bile only 13%, and this is somewhat less than the normal increase during a comparable period in control animals, it is apparent that the choleretic action of extract of aloe and of resin or podophyllum is not a non-specific phenomenon due to foreign or insoluble substances.

The observations made on the effect of low blood pressure indicate that this may be a source of error in acute studies where blood pressure has not been recorded. Values below 60 mm. of mercury may be sufficient for maintenance of the anesthetized animals, but lead to rapid decrease or cessation of the flow of hepatic bile. In one animal

correction of hypotension was followed by a marked increase in bile production.

CONCLUSIONS

Intravenous injection of extract of aloe increases the flow of hepatic bile in the anesthetized dog. The duration of action is relatively long.

Intravenous injection of resin of podophyllum increases the flow of hepatic bile in the anesthetized dog. This action apparently reaches a maximum within two hours after the injection.

Intravenous injection of rosin has no effect upon the biliary flow under the above conditions.

There is a critical level of blood pressure necessary to the maintenance of biliary flow. Evidence presented indicates this to be approximately 60 mm. of mercury for the dog.

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The Assay of Yellow Mercuric Oxide Ointment, U. S. P. XI*

By F. N. Van Deripe and R. A. Konnerth†

The U. S. P. XI assay method for mercury in Ointment Mercury Oxide has given satisfactory results when used on freshly prepared ointments, but not on aged samples. With the latter the figures are lower than those obtained initially on the same samples. This is not due to any loss of mercury from the ointment, but presumably to some change whereby the mercury becomes combined in some form which is unavailable under the conditions of the U. S. P. XI assay. For example, it might gradually react with acids in the ointment base to form mercury soaps in which the mercury is no longer available in so far as the U. S. P. XI assay is concerned. That this is the case has been indicated by the fact that aged samples with a low U. S. P. XI assay value have given results close to the original ones when a somewhat different analytical method (1) is employed whereby the entire mercury content of the sample is determined. These findings show not only that the U. S. P. XI method may with aged samples give results lower than the total mercury present, but also that upon aging changes do occur slowly whereby a small portion of the mercury in this ointment enters into a different state of chemical combination.

EXPERIMENTAL

A laboratory preparation of Ointment Mercury Oxide Yellow, U. S. P. XI, showing 1.01% mercuric oxide by the U. S. P. XI method and 1.03% by the method described below was stored at room temperature and 105° F. for periodic assay by both methods.

Assay.—Weigh accurately (within 0.0005 Gm.) about 2.5 Gm. of the sample and transfer into a dry beaker of about 250 cc. capacity. Dissolve directly by warming on a water bath to 50° C. with 100 cc. of a solvent mixture consisting of benzene, 13 parts by volume, acetic acid (glacial), 2 parts, and alcohol

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