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The site of emetic action of veratrum derivatives.

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The Site of Emetic Action of Veratrum Derivatives

Emesis, or the act of vomiting, is a common occurrence after the administration of a large number of drugs. Many of these drugs would have better clinical application if this side action could be controlled or abolished. The study of drug-induced emesis has mainly centered around the determination of the site of the emetic action. It is at present concluded that emesis may be the result of local irritation of some area of the body such as the duodenum or the result of direct stimulation of the vomiting center in the medulla.

The location of the vomiting center in the medulla was first described by Thumas in 1891. Hatcher and Weiss (10) in 1924 localized the vomiting center to the area of the sensory nucleus of the vagus. Borison and Wang (1) in 1949 more accurately localized the vomiting center in the region corresponding to the solitary fasciculus and nucleus, and the dorsolateral border of the lateral reticular formation in the medulla. Further investigations by Borison and Wang (2) have indicated the presence of an area on the floor of the fourth ventricle which might be considered to be a chemoreceptor area for centrally acting emetics. They have also concluded that the center for emesis is localized in the area of the reticular formation.

The methods described in the literature for the determination of the sites of emetic action of various drugs are numerous. The effect of route of administration on drug-induced emesis has been studied by Eggleston and Hatcher (7). They demonstrated that emesis occurs
much more rapidly after intramuscular injection of apomorphine than
after introduction into the stomach. They concluded that this is not
suggestive of local action but might imply only a different rate of
adsorption. The uniformity of dosage for a given route of administra-
tion of apomorphine has also been demonstrated (7). This suggested
that the emetic action is upon a highly specialized structure such as
the vomiting center.

Application of a drug to the central vomiting apparatus has been
utilized in the study of emesis. Hatcher and Weiss (9) succeeded in
causing emesis by the direct application of apomorphine to the floor
of the fourth ventricle. Hatcher and Weiss (12) have also used this
method in the study of digitalis induced emesis. They were unsuccessful
in causing emesis by direct application of digitalis bodies to the
floor of the fourth ventricle. This type of experiment is not critical
since many factors are involved, such as the abnormality of the animal
after exposing the fourth ventricle.

Several methods have been described for the determination of the
role of irritation of the gastrointestinal tract in drug induced emesis.
Eggleston and Hatcher (7) performed a series of experiments in which
removal of the entire gastrointestinal tract and cocainization of the
esophagus and pharynx did not prevent retching after administration of
apomorphine. Hatcher and Eggleston (9) utilized eviscerated dogs in
their study of digitalis. They demonstrated that digitalis still caused
retching in these dogs. Sadusk (16) made use of complete gastrointes-
tinal evisceration to show that irritation of the gastrointestinal tract
is not involved in sulfapyridine induced emesis.

Denervation of an organ or a particular region of the body has been utilized to a considerable extent in the study of emesis. Hatcher and Weiss (11) have reported that denervation of the abdominal viscera by sectioning of the vagi and splanchnics below the diaphragm did not interfere with emesis after the administration of digitalis bodies. They concluded from these results that irritation of the abdominal viscera is not the cause of digitalis induced emesis. Hatcher and Weiss (12) have performed experiments to determine the role of the thoracic viscera in digitalis induced emesis. They reported that removal of stellate ganglia or sectioning of the cord above the level at which the sympathetic cardiac fibers enter usually prevented nausea and vomiting after the administration of digitalis bodies. Contrariwise, Dresbach and Waddel (5), working on the same problem, found that removal of the cervical ganglia, the stellate ganglia and the thoracic chain and sectioning of the vagus nerves either individually or in combination did not prevent emesis after administration of digitalis bodies. The difference in results of these two groups of workers can perhaps be explained by the fact that Hatcher and Weiss (12) allowed only a few hours while Dresbach and Waddel (5) allowed a few weeks for recovery of the animals after the operation. Haney and Lingren (8) have presented evidence which tends to support the results of Dresbach and Waddel. They used two sets of dogs (1), the hearts were denervated by bilateral removal of the stellate and upper six thoracic sympathetic ganglia and sectioning of both vagi (2). The vagi were cut high in the neck and the spinal cord
was sectioned at C6 and pithed from that point caudally. The production of emesis by digitalis bodies was not abolished in these animals. Kwit and Hatcher (13) have also used the method of denervation of the heart to demonstrate that pilocarpine induced emesis is caused by irritation of receptors on the heart.

The use of various agents such as atropine has also been utilized in the study of drug induced emesis. Hatcher and Weiss (11) have reported that the injection of nicotine with atropine abolished the emetic action of an intravenous or intramuscular dose of a digitalis body but it does not abolish that of an intraperitoneal dose of strophanthidin. It was also shown that nicotine with atropine does not depress the vomiting center markedly since it does not abolish the emetic action of apomorphine. It was concluded therefore that nicotine abolished the emetic action of digitalis bodies by paralyzing afferent endings or possibly by paralyzing the connections in the ganglia through which the afferent fibers from the heart to the vomiting center pass. It was also shown that nicotine does not abolish the emetic action of irritants, including strophanthidin and mercuric chloride, when they are applied directly to the peritoneum. Kwit and Hatcher have also used atropine in their study of pilocarpine induced emesis. They reported that administration of atropine (5 mgm in 1% solution) to the gastric or intestinal mucosa prevented both copper sulfate and pilocarpine induced emesis. The intravenous injection of 0.01 mgm of atropine abolished the emetic action of a minimal dose of pilocarpine but 500 times that dose had no effect on the emesis after administration of apomorphine.
They therefore concluded that moderate doses of pilocarpine caused emesis by their peripheral action.

Perfusion experiments have also been used in the study of digitalis induced emesis. Hatcher and Weiss (12) demonstrated that nausea and vomiting could not be elicited in decerebrate cats by perfusing the brain and medulla with defibrinated blood to which ouabain had been added. Preventing the digitalis bodies from reaching the medulla (after injection into the femoral vein) by perfusing the medulla with diluted defibrinated blood did not prevent emesis from occurring. They therefore concluded that digitalis bodies cause emesis by a peripheral action.

A new technique for the study of the problem of emesis has been described by Borison and Wang (3). Their technique consists of destroying the chemoreceptor areas for centrally acting emetics. This area is located on the floor of the fourth ventricle. They have reported that destruction of this area prevents apomorphine induced emesis but does not prevent emesis due to local irritation such as that observed with copper sulfate. They too have studied the problem of digitalis induced emesis. Their results indicate that the emesis observed within 1 to 3 hours after administration of digitalis is due to a central action. The possibility that digitalis may produce emesis by a peripheral action is still admitted since emesis may occur occasionally even though the central chemoreceptor area is destroyed.

From this review of the literature it may be concluded that (1) no completely satisfactory technique exists for the study of the problem of emesis after drug administration. (2) A series of indirect experi-
ments must be performed to determine the site or sites of emetic action of a drug (3). The possibility of more than one site of emetic action of a drug must be considered.

The hypotensive power of veratrum derivatives has been known for years but variability of response and the side action of nausea and vomiting has considerably reduced its clinical application. Continued success in isolation of purified veratrum derivatives has again stimulated clinical interest in these plants. The pharmacology of these veratrum derivatives has yet to be clearly described. The site of cardiovascular action of these substances is still much in dispute. The fate in the body and the mode of excretion of these derivatives remains to be determined. The problem is still further complicated by the fact that very small amounts (mcg per Kg) are required to produce an effect in the body. Thus the site of emetic action of veratrum derivatives was thought worthy of investigation. Several of the methods previously described have been used. For many of these derivatives the emetic dose had not previously been determined, hence this was the first step. Following the procedures used by Eggleston and Hatcher (7) for the determination of emetic site of apomorphine, the influence of route of administration and the constancy of dosage by a given route was determined. The procedure of using other drugs such as atropine in the study of emesis as presented by Kwit and Hatcher (13) was also utilized. Denervation of the gastrointestinal tract, as described by Hatcher and Weiss (10), was performed to determine if irritation of the gastrointestinal tract is the cause of emesis after administration of veratrum.
Thus, this investigation has been divided into several series of experiments, each of which will be considered separately.

(A) Determination of the emetic dose 50 (ED50) for several veratrum derivatives:

Method: Adult mongrel dogs (5 - 15 Kg) were weighed to the nearest 0.1 Kg. The veratrum derivatives were administered by vein in 5 ml. of physiologic saline. The dogs were observed for a period of 2 hours (actually all emesis occurred within the first 20 minutes). A sufficient number of animals were used to obtain a significant Chi2 value as determined by the method of Litchfield and Wilcoxon (14).

Results: In Table I are listed the ED50 values for the derivatives. In Figure 1, the ED50 values of these derivatives are plotted against standard hypotensive potency (15). Excessive salivation constantly preceded emesis. The dogs collapsed and convulsed for a period of 15 to 45 seconds after the administration of an effective intravenous emetic dose. This effect may be a hypotensive syncope. Every animal which had emesis also had repeated defecation which occurred almost simultaneously with the emesis.

Discussion: The right hand column of Table I represents the ED50 values with 95% confidence limits after conversion to the standard hypotensive dose of 1. The difference in these figures is not statistically significant. Thus, there is a correlation between emetic dose and hypotensive dose. This is illustrated in Figure 1, which shows a straight line relationship between the log of the hypotensive potency and the log of the ED50 values.
Christenson and McLean (4) have suggested a bioassay for veratrum derivatives based on pigeon emesis. They made no comparison of its emetic properties and hypotensive powers in the same species. In this present investigation, the emetic properties and hypotensive potency are compared in the dog. These results indicate another potential assay method for veratrum based on emesis in dogs.

Veriloid was selected as the reference standard and for use in the following experiments because it is an alkaloidal mixture of constant potency, and because the total available information about its actions is greatest.

(B) Comparison of the oral and the intravenous emetic dose of Veriloid.

**Method:** Adult mongrel dogs (5 - 15 Kg) were weighed to the nearest 0.1 Kg. The intravenous dose was dissolved in 5 ml. of physiologic saline and was administered rapidly into the foreleg vein. The oral dose was administered by stomach tube in a total volume of 20 ml. Ten dogs received intravenous or oral administrations of various dosages of Veriloid on successive days.

**Results:** In Table II are presented the results of a large series of animals. The ED50 values were calculated by the method described by Litchfield and Wilcoxon (14). After intravenous administration of an effective emetic dose, the majority of animals had emesis within 3 to 5 minutes. The interval before emesis after an effective oral emetic dose varied from 5 to 80 minutes. No syncope was observed after oral administration of an effective emetic dose.

Table III presents the results of repeated intravenous injections
of various dosages on successive days. The results demonstrate that there exists a dosage which will constantly cause emesis in an individual dog. This dose has been called the minimum effective intravenous emetic dose.

Discussion: The difference between the ED50 for oral administration and the ED50 for intravenous administration is not statistically significant. Thus the oral emetic dose may be considered equal to the intravenous emetic dose. The results of this series of experiments might indicate that (1) Irritation of the gastrointestinal tract after oral administration of Veriloid is the cause of emesis and that Veriloid after intravenous administration circulates to the gastrointestinal tract to also cause emesis. (2) After intravenous administration, Veriloid causes emesis by stimulation of some highly specialized structure such as the vomiting center and that Veriloid is quantitatively absorbed from the gastrointestinal tract to also cause stimulation of the vomiting center. The latter seems more likely since emesis occurs so much earlier after intravenous administration than after oral administration of an effective dose. Further proof is indicated by the fact that the minimum effective intravenous emetic dose for an individual dog is constant (see Table III).

(C) Influence of rate of administration of an emetic dose.

(a) Oral.

Method: Twelve adult mongrel dogs (17 - 28 Kg) were weighed to the nearest 0.1 Kg. Each animal was tested twice with each of three forms of tablets; rapidly dissolving, enteric coated and slow dissolving.
Each animal received a total dose of 1.0 mg. The tablets were administered orally in a small piece of meat. The times required for emesis varied considerably and are of no significance. The dogs were observed for four hours at the end of which time if emesis had not occurred, the experiment was considered negative.

**Results:** The results of administration of the three different types of tablets are presented in Table IV.

**Discussion:** To account for the results of these experiments several assumptions might be made: (1) In some of the animals the enteric coated and slow dissolving tablets passed through the gastrointestinal tract unchanged. This would account for the lower incidence of emesis with these tablet forms (2). Irritation of some portion of the gastrointestinal tract, such as the duodenum, is the cause of emesis and the rate at which the drug reaches this area determine the appearance of emesis (3). The rate of absorption from the gastrointestinal tract determines the incidence of emesis. This would explain why the slow dissolving tablets are the least emetic of the three forms tested.

(b) Intravenous.

**Method:** Slow infusion experiments: Nine adult mongrel dogs (7 - 12 Kg) were weighed to the nearest 0.1 Kg. A dilute solution of Veriloid was administered by vein at a rate of 0.5 mcg per Kg per minute until emesis occurred or until a total dose of 23 mcg per Kg was administered. A total dose of 23 mcg per Kg was selected because it represents an ED90 value (a dose which will cause 90% of the animals to have emesis) as determined from the results of section (A). The following day, any
animal which did not have emesis after the infusion of 23 mcg per Kg was given a quick injection of the same dose. It was assumed that if the animal did not have emesis with the quick injection, a negative response after infusion of the same dose was to be expected. Following the same procedure, a series of eight dogs were infused with a dose of 23 mcg per Kg at the rate of ½ mcg per Kg per hour.

Results: In Table V are presented the results of the slow rate of intravenous administration of Veriloid. At this rate of administration, no syncope was observed. The results of the hourly intravenous injections of Veriloid are presented in Table VI. Emesis occurred after the first injection in only four cases of 38 trials (3 at dose of 15 mcg per Kg) indicating that the individual dose was a sub-emetic one in 34 animals. No emesis was observed in the series of eight animals infused with ½ mcg per Kg per minute.

Discussion: The results of this series of experiments make it unlikely that emesis after administration of Veriloid is due to the hypotensive effect of the substance since other work suggests that the duration of the hypotensive effect of doses below 10 mcg would not last one hour. These results also imply that the rate of destruction or excretion of Veriloid or the emetic cleavage products is less than 7.5 mcg per Kg per hour but more than 5 mcg per Kg per hour. It is also of interest to note that the cumulated emetic dose is but little higher than the single emetic dose.

(D) Attempted drug control of Veriloid induced emesis.

Method: Adult mongrel dogs were used. An effective intravenous emetic
dose was given each dog a day before any other drug was administered. Three injections served as controls for the individual animals. Intravenous injections of tetraethylammonium chloride (Etamon) and Banthine were given 10 minutes before intravenous Veriloid. Intravenous atropine was given 10 minutes prior to oral administration of Veriloid. Oral Banthine and intravenous ephedrine and scopolamine were given 30 minutes before intravenous Veriloid. Oral dramamine was given 40 to 60 minutes prior to administration of Veriloid. The dosage per Kg for oral dramamine varied in the different animals between 3.5 and 16.4 mg. The remaining drugs were administered on a mg per Kg basis. All animals were observed for a period of 2 hours after Veriloid was administered.

Results: Table VII contains the results of this series of experiments. The dosages of scopolamine and atropine used were sufficient to cause hyperactivity in many of the dogs. Scopolamine appeared to be of possible benefit in the control of emesis. No significant decrease in the incidence of Veriloid induced emesis was observed with atropine. The results suggest that a full pressor dose of ephedrine may decrease the incidence of emesis. Oral dramamine in doses up to 16.4 mg per Kg were ineffective in preventing emesis. A high intravenous dose of Banthine appeared to be of some benefit in emesis control. A blocking dose of tetraethyl-ammonium chloride had no effect on the incidence of emesis.

Discussion: The slight beneficial results of scopolamine and Banthine are not significant, because the dose used was too high to be of any practical value. Although Kwit and Hatcher (13) have reported that
atropine abolishes the emesis after oral administration of a local irritant, the usefulness of this drug for the control of emesis is doubtful. Thus, the negative results obtained in this present series of experiments are of no significance. These results, however, do support the fact that as yet no drug has been tested which alleviates veratrum induced emesis.

(E) The role of the stomach in emesis after administration of veratrum derivatives.

Method: In 30 dogs, the pylorus was ligated under thiopental anesthesia. After sufficient time was allowed for recovery from the anesthesia, 10 dogs were given a previously determined effective oral emetic dose by stomach tube. Ten other dogs were given 10 times the effective emetic oral dose by stomach tube. The remaining 10 dogs were given orally a capsule containing 9.6 mg per Kg of crude ground root of veratrum. If the animals failed to have emesis within two hours after administration of the drug, they were given an intravenous injection of an effective emetic dose.

Results: Table VIII contains the results of this series of experiments. Those animals which received the intravenous dose had emesis within the first 20 minutes.

Discussion: The intravenous dose was given these animals to determine if they were capable of having emesis after the operation for ligation of the pylorus. The results of the experiments in which oral dosages of Veriloid and crude root were prevented from escaping from the stomach, demonstrate that irritation of the gastric mucosa cannot be a significant
factor in the production of emesis. The dose of crude root used was more than 10 times the standard hypotensive dose (see footnote on Table 1). These results do not eliminate the possibility that local irritation of mucosa of the duodenum, jejunum or ileum may cause emesis.

(F) Denervation of the gastrointestinal tract.

Method: After the minimum effective emetic oral and intravenous dose had been determined, bilateral supradiaphragmatic splanchnicectomy and vagotomy were performed on six dogs. A week was allowed for recovery from the operation. The minimum effective oral and intravenous emetic dose was then again determined.

Results: The oral emetic dose for these six dogs was raised about four-fold, but the intravenous emetic dose did not change (see table IX). The minimum effective intravenous dose for these animals was the same as originally determined.

Discussion: The results of this series of experiments indicate that irritation of nervous receptors of the gastrointestinal tract is a negligible factor in the production of emesis after administration of Veriloid. The change in the minimum effective oral emetic dose may be explained on the basis of decreased activity of the gastrointestinal tract with poor gastric emptying after denervation.

General Discussion: The determination of the site of emetic action of a drug has presented many problems to the investigator. The report of Eggleston and Hatcher (7) in 1912 of the vomiting center as the site of emetic action of apomorphine is probably the only one in which definite conclusions could be presented. The determination of the site for digitalis bodies has involved elimination of the possibility of
of local action on some area of the body such as the stomach, and accumulation of indirect evidence as to direct stimulation of the vomiting center. This present investigation of the site of emetic action of veratrum derivatives has also been concerned with the previously mentioned objectives. Using a method of denervation it has been demonstrated that irritation of nerve endings of the gastrointestinal tract is not essential for production of emesis after the administration of Veriloid. Elimination of extreme hypotension as the cause of Veriloid induced emesis is still to be accomplished despite the fact that the intravenous emetic dose is constant regardless of the rate of administration. It has been demonstrated that Veriloid causes emesis in animals who had a full pressor dose of ephedrine. The more rapid production of emesis after intravenous administration than after oral administration of Veriloid is not in accordance with local action. The constancy of the minimum effective intravenous emetic dose suggests that the emetic action is upon a highly specialized structure such as the vomiting center in the medulla.
## Table I

I.V. ED50 (19/20 C.L.) for Veratrum Derivatives

<table>
<thead>
<tr>
<th>DRUG</th>
<th>mcg/Kg.</th>
<th>Hypotensive Potency in Standard Dose</th>
<th>ED50 in Terms of Standard Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germitrine</td>
<td>$2.5 (2.0 - 3.2)$</td>
<td>$0.094$</td>
<td>$26.3 (20.6 - 33.3)$</td>
</tr>
<tr>
<td>Germerine</td>
<td>$4.2 (2.54 - 6.0)$</td>
<td>$0.192$</td>
<td>$21.84 (13.2 - 31.2)$</td>
</tr>
<tr>
<td>Protoveratrine (Lilly)</td>
<td>$5.0 (3.2 - 7.8)$</td>
<td>$0.218$</td>
<td>$22.7 (14.7 - 35.8)$</td>
</tr>
<tr>
<td>Germidine</td>
<td>$8.1 (7.1 - 9.2)$</td>
<td>$0.416$</td>
<td>$19.4 (17.1 - 22.1)$</td>
</tr>
<tr>
<td>Veriloid³</td>
<td>$15.2 (12.2 - 18.4)$</td>
<td>$0.71$</td>
<td>$20.52 (16.5 - 24.8)$</td>
</tr>
<tr>
<td>KP (3)</td>
<td>$18.8 (16.1 - 21.9)$</td>
<td>$1.0$</td>
<td>$18.8 (16.1 - 21.9)$</td>
</tr>
<tr>
<td>Veratradine</td>
<td>$46.0 (31.9 - 66.2)$</td>
<td>$2.13$</td>
<td>$21.6 (15.0 - 31.1)$</td>
</tr>
<tr>
<td>Ext. V. viride USP IX</td>
<td>$780 (655 - 929)$</td>
<td>$42.3$</td>
<td>$18.7 (15.7 - 22.3)$</td>
</tr>
</tbody>
</table>

(1) These data are from Maison, Gotz and Stutzman (16). The standard dose is an estimate of micrograms per kilogram per minute over a 10 minute period required to produce an average fall of mean arterial pressure of 30% in a large number of anesthetized dogs.

(2) Calculated from: ED50 divided by the hypotensive potency in standard dose. This figure represents ED50 after allowing for differences in hypotensive potency.

(3) KP is Veriloid reference standard.
Figure 1

Hypotensive potency in standard dose**

* Each dot represents the ED50 value for an individual veratrum derivative (See Table 1)

** See footnote (1) on Table 1
### Table II
Comparison of Oral and Intravenous Emetic Dose

<table>
<thead>
<tr>
<th>ROUTE</th>
<th>ED50 mcg/Kg (19/20 C.L.)</th>
<th>Number of Trials</th>
<th>Number of Dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (Stomach Tube)</td>
<td>17.0 (14.4 - 20.1)</td>
<td>146</td>
<td>124</td>
</tr>
<tr>
<td>Intravenous</td>
<td>19.5 (17.5 - 21.6)</td>
<td>192</td>
<td>85</td>
</tr>
</tbody>
</table>

### Table III
Incidence of Emesis after Intravenous Administration of Various Dosages of Veriloid
(Times Emesis / Times Tested)

<table>
<thead>
<tr>
<th>Dog Number</th>
<th>10 mcg/Kg</th>
<th>15 mcg/Kg</th>
<th>18 mcg/Kg</th>
<th>21 mcg/Kg</th>
<th>25 mcg/Kg</th>
<th>28 mcg/Kg</th>
<th>30 mcg/Kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0/2</td>
<td>1/5</td>
<td>4/8</td>
<td>5/5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0/1</td>
<td>0/3</td>
<td>2/9</td>
<td>8/8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0/2</td>
<td>2/7</td>
<td>6/6</td>
<td>1/1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0/1</td>
<td>0/7</td>
<td>3/6</td>
<td>5/5</td>
<td>4/4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0/1</td>
<td>1/6</td>
<td>4/5</td>
<td>6/6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0/1</td>
<td></td>
<td>1/6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>0/3</td>
<td>0/1</td>
<td>0/4</td>
<td>1/3</td>
<td>5/5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>0/2</td>
<td>0/3</td>
<td></td>
<td></td>
<td></td>
<td>2/2</td>
</tr>
<tr>
<td>9</td>
<td>0/1</td>
<td>4/8</td>
<td>3/4</td>
<td>5/5</td>
<td></td>
<td></td>
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<tr>
<td>10</td>
<td>0/1</td>
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<td></td>
</tr>
</tbody>
</table>
Table IV

Incidence of Emesis after Oral Administration of Various Tablet Forms*

<table>
<thead>
<tr>
<th>Tablet Form</th>
<th>Number of Trials</th>
<th>Incidence of Emesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapidly Dissolving</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Enteric Coated</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>Slow Dissolving**</td>
<td>24</td>
<td>8</td>
</tr>
</tbody>
</table>

* Same 12 dogs with weight range such that the dose varied from 35 - 58 mcg per Kg.

** The slow dissolving tablets were shellac bound with estimated disintegration time of 40 minutes.
Table V

Influence of Rate of Administration on Veriloid Induced Emesis (Intravenous)

<table>
<thead>
<tr>
<th>Dog Number</th>
<th>Rate</th>
<th>Time of Emesis (min.) after start of infusion</th>
<th>Total Dose Admin. (mcg/Kg)</th>
<th>Control stat I.V. Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\frac{1}{2}$ mcg per Kg per min.</td>
<td>36</td>
<td>18</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>46</td>
<td>23</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>—</td>
<td>23</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>32</td>
<td>16</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>30</td>
<td>15</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>—</td>
<td>23</td>
<td>Positive</td>
</tr>
<tr>
<td>7</td>
<td>&quot;</td>
<td>26</td>
<td>13</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>&quot;</td>
<td>46</td>
<td>23</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>&quot;</td>
<td>25</td>
<td>12.5</td>
<td>—</td>
</tr>
</tbody>
</table>
Table VI

Incidence of Emesis after Hourly Injections of Veriloid

<table>
<thead>
<tr>
<th>Dose (mcg/Kg)</th>
<th>Number of Trials</th>
<th>Results (Incidence of Emesis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>5</td>
<td>All negative at 6th injection.</td>
</tr>
<tr>
<td>7.5</td>
<td>5</td>
<td>2 negative on 6th injection. 3 positive on 3rd to 5th injection.</td>
</tr>
<tr>
<td>10</td>
<td>19</td>
<td>5 negative, 14 positive on 1st to 6th injection.</td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>4 positive 3rd to 6th injection.</td>
</tr>
<tr>
<td>15</td>
<td>5</td>
<td>5 positive on 1st or 2nd injection.</td>
</tr>
</tbody>
</table>
Table VII

Attempted Drug Control of Emesis after Administration of Veriloid

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ROUTE</th>
<th>DOSE (mg/Kg)</th>
<th>Number with Emesis</th>
<th>Number without Emesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopolamine</td>
<td>I.M.</td>
<td>0.5</td>
<td>1*</td>
<td>2</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>I.M.</td>
<td>0.2</td>
<td>1*</td>
<td>2</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>I.M.</td>
<td>0.025</td>
<td>2*</td>
<td>1</td>
</tr>
<tr>
<td>Atropine</td>
<td>I.V.</td>
<td>1.0</td>
<td>7**</td>
<td>3</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>I.M.</td>
<td>2.0</td>
<td>2*</td>
<td>4</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>I.M.</td>
<td>1.0</td>
<td>4*</td>
<td>2</td>
</tr>
<tr>
<td>Etamon</td>
<td>I.V.</td>
<td>15.0</td>
<td>6*</td>
<td>0</td>
</tr>
<tr>
<td>Dramamine</td>
<td>Oral</td>
<td>3.5 - 7.8</td>
<td>6*</td>
<td>0</td>
</tr>
<tr>
<td>Dramamine</td>
<td>Oral</td>
<td>7.3 - 15.9</td>
<td>4*</td>
<td>2</td>
</tr>
<tr>
<td>Dramamine</td>
<td>Oral</td>
<td>4.3 - 16.4</td>
<td>7*</td>
<td>1</td>
</tr>
<tr>
<td>Banthine</td>
<td>I.V.</td>
<td>5.0</td>
<td>4*</td>
<td>3</td>
</tr>
<tr>
<td>Banthine</td>
<td>Oral</td>
<td>5.0</td>
<td>8*</td>
<td>2</td>
</tr>
</tbody>
</table>

* Veriloid administered intravenously in dose of 23 mg/Kg

** Veriloid administered by stomach tube in dose of 23 mg/Kg
Table VIII

Determination of Role of Stomach in Veratrum Induced Emesis

<table>
<thead>
<tr>
<th>Before Ligation of Pylorus</th>
<th>After Ligation of Pylorus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emesis after 23 mcg/Kg by stomach tube.</td>
<td>Emesis after oral administration</td>
</tr>
<tr>
<td>23 mcg/Kg</td>
<td>230 mcg/Kg</td>
</tr>
<tr>
<td>Veriloid</td>
<td>Veriloid</td>
</tr>
<tr>
<td>Veriloid</td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>10 of 10*</td>
</tr>
<tr>
<td>Group II</td>
<td>10 of 10*</td>
</tr>
<tr>
<td>Group III</td>
<td>10 of 10*</td>
</tr>
</tbody>
</table>

* Projectile type of emesis.

** Regurgitant type of emesis.
Table IX
Effect of Denervation on Oral and Intravenous Veriloid Induced Emesis

<table>
<thead>
<tr>
<th>Dog Number</th>
<th>Min. Emetic I.V. Dose (mcg/Kg)</th>
<th>Min. Emetic Oral Dose (mcg/Kg)</th>
<th>Min. Emetic I.V. Dose (mcg/Kg)</th>
<th>Min. Emetic Oral Dose (mcg/Kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>28-30</td>
<td>30</td>
<td>75-125</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>21-25</td>
<td>25</td>
<td>50-75</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>15-18</td>
<td>18</td>
<td>60-80</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>23-25</td>
<td>25</td>
<td>80-100</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>18-23</td>
<td>21</td>
<td>75-100</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>100-120</td>
</tr>
</tbody>
</table>
References

Footnotes

(1) This work was supported in part by a grant from the Massachusetts Heart Association to the Department of Pharmacology, Boston University School of Medicine.

(2) The substances utilized were kindly provided by the following sources:

Eli Lilly and Company, Indiana: Protoveratrine
Riker Laboratories, Los Angeles California: Veriloid, KP and Veratridine
Squibb Institute for Medical Research, New Brunswick New Jersey: Germitrine and Gemidine.

(3) Veriloid (Trademark of Riker Laboratories) is a biologically standardized alkaloidal extract of Veratrum viride of uniform hypotensive potency.

(4) The substances utilized were kindly provided by the following sources:

G. D. Searle and Company, Chicago Illinois: Banthine and Dramamine
Parke Davis and Company, Detroit Michigan: Etabon
Abstract

The effects of veratrum derivatives in the treatment of hypertension have long appeared desirable. Their use has been mainly limited by the side action of nausea and vomiting. This problem of nausea and vomiting has been investigated by, (1) an attempt to find a veratrum derivative with high hypotensive potency and with low emetic properties by the determination of the emetic dose 50 (ED50) values for all the known potent alkaloids. (2) An attempt to determine the site of emetic action which might present an approach to the control of nausea and vomiting. (3) Effort to prevent veratrum induced emesis by the use of various antemetic drugs.

The determination of the emetic dose 50 values for several of the pure ester alkaloids of veratrum was the first step in this series of experiments. The results are listed in Table I. There exists a close correlation between the emetic dose and the hypotensive dose. This is illustrated in Figure I, which shows a straight line relationship between the log of the hypotensive potency and the log of the ED50 values. These results suggest a method of assay for veratrum based on the emetic response of the dog.

The influence of rate of administration on veratrum induced emesis has been investigated. The intravenous emetic dose was found to be constant regardless of the rate of administration (at least until the emetic dose was administered over a period of 45 minutes). The cumulative effect of the emetic properties has been demonstrated by the fact that the intravenous injection of a sub-emetic dose once an
hour caused emesis. Elimination of extreme hypotension as the cause of emesis has not been accomplished but these results suggest that the emesis observed after administration of veratrum is not caused by the hypotensive action of these drugs.

The control of emesis by the use of various agents has been investigated. Tetraethylammonium chloride, atropine, scopolamine, ephedrine, Banthine and dramamine were found to be ineffective for alleviation of Veriloid induced emesis. The ineffectiveness of the pressor drug, ephedrine, suggested that extreme hypotension is not the cause of emesis.

The role of the stomach in emesis after oral administration of veratrum derivatives has been determined by ligation of the pylorus thus preventing the escape of an oral dose from the stomach. The results of these experiments indicate that irritation of the stomach is not involved in the production of emesis after oral administration of Veriloid. These experiments also suggest that veratrum is not significantly absorbed from the stomach. Emesis after oral administration of crude root of veratrum has been shown not to be due to irritation of the stomach.

A series of six experiments were performed in which the gastrointestinal tract was denervated by bilateral supradiaphragmatic splanchnicectomy and vagotomy. In these animals the oral emetic dose was raised fourfold but the intravenous emetic dose remained constant. These results indicate that irritation of the gastrointestinal tract is a negligible factor in Veriloid induced emesis. The change in oral emetic dose is most likely due to decreased activity of the gastrointestinal
tract.

The results of this series of experiments suggest that emesis after the administration of veratrum is not due to peripheral irritation but is the result of stimulation of the vomiting center in the medulla.