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Treatment of Vincristine-Induced Ileus with Sincalide, a Cholecystokinin Analog

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Summary. *Sincalide, a synthetic analog of cholecystokinin capable of stimulating bowel motility, has been administered to 12 patients with symptoms and signs of vincristine-induced ileus. Patients were given intravenous infusions of sincalide 0.01 μg/kg/h over 2–24 h (mean, 8 h) for 1–12 days (mean, 5 days), usually until all evidence of ileus had resolved. Improvement was noted within 48 h of initiation of therapy in eight patients (75%), whereas marginal or no responses were observed in four patients. The mean duration of ileus was 3.6 days in responders and 7.7 days in nonresponders. Toxicity was minimal and consisted of diarrhea in two patients, in whom symptoms promptly resolved with discontinuation of the drug. Further exploration of this promising agent in the treatment of vincristine-induced ileus appears warranted.*

Introduction

Vincristine, an alkaloid with antimitotic properties obtained from the plant *Vinca rosea* (L), has been widely used in cancer chemotherapy due to its lack of myelosuppression at the conventional dosage. Neurotoxicity has been its principal limiting side-effect and is usually manifested in a peripheral mixed sensorimotor neuropathy with symmetrical signs and symptoms. Constipation and paralytic ileus have been the most frequent indicators of autonomic neuropathy and may occur following short- or long-term administration [6]. There is no known treatment of vincristine-induced neurotoxicity other than discontinuation or reduction of the dose and/or frequency of administration of the agent.

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During a recent clinical trial of continuous intravenous (IV) vincristine infusion in our institution, ileus was found to be the main cause of treatment-related morbidity [7]. Rapid reversal of this process was often very difficult despite the use of cathartics, enemas, nasogastric suction, and rectal tubes. Sincalide, a synthetic analog of cholecystokinin capable of stimulating bowel motility [2], has been investigated as an alternative method of treating vincristine-induced ileus and is the subject of this report.

Materials and Methods

Subjects. Twelve patients seen in our institution between January 1980 and January 1981 received sincalide after developing ileus following the administration of vincristine. Ileus was usually characterized by constipation, abdominal distension, and a bloated sensation; a roentgenographic picture of adynamic ileus when abdominal films were obtained; and (less frequently) pain, nausea, and vomiting. Ten patients developed ileus after 5-day infusions of vincristine which were preceded by a bolus injection of vincristine; and this complication was observed 1–9 days after infusion (mean 4 days). Ileus occurred in two patients following IV bolus injection only and was noted to occur 4 and 44 days after administration of vincristine. Patient characteristics are given in Table 1.

Drug Dosage and Administration. Sincalide (Kinevac), a C-terminal octapeptide of cholecystokinin, was generously provided by E. R. Squibb & Sons, Inc., Princeton, NJ, USA. Patients received IV infusions of sincalide, 0.01 μg/kg/h. The total dosage was somewhat greater than that used in radiographic procedures such as cholecystographic roentgenography; the technique of administration (IV infusion) had been used in previous human physiologic investigations [2]. The infusate was prepared by adding the daily dosage of sincalide to 250–1,000 ml 5% dextrose in water and was infused over 2–24 h (mean, 8 h) for 1–12 days (mean 5 days) (Table 2). Patients usually received continuous infusions of sincalide until all evidence of ileus had resolved. A positive result was recorded with relief of constipation associated with decreased abdominal distension within 48 h of initiation of sincalide administration.

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Table 1. Patient characteristics

Patient	Age (years)	Sex	Diagnosis	Vincristine dosage	
				Bolus day 1 (mg)	Infusion day 1–5 (mg/m^2)
M. H.	52	F	Breast cancer	0.5	0.25
A. M.	74	F	Lymphoma	0.5	0.25
D. L.	68	M	Prostate cancer	0.5	0.50
L. P.	64	F	Breast cancer	0.5	0.50
W. H.	61	F	Breast cancer	0.5	0.50
H. P.	77	M	Myeloma	0.5	0.50
S. H.	41	M	ITP[a]	0.5	0.50
A. A.	37	F	Breast cancer	0.5	1.00
N. S.	60	F	Breast cancer	0.5	1.00
S. T.	71	F	Leukemia	0.5	1.00
T. P.	58	F	Lung cancer	2.0	–
R. M.	54	M	Lung cancer	2.0	–

[a] ITP, idiopathic thrombocytopenic purpura

Table 2. Dosage, schedule, and results of sincalide administration for vincristine-induced ileus

Patient	Dosage (μg/kg/h)	Infusion period (h)	Duration (days)	Result	Side-effects
M. H.	0.01	8	4	(+)	–
A. M.	0.01	7	12	(−)	–
D. L.	0.01	24	1	(+)	–
L. P.	0.01	6	4	(+)	–
W. H.	0.01	4	3	(+)	Diarrhea
H. P.	0.01	8	7	(−)	–
S. H.	0.01	4	3	(−)	–
A. A.	0.01	2	7	(+)	–
N. S.	0.01	8	4	(+)	Diarrhea
S. T.	0.01	8	7	(−)	–
T. P.	0.01	8	3	(+)	–
R. M.	0.01	8	3	(+)	–

Results

Increased bowel motility associated with induction of defecation and decreased abdominal distension was observed in eight of 12 patients (66%) within 48 h of initiation of sincalide administration (Table 2). Marginal or no response was noted in four patients, all of whom received infusions of sincalide over 4 h or more per day for at least 3 days.

Although improved, abdominal distension beyond 48 h after initiation of sincalide infusion was usually observed even in responding patients who had prompt reduction of the symptoms of constipation and bloating following treatment. Total resolution of symptoms and signs associated with vincristine-induced ileus required lengthy periods of time in almost all patients (responders 1–7 days, mean 3.6 days; nonresponders 5, 7, 7, and 12 days).

Toxicity of the treatment was minimal. Diarrhea occurred in two patients, one each on the second and third treatment days; discontinuation of sincalide resulted in prompt resolution of the diarrhea. No skin irritation or phlebitis was noted at the site of administration.

Discussion

The major antitumor effect of vincristine appears to be related to its high-affinity binding to tubulin, the basic protein subunit of microtubules, which results in disruption of the mitotic spindle apparatus and arrest of cells in metaphase [6]. Similarly, the disruption of microtubules in neural tissue has been suggested as the mechanism causing neurotoxicity [3]. Autonomic neuropathy has been observed in the form of acute

urinary retention, postural hypotension, and most commonly, constipation with or without symptoms and signs of ileus [6]. Damage of the myenteric plexus neurons of the bowel may be responsible for vincristine-induced ileus [4, 9].

Sandler et al. noted abdominal pain or constipation or both in 23 of 50 patients (46%) who received vincristine by IV bolus injection; and six of these patients (12% of the total) developed ileus [8]. Holland et al. observed constipation in 129 of 392 patients (33%) following vincristine IV injection; and 11 patients (3% of the total) developed ileus, of whom four died [5]. Holland et al. noted an increased frequency of gastrointestinal symptoms with higher doses of vincristine. Similarly, we have observed a relationship between dosage and development of ileus during a phase I clinical trial of vincristine infusion; this complication was noted in one of 15 patients receiving 0.50 mg/m^2/day, three of seven receiving 0.75 mg/m^2/day, and seven of ten at the 1.0 mg/m^2/day dose level [7]. Three patients in the last study mentioned received sincalide (A. A., N. S., S. T), all of whom had received 1.0 mg vincristine/m^2 daily for 5 days; response to sincalide was observed in two of them.

Ileus following vincristine administration often lasts for several days. Symptoms and signs of this complication were observed for 3–11 days (mean 7 days) following infusion of vincristine in a previous trial in our institution [7]. Similarly, the duration of ileus was 5–12 days (mean 7.7 days) in patients not exhibiting a response to sincalide in the present study. Patients showing evidence of response to sincalide within 48 h of its administration appeared to have a shorter duration of ileus (1–7 days, mean 3.6 days).

Administration of sincalide, a synthetic analog of cholecystokinin, has proved to be helpful in ameliorating the symptoms of vincristine-induced ileus in the majority of patients in the present study; toxicity has been minimal. Further investigation will be required to establish the optimum dosage and schedule of administration of this agent. Lactulose [4] and caerulein [1, 10] have also been noted to be of clinical benefit in the management of vincristine-induced bowel hypomotility. Further exploration of these and similar agents will allow palliation of this rather tenacious side-effect of vincristine until methods for the primary prevention of the development of neurotoxicity associated with its clinical use are developed.

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