A NEW ANTI-EMETIC FOR MUSTINE NAUSEA*

R. SEALY, M.A., M.MED. (RAD. T.), F.F.R. AND H. S. KING, M.B., CH.B., *Radiotherapy Department, Groote Schuur Hospital and University of Cape Town*

While a considerable amount of attention has been given to the treatment of radiation sickness, surprisingly little has been given to that following alkylating and other chemotherapeutic agents for cancer. The symptoms of nausea and vomiting following treatment by these means can often be profound and cause the patient considerable mental and physical distress.

These symptoms are one of the factors which have to be considered when prescribing therapy of this kind, and has in our experience sometimes led to refusal of treatment by patients. Moreover, since this type of therapy is often symptomatic or palliative, the alleviation of nausea and vomiting would take treatment of this kind nearer the ideal cancer palliative—loss of symptoms without causation of symptoms.

We have habitually treated mustine nausea by premedication with sodium gardenal and have found this to be fairly effective, provided the patient could sleep afterwards, but it is less effective when used in the outpatient treatment of mustine sickness. Many patients seem to prefer outpatient therapy, provided an early return to their homes is possible after the injection, since this causes less disruption and home surroundings are nearly always preferable to hospitalization.

Stoll[1] found phenothiazines to be most effective in the treatment of radiation sickness, and it is well known that these drugs act by depressing the superficially situated chemoreceptor trigger zone for the vomiting centre in the dorsal portion of the lateral reticular formation in the medulla.[2]

Apomorphine[3] and the emetic action of radiation[4] exert their actions via this zone. It may be, however, that the site of action of nitrogen mustard in the induction of vomiting is on the gut as well as centrally,[5] since it has been found with massive doses in cats that ablation of the chemoreceptor zone with and without gut denervation did not prevent vomiting. Further work is indicated here since elucidation of this point, using clinical dosage levels, would be of importance in further consideration of the treatment of mustine nausea.

CONTROLLED TRIAL

A new phenothiazine derivative, 9965 RP, with the chemical formula of 2 methyl sulphonyl - 10 - 3'- (4 carbamoyl piperidino) propyl phenothiazine, has been tested. This agent has a very low toxicity and has been shown to be between 100 and 250 times more effective in preventing apomorphine-induced vomiting in dogs than chlorpromazine. There is no effect on the vomiting induced by installation of copper sulphate solution into the stomach and it seems to exert its effects entirely by a central action. Under laboratory conditions the blood pressure changes are similar in degree to those seen with chlorpromazine and there is a high antiserotonin effect.* Drowsiness has been noted in other evaluations of the drug, but no side-effects of any kind have been noted in our patients.

*Date received: 21 November 1968.

*Preclinical information supplied by manufacturers.

Since 9965 RP is one of the most powerful anti-emetics known, it seemed that a controlled trial of this agent was indicated in mustine-induced nausea. All 38 patients taking part in the trial had confirmed malignant disease with a limited life expectancy and required palliation of symptoms.

Those who already had nausea and vomiting were excluded. The diagnoses of the patients treated are shown in Table I. There were 29 males and 9 females in the trial, with ages ranging from 17 to 81 years. The two agents to be tested were prepared in ampoules containing 5 mg. of 9965 RP and 200 mg. of sodium gardenal, respectively, and were randomly allotted A or B designations. Two injections of mustine, each 0·2 mg./kg. body-weight, were given on 2 successive days, and the contents of one of the series of ampoules (A or B) were given intramuscularly at the time of the mustine injection.

TABLE I. DIAGNOSIS OF DISEASES TREATED WITH MUSTINE AND 9965 RP

Diagnosis	*No. of cases*
Carcinoma of bronchus	17
Hodgkin's disease	14
Reticulum-cell sarcoma	2
Carcinoma of bladder	2
Giant follicular lymphoma	1
Carcinoma of stomach	1
Mesothelioma	1
Total	38

One week later the patient was questioned by one of us, who scored the degree of nausea and vomiting as assessed by the patient after the two injections. Four degrees of severity were recorded, i.e. severe, moderate, mild and none. These corresponded to marked vomiting, vomiting, nausea only and no symptoms. Respective scoring values of 3 - 0 were given. The individually recorded results were scored by a third person who had no contact with the patients. For a result to be regarded as significant, it was required that there be at least a scoring difference of two between the values given by the patients.

Of the 38 patients taking part in the trial, 19 showed no preference for either compound, 15 preferred 9965 RP and 4 preferred sodium gardenal. The results were plotted by sequential analysis and the new compound is favoured ($2\alpha = 0{\cdot}2$).

DISCUSSION

It is perhaps a little disappointing that 50% of those in the trial returned a 'no preference' result, but it is to be noted that out of the 76 mustine injections nearly half (31) were followed by no (15) or mild (16) symptoms, and 6 patients did not vomit with either drug. However, 13 patients with moderate or severe symptoms failed to show any preference. The possible explanation for this might be a peripheral action of mustine, apart from a possible failure of central control. We nevertheless consider this new agent to be of value, and it is to be preferred to sodium gardenal and to chlorpromazine. It would be interesting to compare its efficacy with that of trifluoperazine (Stelazine) which was found by Stoll[1] to be one of the more effective agents for the relief of radiation nausea.

SUMMARY

A clinical trial comparing the efficiency of sodium gardenal and a new phenothiazine derivative in mustine nausea has been undertaken. The new compound is favoured. Some aspects of radiation and chemotherapy nausea are discussed.

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