A COMPARATIVE STUDY OF ELEVEN ANTI-EMETIC DRUGS IN DOGS

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THE PAPERS written on postoperative nausea and emesis, its prevention and treatment, are legion indeed. The keen interest shown in that subject indicates that it is a major problem to the anaesthetist and that a solution satisfactory to the majority of physicians has yet to be found in spite of the multiplicity of new antinauseants that have been introduced in recent years. This is especially remarkable since some of these new agents undoubtedly possess a high therapeutic index and a fair degree of specificity with a low incidence of side-effects. Yet none of them have been universally accepted and despite some excellent clinical reports they are favoured only by some and rejected by others. The reason for this lack of uniformity in acceptance, and therefore probably in performance, might be found in the multiplicity of excitory causes for postoperative nausea and emesis, and in the fact that no one agent is capable of suppressing them all.

Vomiting is caused by a direct discharge from the vomiting centre in the dorsal part of the lateral reticular formation in the medulla oblungata. This centre may be made to discharge in a variety of ways. Stimuli may reach it from the chemoreceptor trigger zone in the ala cinerea or along vagal or sympathetic fibres from the gastrointestinal tract. In vertigo and motion sickness it is stimulated via the eighth cranial nerve and the vestibular nucleus. Hypoxia or interference with the blood supply of the centre, as may occur when the intracranial pressure is raised, may initiate vomiting, while in hyperemesis gravidarum increased excitability of the centre is presumed to exist. Uraemia, acidosis, radiation, administration of digitalis and other non-specific emetics, migraine, psychogenic factors, and the like are other causes of vomiting. There is no good evidence that any drug exerts a direct action on the vomiting centre;[1] rather it is believed that all act via the chemoreceptor trigger zone. Any of the factors mentioned or combinations of them may be the cause of postoperative nausea and emesis. Hence this phenomenon in the postoperative period is a complex one, and it may well be that not all agents are equally effective in combating the different types of vomiting. The many causes of postoperative vomiting have been clearly enumerated by Simonsen and Vandewater.[2]

This study was conceived to shed some light on this point and to see whether some antinauseant drugs are more indicated than others under certain conditions.

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Study

Eleven antinauseant drugs were studied as to their efficacy against apomorphine-induced and copper-sulphate-induced vomiting. Ten dogs were used in each series and each dog received all eleven drugs in a random sequence with intervals of at least two days between tests. Pilot experiments on the same animals had previously established the minimum of the challenging agent that would cause consistent vomiting in all dogs. All animals had been given a standard meal 15–20 minutes before the experiment. Following the intramuscular administration of the drug under study apomorphine was administered intramuscularly 30 minutes later. The copper sulphate study was conducted in a similar way except that gastric fistulae had been produced some two weeks previously to allow the direct instillation of copper sulphate into the stomach. Four groups of experiments were carried out for each of apomorphine and copper sulphate. In three of these the doses of the antinauseants were varied in an attempt to reach 90–100 per cent protection for each, and in the fourth the amount of the challenging agent was altered against the optimum antinauseant dose previously determined. Not counting the pilot experiments, a total of 870 tests were carried out.

The drugs under investigation were chlorpromazine (Largactil®), promazine (Sparine®), trifluoperazine (Stelazine®), levomepromazine (Nozinan®), proclorperazine (Stemetil®), perphenazine (Trilafon®), thiethylperazine (Torecan®; GS-95), trimethoxybenzamide (Tigan®), dimenhydrinate (Dramamine®; Gravol®), cyclizine (Marzine®), and L-hyoscine (scopolamine). With the exception of thiethylperazine these agents are well known and require no special introductory remarks.

Thiethylperazine dimalate is a phenothiazine derivative with specific anti-emetic properties and has proved highly effective in animals in the prevention of vomiting induced by various means. In as yet unpublished clinical series effective anti-emetic doses have produced few side-effects, none of a dangerous or disturbing nature.

Results

Apomorphine Study

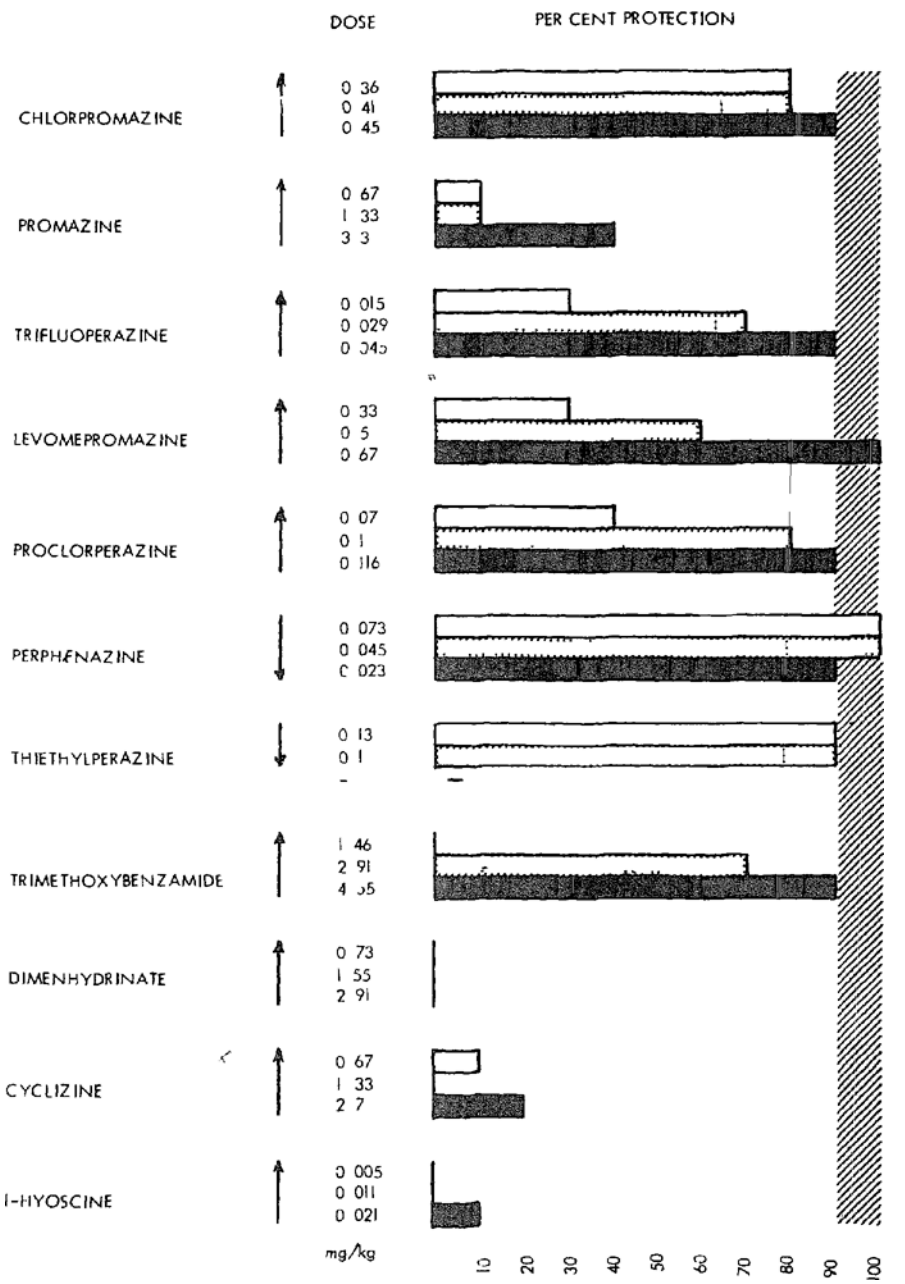
With a challenging dose of 0.06 mg./kg. apomorphine (Table I) a 90–100 per cent protection range was obtained only with perphenazine and thiethylperazine, using doses based on those commonly employed in clinical practice. Chlorpromazine was the next most successful agent by affording 80 per cent protection. When the amount of antinauseant was increased in successive groups adequate protection was eventually obtained with trifluoperazine, levomepromazine, proclorperazine, and trimethoxybenzamide. Decreasing the dosage of perphenazine and thiethylperazine did not significantly change the efficacy of these two agents. Despite significant increases in the dosage promazine, dimenhydrinate, cyclizine, and L-hyoscine remained unsatisfactory agents throughout, although promazine had been increased to 3.3 mg./kg., which is equivalent to almost 250 mg. in a 75 kg. man.

In the next series of experiments the dose of apomorphine was increased to 0.073 mg./kg. (Table II) against the optimum anti-emetic dose in the preceding

TABLE I

VOMITING RESPONSE TO A CHALLENGING DOSE OF APOMORPHINE, 0 06 MG /KG.

White bars denote first series of experiments based on low clinical doses, stippled bars represent next dose range, and black bars denote experiments with a third dose Arrows indicate whether subsequent doses of the anti-emetic were increased or decreased Hatched area represents the 90–100 per cent protection rate at which results were aimed

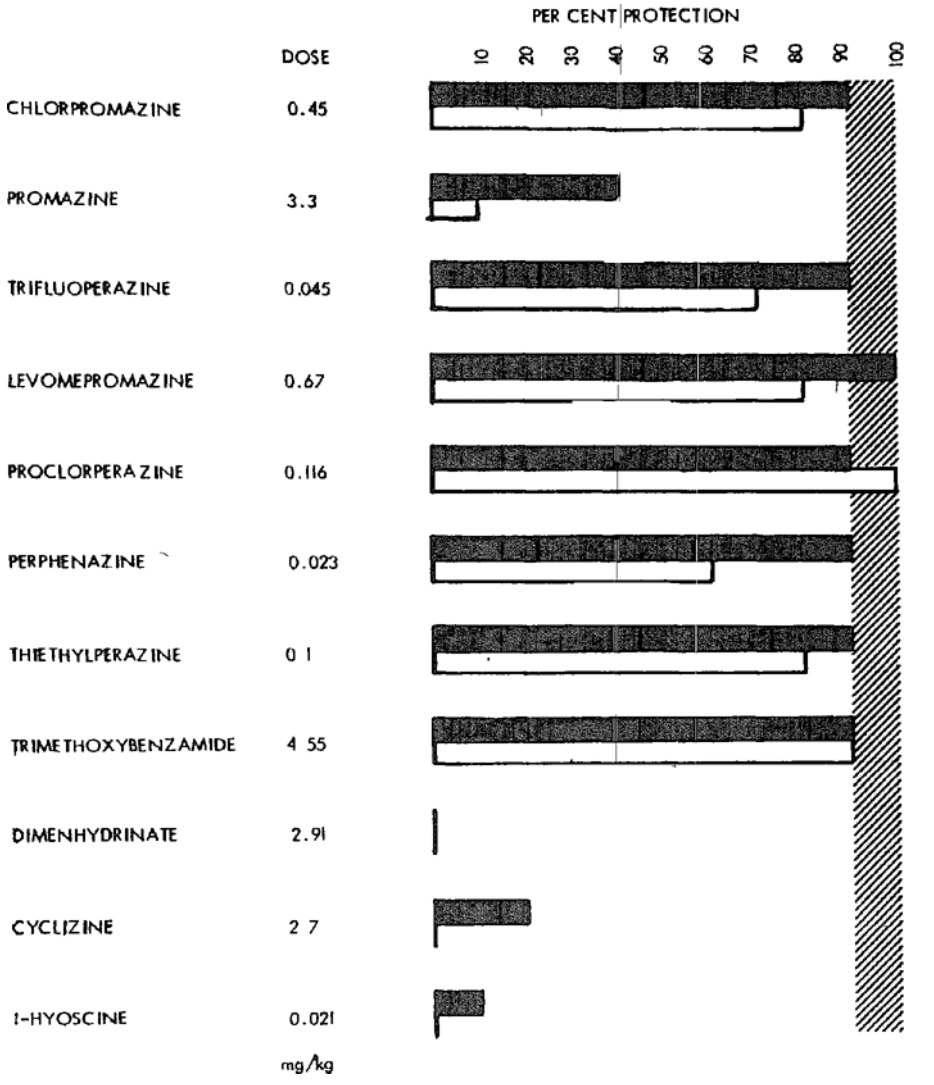


experiments. All drugs, with the exception of proclorperazine, showed some diminution in protection although this reduction was frequently insignificant from a statistical point of view, ranging between 10 and 20 per cent.

TABLE II

INCREASED CHALLENGE: APOMORPHINE, 0.073 MG./KG.

Black bars represent best results obtained with apomorphine, 0.06 mg./kg.; white bars represent results with the increased challenge.

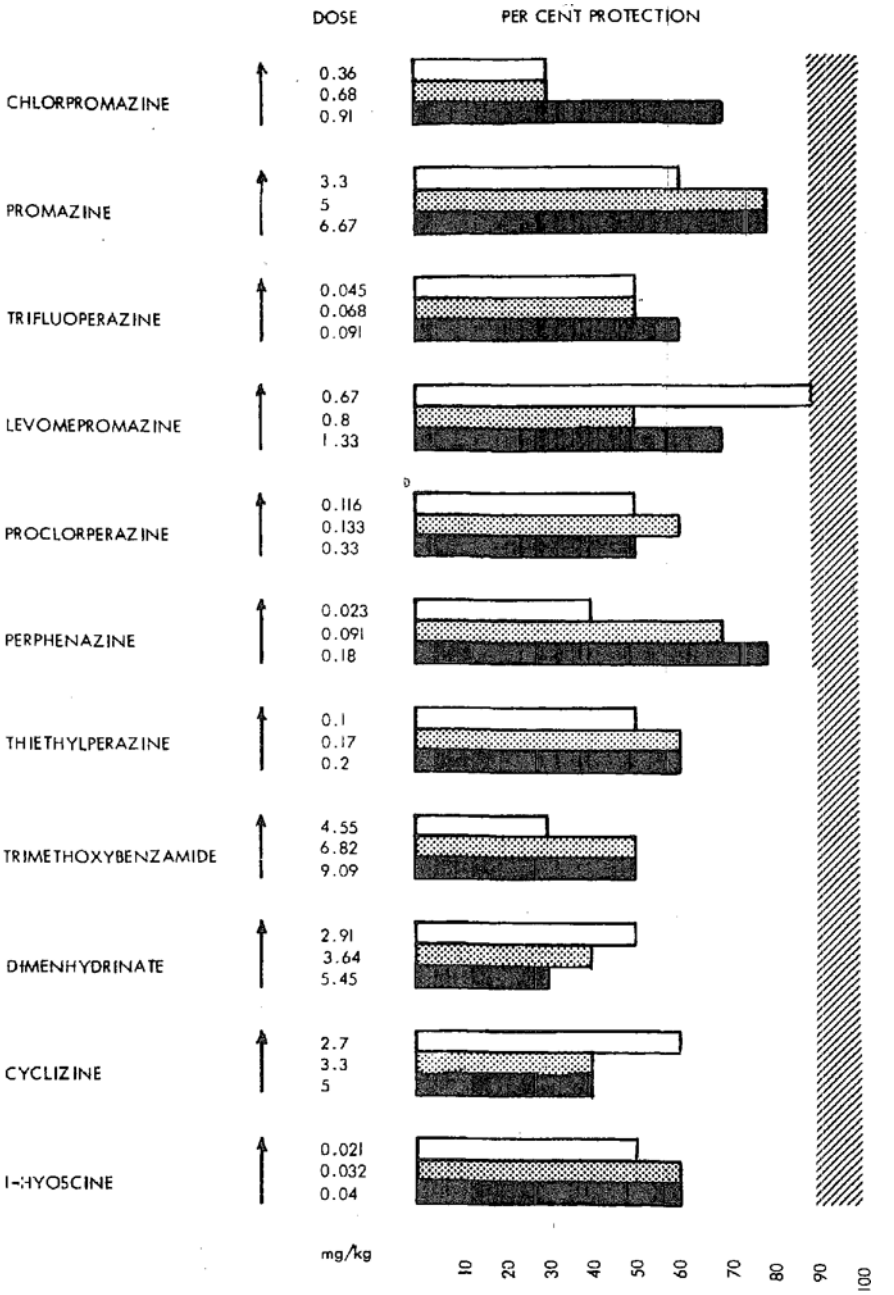


Copper Sulphate Study

In this series a challenge of 3.2 mg./kg. copper sulphate was used initially against the optimum effective protection dose arrived at during the apomorphine experiment (Table III). This revealed that in all cases there was a marked reduction in the efficacy for those agents that had best protected against apomorphine, whereas with those that had provided minimal protection, a marked increase in efficacy was now observed. Only by a further substantial increase of dose was the goal of 90 per cent protection reached with levomepromazine, while with chlorpromazine, promazine, and perphenazine an 80 per cent protection was thus attained. Although dimenhydrinate, cyclizine, and L-hyoscine never exceeded 60 per cent protection, they were obviously very much more active against copper-sulphate-induced vomiting than against apomorphine.

TABLE III

VOMITING RESPONSE TO A CHALLENGING DOSE OF COPPER SULPHATE, 3.2 MG./KG. White bars denote first series of experiments based on optimum anti-emetic doses of the apomorphine study. All other legends as in Table I.

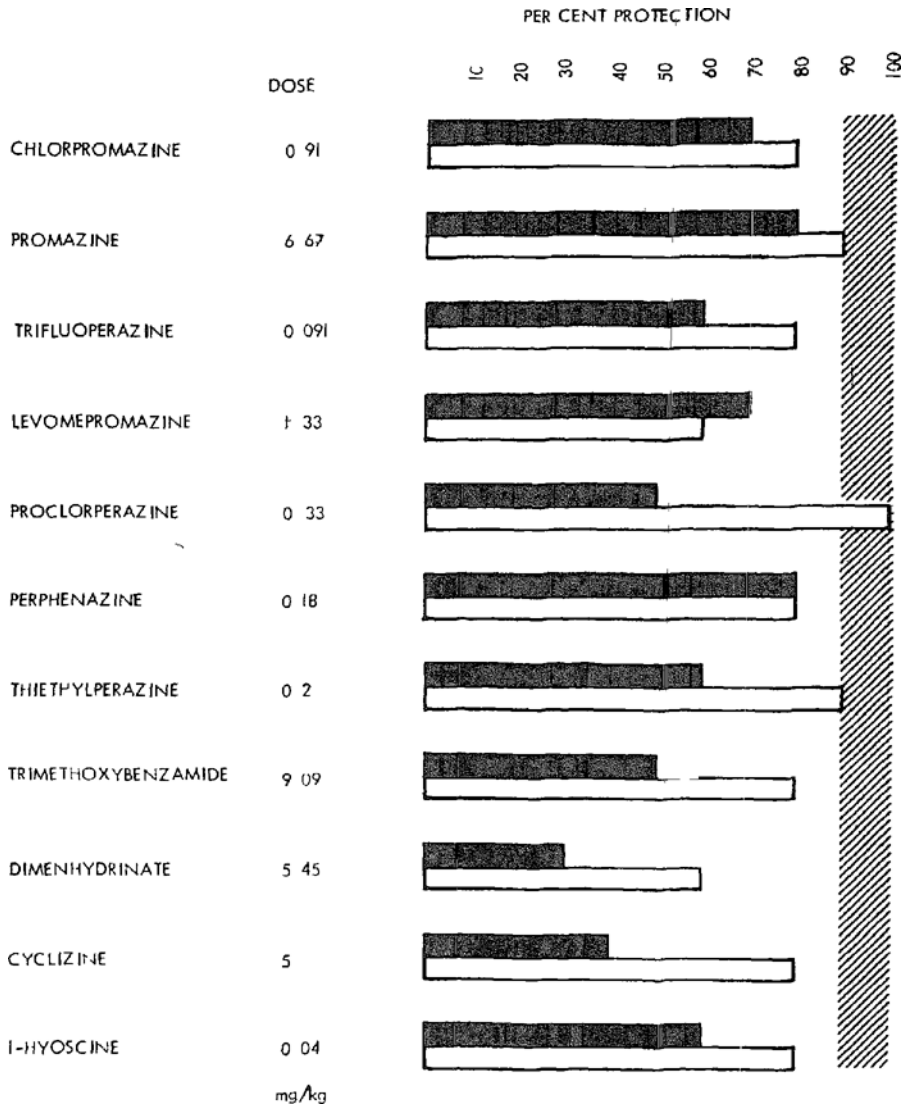


In the last series of tests (Table IV) the optimum protective dose was administered in the presence of a challenge of copper sulphate decreased to 2.35 mg./kg. In these tests the 90–100 per cent protection goal was reached with promazine, proclorperazine, and thiethylperazine, and 80 per cent was reached with chlorpromazine, trifluoperazine, trimethoxybenzamide, cyclizine, and L-hyoscine; perphenazine remained unchanged at 80 per cent. Again the now more adequate

TABLE IV

DECREASED CHALLENGE: COPPER SULPHATE, 2.35 MG./KG.

Black bars represent best results obtained with copper sulphate, 3.2 mg./kg.; white bars represent results with the decreased challenge.



performance of cyclizine, hyoscine, and promazine is noteworthy in comparison with apomorphine-induced vomiting.

DISCUSSION

In interpreting the results of this study, it is well to remind oneself that the tests reported were carried out on animals and not in man. This may explain why in some instances the dose of the anti-emetics had to be raised to levels that are quite unrealistic from a clinical point of view. They would almost certainly have caused in man such undesirable side-effects as drowsiness, hypotension, and dizziness, so as to preclude their clinical use. While some animals showed signs of

sleepiness in some instances, these were isolated and followed no logical pattern. A further explanation of the high doses needed may have been the magnitude and acuteness of the emetic challenge administered, although it was a *minimum* consistent stimulus for the animals studied.

Ignoring, therefore, the anti-emetic doses as absolute values, some patterns nevertheless emerge which would seem to be significant, especially since they tend to coincide with clinical impressions and published studies in man.

Where vomiting is due to stimulation of the emetic trigger zone (as with the administration of apomorphine), phenothiazines, related agents, and trimethoxybenzamide are clearly superior anti-emetics to those agents belonging to other chemical groups. The only exception in this regard was promazine, which surprisingly enough made a poor showing in this regard, while perphenazine and diethylperazine proved best. No increase in dose within realistic limits could bring the efficacy of dimenhydrinate, cyclizine, or L-hyoscine even close to acceptability. That the protection afforded by any particular agent depends primarily upon the dose of that drug, while the intensity of the stimulus-provoking emesis is of lesser, if any importance, is clearly evident from that portion of the study in which the dose of the challenge was altered.

An entirely different picture emerges in vomiting caused by gastrointestinal stimulation, as represented by the copper sulphate series. None of the previously highly effective agents reached the same peak of performance, while the entirely unsatisfactory agents improved to the point of equality with the former. This time variation in the challenging stimulus was more clearly reflected in the rate of protection.

Thus there appears to exist a specificity of action which must be borne in mind when antinauseants are prescribed. It would appear that best results can consistently be obtained by the use of such agents as chlorpromazine, trifluoperazine, levomepromazine, proclorperazine, perphenazine, thiethylperazine, and trimethoxybenzamide, irrespective of the cause of emesis. The ultimate choice will depend upon personal preference and incidental side-actions of each agent, deliberately sought or to be avoided. If agents, such as dimenhydrinate or cyclizine, are to be prescribed, a thorough evaluation of the cause of vomiting is necessary, and its origin from the gastrointestinal tract must be established with certainty if failures in treatment are to be avoided. Since such diagnosis is often difficult, if not impossible, in the postoperative period, one would be safer to curtail their use drastically under those circumstances.

It must not be forgotten in the general discussion of the usefulness of various anti-emetics that this study does not include other types of emesis in which specific indications may well exist for some drugs that have been unimpressive in the present tests. For instance, it has been well proved by Gay *et al.*[3,4,5] and by Chinn and co-workers[6,7] that L-hyoscine and some of the antihistaminics, such as dimenhydrinate, are most useful agents in combating motion sickness. This as well as some other forms of vomiting has not been investigated by us Hence there might exist an even greater specificity of anti-emetic therapy than this present study would suggest.

Summary

Using a cross-over technique in which each animal served as its own control, it was found that not all anti-emetics are equally effective against both apomorphine-induced and copper-sulphate-induced vomiting. Trimethoxybenzamide and the phenothiazines, with the exception of promazine, were highly effective in controlling apomorphine-induced emesis; they were effective to a lesser degree, but still satisfactorily, against the emetic challenge of copper sulphate. Dimenhydrinate, cyclizine, and L-hyoscine were entirely ineffective in controlling apomorphine-induced vomiting but were reasonably satisfactory in combating the effect of copper sulphate, in that they afforded protection similar to trimethoxybenzamide and the phenothiazine derivatives.

It is therefore concluded that in the postoperative period, when multiple factors are at work in the production of emesis, trimethoxybenzamide or one of the phenothiazines be used to control emesis unless there is a clear indication that vomiting is entirely of gastrointestinal origin, in which case one of the other agents may be successfully employed.

Our findings were in keeping with our clinical impressions. The doses required for some of the phenothiazines to control vomiting in dogs were so large that one would surmise that if the same dose relationship exists in man, marked side-effects would be produced in addition to satisfactory control of emesis.

Résumé

Nous avons étudié l'efficacité de onze médicaments anti-émétiques sur des chiens chez lesquels des vomissements avaient été provoqués par de l'apomorphine et du sulfate de cuivre. Nous avons employé des animaux dans chaque série et chacun des chiens a reçu les onze médicaments dans un ordre indéterminé à un intervalle d'au moins deux jours entre les tests. Au cours de chacune des études de l'apomorphine et du sulfate de cuivre, nous avons essayé de trouver la dose protégeant pour un pourcentage de 90 à 100 pour cent, ou autrement établir la protection offerte par des doses raisonnables à chacun des antinauséeux. La dose donnant le meilleur résultat était par la suite essayée dans un test avec une plus forte dose d'apomorphine. Au cours de l'étude du sulfate de cuivre, la dose anti-émétique optima trouvée au cours de l'étude de l'apomorphine était d'abord employée et était ensuite augmentée dans le but d'obtenir un taux de protection de 90 à 100 pour cent pour chaque médicament. Ensuite, la dose optima pour chaque médicament était de nouveau essayée dans un test différent au sulfate de cuivre dont la dose, cette fois, était diminuée. En général, nous avons trouvé que les dérivés du triméthoxybenzamide et de la phénothiazine, à l'exception de la promazine, donnaient les meilleurs résultats dans les vomissements provoqués par l'apomorphine alors que la protection offerte par tous les autres agents s'est avérée négligeable. Ces mêmes médicaments non satisfaisants se sont toutefois montrés beaucoup plus efficaces contre les vomissements provoqués par le sulfate de cuivre alors que les phénothiazines qui nous avaient donné satisfaction antérieurement ne nous ont pas donné une aussi bonne protection.

Nous en venons donc à la conclusion que, à moins que les vomissements prennent origine exclusivement du système gastro-intestinal, les dérivés du triméthoxybenzamide et de la phénothiazine sont préférables. Toutefois, il faut se souvenir que les phénothiazines produisent d'autres effets secondaires qui peuvent nous faire hésiter à employer quelques-unes d'entre elles aux doses requises pour obtenir une suppression satisfaisante des vomissements chez les chiens.

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REFERENCES

1. Borison, H. L. & Wang, S. C. Physiology and Pharmacology of Vomiting. Pharmacol. Revs. *5*(2): 193–230 (1953).
2. Simonsen, L. E. & Vandewater, S. L. Postoperative Vomiting: A Review and Present Status of Treatment. Canad. Anaesth. Soc. J. *9*(1): 51–60 (1962).
3. Gay, L. N. & Carliner, P. E. The Prevention and Treatment of Motion Sickness. I. Seasickness. Bull. Johns Hopkins Hosp. *84*: 470–487 (1949).
4. Gay, L. N. Prophylactic and Therapeutic Control of Vestibular Disturbances with Dimenhydrinate. J.A.M.A. *145* (10): 712–715 (1951).
5. Gay, L. N. A Subsequent Report on Dramamine. The Prophylactic and Therapeutic Control of Motion Sickness and Vestibular Disturbances. Mil. Surgeon *108*: 324–331 (1951).
6. Chinn, H. I.; Noell, W. K.; & Smith, P. K. Prophylaxis of Motion Sickness. Evaluation of Some Drugs in Seasickness. Arch. Int. Med. *86* (6): 810–822 (1950).
7. Chinn, H. I.; Handford, S. W.; Cone, T. E.; & Smith, P. K. The Effectiveness of Various Drugs for the Prophylaxis of Seasickness. Am J. Med. *12*: 433–439 (1952).