PERPHENAZINE IN CLINICAL ANAESTHESIA[1]

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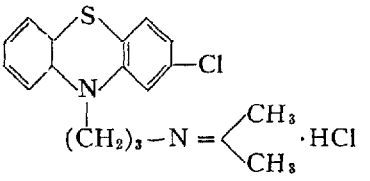
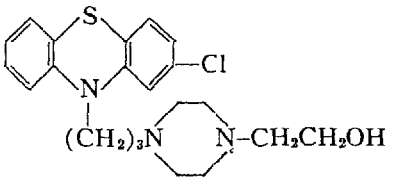
PERPHENAZINE (Trilafon®) is 1-(2-hydroxyethyl)-4-[3-(2-chloro-10-phenothiazyl)-propyl]-piperazine. The chlorophenothiazine derivative is obtained as a white crystalline solid which is soluble in organic and inorganic acids. It combines with hydrochloric or maleic acid to give crystalline salts which are water soluble. Tablets for oral administration contain 2, 4, and 8 mg. The intramuscular and intravenous preparation is provided in colourless ampoules containing 5 mg. in 1 ml. The pH of this solution is 5.9 and causes no irritation when injected by vein or into the muscles. Perphenazine is one of the "broad spectrum" group of tranquillizers. The structural relationship to chlorpromazine is shown below:



CHLORPROMAZINE (LARGACTIL®)



PERPHENAZINE (TRILAFON®)

Following initial reports of the wide range of neuro- and psycho-sedative effects and the potent anti-emetic activity of perphenazine (1, 2), a preliminary trial was made with this drug in association with anaesthesia. Perphenazine was reported to provide a satisfactory sedative response without excessive hypnosis, and it appeared to be effective in alleviating nausea and vomiting, at a dose level which did not cause a significant change in blood pressure, pulse rate, or respiration (3). A more extensive trial was therefore undertaken to test perphenazine for two specific applications in anaesthesia. Animal studies were carried out to determine whether perphenazine was effective in suppressing epinephrine-provoked cardiac arrhythmias in dogs under anaesthesia (4, 5). Clinical studies were carried out mainly to determine the anti-emetic effects of perphenazine in association with anaesthesia.

METHOD

Those patients with a previous definite unpleasant history of postoperative vomiting were premedicated with perphenazine, usually without a narcotic supplement, and the incidence of postoperative vomiting was recorded. Perphenazine was also administered during the course of regional anaesthesia in patients who required supplementary sedation or relief of hiccoughs, or who developed nausea and vomiting during the operation. Patients who had nausea,

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retching, and vomiting in the early postoperative period were treated with perphenazine either intravenously or intramuscularly to determine whether these symptoms could be alleviated immediately while the patient was under direct supervision in the postanaesthetic recovery ward.

The study was set up in this way because many of the patients who were scheduled for major operations were premedicated with other phenothiazine derivatives (promethazine, levomepromazine, promazine, and proclorperazine) which would reduce the incidence of nausea and vomiting postoperatively.

From July, 1956, to October, 1957 (16 months), the over-all incidence of nausea and vomiting among patients admitted to the recovery room, *excluding those who arrived with gastric suction*, was 705 in a total of 4,563 (15.5 per cent). Perphenazine was under trial from November, 1957, to February, 1959 (16 months). During this time the incidence of nausea and vomiting was 818 in a total of 5,383 (15.2 per cent). Aside from the introduction of Fluothane, and Fluothane-ether anaesthesia, there were no remarkable changes in the types of anaesthetics used in the second period.

In the first period, over 14 per cent received a phenothiazine for premedication, while in the second period over 16 per cent received a phenothiazine for premedication. This did not materially affect the data that were analysed, because most of these patients underwent major abdominal operations and gastric suction was used in many of them.

Since it was not desirable to administer additional drugs as a routine prophylactic against symptoms which might require treatment in less than 15 per cent of patients, it was left up to the senior nurses of the recovery room to request treatment for those patients who were having persistent nausea, retching, and vomiting, and to record whether administration of perphenazine intravenously or intramuscularly was effective in relieving the patient promptly. This method was considered valid in handling a situation where the course of the untreated symptom is notoriously variable, and where the trap of *post hoc* reasoning might be fallen into if every patient received the same treatment.

Results

During this trial, 107 patients had a definite previous history of vomiting after general anaesthesia. Perphenazine was used for premedication intramuscularly about one hour before scheduled operation in each of these. Postoperative vomiting occurred in 11 patients of this group (10 per cent).

During the course of regional anaesthesia, 73 patients were given perphenazine 5 mg. intramuscularly or intravenously as supplementary sedation In each patient the resulting sedation was satisfactory and two of these vomited postoperatively. Perphenazine was administered to 54 patients in whom nausea or vomiting developed during spinal anaesthesia, with prompt and complete relief in all but one. In 233 other patients who received low spinal anaesthesia, nausea and vomiting occurred in 29 (13 per cent). Hiccough was treated only seven times, with prompt relief in six patients.

Persistent nausea, retching, and vomiting was treated in 411 of 818 patients in

the recovery room. Of these, 362 received perphenazine. All but 18 obtained prompt and complete relief (95 per cent effective). The other 49 patients were given a variety of other anti emetic drugs by choice of the surgeon, and will not be considered here. Many of the patients who were not given specific drug therapy had a long period of vomiting and were treated with gastric suction.

During the period that perphenazine was under trial, it was noted that the onset of nausea and vomiting in the recovery room followed the administration of pain-relieving drugs (meperidine, morphine, and codeine) in 212 patients (26 per cent).

Discussion

Nausea and vomiting are often regarded as a protective function for the removal of noxious substances in the gastro-intestinal tract and an important diagnostic sign. However, the development of these symptoms in the immediate postanaesthetic period serves no apparent useful purpose, and often may be detrimental to the patient. Retching and emesis during this period may increase pain at the operative site, aggravate emotional upsets related to the operation, and, if persistent, may upset water and electrolyte balance. Fear and anxiety associated with vomiting may also rapidly exhaust the postoperative patient.

Many drugs are available to the anaesthetist now which have sedative and anti-emetic activity when used for premedication. It is also thought that with the newer anaesthetic agents, and improvements in technique, the incidence of nausea and vomiting directly related to the effect of anaesthesia itself is in sharp decline. For these reasons, the main part of this study was directed to evaluating the effect of perphenazine on nausea, retching, and vomiting after their development.

It has become apparent that even with the use of a variety of tranquillizing drugs, there are still between 5 and 10 per cent of all postanaesthetic patients who vomit, regardless of the anaesthetic technique. Though the pharmacological and physiological bases for nausea and vomiting have been studied in great detail, the site of action of emetic drugs and other noxious stimuli have not been clearly elucidated (6). When one looks more closely at this problem in the postoperative patient, two etiological factors might appear to emerge more clearly. First and foremost, anxiety and fear might be important causes of vomiting, owing either directly to the cortical and subcortical effects of emotion, or secondarily to the effects of hypotension, due to blood loss, surgical trauma, anaesthetic drugs, or the anxiety itself. Secondly, aside from effects of induction and emergence from anaesthesia (ether especially), the analgesic drugs may cause nausea and vomiting. In over one-quarter of the patients who developed nausea and vomiting postoperatively, the onset followed the administration of a pain-relieving drug. It is highly likely, therefore, that the analgesics themselves act as an emetic stimulus after general anaesthesia. This observation is well known, but is seldom mentioned or considered in reports on prophylactic and therapeutic trials of anti-emetic drugs.

The observation that administration of some of the tranquillizer drugs as preoperative medication or immediately preceding the end of an operation

produced an anti-emetic effect may be explained on the basis of a prolongation of the analgesic and sedative effects of the anaesthetic. This permitted a longer postoperative period of narcosis and "belle indifference." There may also be direct suppression of the medullary emetic trigger zone by such drugs. These mechanisms were considered with chlorpromazine, and probably apply to perphenazine (7–10).

Since it is difficult to estimate a patient's capacity to control his tension and anxiety and to suppress feelings of dependence and helplessness, it is wisest, in most cases, to observe the response to surgical trauma and pain, and treat the complaints and symptoms as they arise, employing only those agents which are proven to be highly effective. Perphenazine relieved nausea, retching, and vomiting in 95 per cent of the patients treated in this study, without causing an undesirable hypnotic effect, or depression of blood pressure or respiration.

Others have reported the efficacy of perphenazine as a postoperative anti-emetic. In a blind study of perphenazine and a placebo, alternate patients were given perphenazine intramuscularly immediately preoperatively and then intramuscularly every 6 hours for 3 doses. The dose selected was 3.75 mg. perphenazine for all patients over 12 years of age, so that each patient received a total of 15 mg. in 18 hours. No alteration was made in the usual routine premedication. They found that the incidence of vomiting was reduced from 18 per cent (placebo) to 6.3 per cent (perphenazine) in a series of over 600 cases. They also found that perphenazine did not cause hypotension or prolonged narcosis (11). In the second study (12), alternate patients in a series of 200 were given 5 mg. of perphenazine intramuscularly at the end of the operation, and they were observed closely for the first 6 hours after operation for incidence of vomiting. These patients were unselected, except that patients with stomach tubes and those scheduled for a gastrectomy were omitted. There was no evident difference between the control and treated group regarding premedication, anaesthetic agent, or operation which might contribute to the vomiting rate The control group had a vomiting rate of 21 per cent, of those who received perphenazine, 7 per cent vomited in the first 6 hours postoperatively No side-effects of perphenazine were observed

The present investigation revealed that premedication with perphenazine reduces the incidence of postoperative vomiting in patients with a previous history of such a disturbance, and it is highly effective in relieving these symptoms when they occur in the operating room during regional anaesthesia. It was 95 per cent effective in relieving nausea, retching, and vomiting without delay in the recovery room. It was also uniformly effective in providing adequate sedation during regional anaesthesia in every case in which it was used as a supplement.

Summary and Conclusions

An evaluation of perphenazine was carried out to test its prophylactic and therapeutic effects on nausea, retching, and vomiting, which occurred during or after anaesthesia.

The prophylactic effect was tried in patients who had a previous history of vomiting after general anaesthesia. Only 10 per cent of these patients vomited postoperatively. When administered as supplementary sedation during spinal anaesthesia, the incidence of postoperative vomiting was much less (2 per cent) than in those who did not receive perphenazine (13 per cent).

Nausea, retching, or vomiting which developed during regional anaesthesia or in the postanaesthetic recovery period was effectively and promptly relieved in 95 per cent of the patients who were treated with perphenazine

The single administration of 5 mg perphenazine intramuscularly as premedication, or as supplementary sedation, is effective prophylaxis for reducing the incidence of postoperative nausea and vomiting. The same dose administered intravenously or intramuscularly is highly effective therapy for nausea, retching, and vomiting which develop during regional anaesthesia or after general anaesthesia. This dose has no significant effect on the blood pressure, pulse rate, or respiration

Acknowledgments

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Résumé

Au cours de l'anesthésie régionale ou à la suite de n'importe quelle anesthésie, l'apparition de nausées, de haut-le-cœur et de vomissements ne présente aucune utilité pour le malade et souvent devient nuisible au malade Cela augmente la douleur au site opératoire et le stress psychique qui accompagne l'opération et cela peut même troubler l'équilibre hydrique et électrolytique. La crainte et l'anxiété ajoutées aux vomissements peuvent aller jusqu'à épuiser le malade au cours des suites opératoires

A part l'induction et le réveil de l'anesthésie, la crainte et les agents analgésiques ont été comptés comme des facteurs responsables des nausées et vomissements A cause de cela, puisqu'il est très difficile de prédire si un malade vomira, il nous semble plus sage, dans la plupart des cas, d'observer la réponse à l'anesthésie, au traumatisme chirurgical, à la douleur et de traiter ensuite les plaintes et les symptômes tels qu'ils se présentent en employant exclusivement les substances qui se sont avérées des plus efficaces.

Nous avons fait une étude de la perphenazine (Trilafon®) pour apprécier ses effets prophylactiques et thérapeutiques des nausées haut-le-cœur et vomissements observés au cours et après l'anesthésie.

Nous avons étudié le pouvoir prophylactique chez des malades qui présentaient une histoire antérieure de vomissements à la suite d'anesthésie générale. Seulement 10 pour cent de ces malades ont vomi après l'opération. Lorsque nous avons donné de la perphenazine comme sédatif additionnel au cours de la rachianes-

thésie, la fréquence des vomissements post-opératoires a été réduite de beaucoup (2 pour cent) comparativement aux malades qui n'en avaient pas reçu (13 pour cent).

Chez les malades qui, au cours d'une anesthésie régionale ou au cours du réveil de l'anesthésie, présentaient des nausées, des haut-le-cœur et des vomissements, le traitement à la perphenazine a été promptement efficace dans 95 pour cent des cas.

Le seul fait d'administrer 5 mg. de perphenazine par voie intramusculaire en prémédication ou comme sédatif additionnel devient une prophylaxie efficace pour diminuer la fréquence des nausées et des vomissements post-opératoires. Cette même dose donnée par voie endoveineuse ou intramusculaire est un traitement très efficace des nausées, haut-le-cœur et des vomissements qui apparaissent au cours des anesthésies régionales et après l'anesthésie générale. A cette dose, nous n'avons pas noté d'effets appréciables sur la tension artérielle, la vitesse du pouls et la respiration.

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