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Combination Antiemetics

Nausea and vomiting secondary to agents such as cisplatin are a major cause of morbidity in cancer chemotherapy (1). Gastrointestinal upset occurs in as many as 83% of these patients and may, in fact, be the limiting factor in chemotherapy (2). At the present time, only three major drug classes have been considered to be effective antiemetics: antihistamines, anticholinergics, and dopamine antagonists. These drugs are thought to act on the chemoreceptor trigger zone and/or emetic center in the medulla oblongata (2) where recent neuropharmacologic techniques have demonstrated the presence of histamine H_1 (3), muscarinic cholinergic (4), and dopamine (5) receptors. However, no single agent has yet proved to be effective in relieving severe nausea and vomiting. It thus follows logically that antiemetic efficacy might be improved by combining drug effects at all three proposed sites of action.

Morran et al (1) reported that the combination of fluphenazine and nortriptyline significantly reduced the incidence and severity of nausea and vomiting during cancer chemotherapy. The effectiveness of nortriptyline, an antidepressant, was thought to be related "to the relief of psychiatric morbidity which is common in patients receiving chemotherapy" (1). More likely, nortriptyline's antiemetic actions derive from its potent antihistamine and anticholinergic properties which have been documented in neurotransmitter receptor binding studies (6). In combination with fluphenazine, simultaneous blockade of histamine H_1, muscarinic cholinergic, and dopamine receptors occurs.

Other evidence also supports this hypothesis. Eight oncology patients at Stanford University Hospital were treated with prochlorperazine (10 mg iv every 4 hours) and diphenhydramine (25 mg iv every 4 hours) beginning 30 minutes prior to a 24-hour cisplatin infusion. Each patient had previously received between two and 11 cycles of cisplatin. Seven of the eight patients reported subjective preferences for the drug combination over any single agent used during prior chemotherapy cycles. The eighth patient denied any significant decrease in the amount of nausea and vomiting experienced during the cisplatin infusion. As with fluphenazine and nortriptyline, the simultaneous use of prochlorperazine and diphenhydramine results in blockade of dopamine, muscarinic cholinergic, and histamine H_1 receptors.

In summary, dopamine, cholinergic, and histamine antagonists all display antiemetic actions which are mediated via different pathways (2). Current neuropharmacologic techniques such as receptor binding assays provide a rapid and accurate measure of antiemetic effects at central nervous system receptor sites. It seems logical to employ these techniques to maximize antiemetic actions in the central emetic pathway. We are presently conducting a clinical trial to further investigate this hypothesis.

REFERENCES

1. Morran C, Smith DC, Anderson DA, et al. Incidence of nausea and vomiting with cytotoxic chemotherapy: a prospective randomised trial of antiemetics. Br Med J 1:1323–1324, 1979.
2. Seigel LJ, and Longo DL. The control of chemotherapy induced emesis. Ann Intern Med 95:352–359, 1981.
3. Palacios JM, Wamsley JK, and Kuhar MJ. The distribution of histamine-H_1 receptors in the rat brain: an autoradiographic study. Neuroscience 6:15–37, 1981.
4. Wamsley JK, Lewis MS, Young WS, III, et al. Autoradiographic localization of muscarinic cholinergic receptors in rat brainstem. J Neurosci Res 1:176–191, 1981.
5. Stefanini E, and Clement-Cormier Y. Detection of dopamine receptors in the area postrema. Eur J Pharmacol 74:257–260, 1981.
6. Peroutka SJ, and Snyder SH. Long-term antidepressant treatment decreases spiroperidol-labeled serotonin receptor binding. Science 210:88–90, 1980.

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Streptozocin-Induced Eosinophilia and Fever: A Case Report[1]

Streptozocin, a nitrosourea compound, has been used alone or with 5-FU to treat pancreatic islet cell carcinoma and carcinoid tumors (1–4). Its major toxic effects are renal and gastrointestinal. Uremia

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