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Antiemetics in Cancer Chemotherapy

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A. Introduction

Nausea and vomiting induced by several cancer chemotherapy agents is often the most distressing side effect of treatment. The mechanisms are quite complex. The vomiting center in the reticular formation can be stimulated by either afferent stimuli from the gastrointestinal tract or by the chemoreceptor trigger zone (CTZ). The latter is probably the primary site for emetic activity of most cancer chemotherapeutic agents and is accessible to drugs that do not cross the blood–brain barrier. It is quite possible that several agents have different receptors. The wide spectrum of antiemetics is in contrast to the often observed lack of effectiveness. The more successful trials have concentrated on agents, doses, schedules, or routes of administration that were not generally used prior to 1980. An effective study design has reduced methodological difficulties and reproducible data have been reported.

For most chemotherapeutic agents with emetic properties, the onset of emesis occurs 2–3 h after administration in previously untreated patients. In most instances, the drug dose and the route of administration are important variables affecting the incidence of nausea and vomiting. Many patients manifest prechemotherapy emesis; the anticipatory vomiting overlaps continuously with the drug-induced symptoms.

Therefore, successful antiemetic treatment needs prophylactic pharmaceutical intervention, starting 1–12 h before administration of emetic cancer chemotherapy to prevent or lessen the initial occurrence of vomiting.

B. Antiemetic Agents

I. Phenothiazines

Phenothiazines can prevent apomorphine-induced vomiting. The antiemetic effectiveness in various chemotherapeutic regimens has been examined under randomized conditions. Phenothiazine derivatives are therefore the most frequently used agents to prevent emesis in cancer chemotherapy. Toxicity usually consists of sedation, with occasional extrapyramidal and "paradoxical" reactions.

II. Butyrophenones

Droperidol and haloperidol are also effective antiemetics. Like the other agents, the antiemetic activity probably acts on the CTZ of the area postrema. Several clinical studies have shown, in addition to the high antiemetic qualities, a very low incidence of side effects, including sedation and extrapyramidal reactions.

III. Cannabinoids

Tetrahydrocannabinol (THC), the psychoactive substance of cannabis, has antiem-

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etic properties. THC and synthetic cannabinoids (nabilone, levonantradol) have been studied in randomized trials. Some authors reported a higher antiemetic activity than conventional agents, but toxicity has been frequent. The side effects include sedation, hypotension, dizziness, and a psychotropic "high". The psychogenic reactions have caused a decreased acceptance of cannabinoids.

IV. Benzamides

Metoclopramide, alizapride, and benzquinamide are also widely used as antiemetics. It has been postulated that these agents exert their antiemetic potency by blocking dopamine receptors in the CTZ and the gastrointestinal tract. Low doses of metoclopramide failed to show antiemetic activity in chemotherapeutic-induced vomiting. Given in high doses (1–2 mg/kg every 2 h) to patients receiving Cisplatin chemotherapy, metoclopramide demonstrated antiemetic efficacy. Sedation is the most frequent side effect. Occasionally dystonic reactions and akathisia have been reported.

V. Corticosteroids

In most clinical trials, dexamethasone or methylprednisolone have been used. Useful antiemetic results have been reported. The mechanisms are unknown. Toxicity with short-course regimens of steroids has been mild. Interactions with the antitumor efficacy of the chemotherapeutic drugs were not noted. Corticosteroids are effective antiemetics with a low degree of toxicity.

C. Conclusions

Successful antiemetic treatment needs prophylactic pharmaceutical intervention starting before administration of emetic cancer chemotherapy to prevent or lessen the initial occurrence of vomiting. Phenothiazines, butyrophenones, cannabinoids, benzamides, and corticosteroids given in high doses have demonstrated antiemetic efficacy and represent to date the most active agents. It is possible that the chemotherapeutic drugs exert their emetic effects through different pathways. Therefore, combination regimens may be expected to produce an improvement in patient care.