Sleep Protects against Chemotherapy Induced Emesis

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BACKGROUND. We present a clinical trial to assess the hypothesis that chemotherapy related acute emesis is reduced when drugs are delivered while the patient is sleeping.

METHODS. Adults without previous sleep disturbances or vomit inducing conditions who were going to receive their first courses of 100 mg/m^2 cisplatin were included. We reduced antiemetic prophylaxis consisting of ondansetron and dexamethasone in subsequent groups of patients.

RESULTS. Twenty-one individuals were needed to decrease the antiemetic prophylaxis to zero. Significant vomiting was observed only when prophylaxis was abolished but not in previous steps employing negligible doses of prophylaxis.

CONCLUSIONS. Our data show that when cisplatin is administered during sleep, the reduction of antiemetic prophylaxis is not followed by the expected increase in emetic toxicity. This antiemetic property of sleep is, as far as we know, unassessed in a controlled way. Further study of the clinical utility of this method in the prevention of chemotherapy related emesis is indicated. ***Cancer* 1996; 77:1566–70.**
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We designed the present trial to assess the hypothesis that chemotherapy results in less acute nausea and vomiting if it is administered while the patient is sleeping.

Chemotherapy and radiotherapy induced nausea and vomiting erode the patient's quality of life more so than any other adverse effect associated with these treatments.[1]

Emesis is occasionally so severe that it requires treatment withdrawal or is associated with dehydration, metabolic emergencies, suture dehiscence, Mallory-Weiss syndrome, or nutritional disorders demanding parenteral nutrition.

The emetogenic potential of anticancer drugs varies widely. Cisplatin is a commonly used chemotherapeutic agent. It will produce severe vomiting in virtually every patients if vigorous prophylaxis is not instituted. Active research about cancer treatment related emesis dates back to the 50s.[2] The therapeutic achievements made during the last two decades provide us with no less than 20 different drugs with proven antiemetic potential.[3] The use of antiemetic prophylactic regimes that combine these drugs in various ways and the increasing interest in this research area points out the lack of a simple, efficient, safe, and cheap antiemetic prophylaxis.

Metoclopramide is probably the most widely used single agent in the antiemetic prophylaxis setting. When used at high doses by the intravenous (i.v.) route, it is effective in the prophylaxis and treatment of chemotherapy-associated emesis, including cisplatin containing regimes.[4] Ondansetron is the first member of the new chemical group of carbazols which act by inhibiting the central (VC and CTZ) and peripheral (gastroin-

TABLE 1
Antiemetic Prophylaxis Reduction in Steps

Day	Drug	Minutes pre CDDP	mg in each step					
			0	1	2	3	4	5
—								
1	Dexamethason i.v. bolus	40′	20	16	8	5	2	0
1	Ondansetron i.v. bolus	35′	8	6	3	2	1	0
1	Ondansetron i.v. 24-hour perfusion	0′	24	18	9	6	3	0
2–4	Ondansetron po	[a]	..... 8 mg tid					

Oral ondansetron is initiated 24 hours after cisplatin
CDDP: cis-diamminedichloroplatinum

TABLE 2
National Cancer Institute Grading of Emetic Toxicity

Grade	Emesis
0	Absence of nausea or vomiting.
	Nausea or 1 vomiting episode in 24 hours.
1	Able to eat reasonable intake.
	Two to 5 vomiting episodes in 24 hours.
2	Intake significantly decreased.
	Six to 10 episodes in 24 hours.
3	No significant intake.
	More than 10 episodes in 24 hours.
4	Requires parenteral nutrition.

testinal tract) serotonin receptors. Ondansetron is now fully introduced in current clinical practice. It is superior to high dose metoclopramide in the prevention of cisplatin emetic toxicity but the difference is not great and the cost issue favors the use of metoclopramide.[3] A recent paper questions the usefulness of ondansetron against drugs with lower emetogenic potential.[5]

The sleep-wakefulness cycle presents several variations in physiologic and pathologic processes.[6] Gastrointestinal function is not devoid of such phenomena. Gastric acid secretion oscillates with a circadian rhythm in which vagal control seems to play an important role.[7] Gastric[8] and colonic[9] motor activities are slower during sleep and anal sphincter reflexes also show alterations.[10] Swallowing is significantly suppressed[11] and salivary flow nearly ceases.[12] It seems appropriate to think that emetic reflexes could also differ during sleep.

PATIENTS AND METHODS

In a Phase I clinical trial, we assessed the relationship between the dose of an experimental drug and its toxicity. The drug is started at a low dose not expected to be toxic and increased thereafter in steps according to a scheme, often based on the Fibonacci series.[13]

We have devised a modified Phase I study in which the antiemetic medications were gradually reduced to evaluate the antiemetic effect of the sleep process. Cisplatin including chemotherapy was administered while sleeping. Acute emesis, defined as nausea and vomiting occurring during the first 24 hours after cisplatin infusion, was the target toxicity. The ultimate objective of the trial was to describe how nausea and vomiting increased when antiemetic prophylaxis was withdrawn in patients receiving cisplatin while they were asleep.

Selection of Patients

Every patient who was to receive chemotherapy for the first time during the study term (May 5, 1993 to October 27, 1994) was eligible if the treatment schema included cisplatin. We excluded patients with chronic sleep disorders, those who consumed drugs with antiemetic potential, those who presented emesis inducing conditions other than neoplasm, and those not willing to participate in the trial. If a patient failed to get to sleep, treatment was not initiated and the procedure was repeated the next night. Patients not able to fall asleep at the second attempt were not evaluable.

Every individual in whom the chemotherapy perfusion was started during sleep was considered evaluable, disregarding the quality, continuity, or duration of the sleep.

Antiemetic Prophylaxis Reduction

The study comprised a maximum of 6 steps, numbered 0 to 5. We employed our institution's standard antiemetic prophylaxis for cisplatin containing regimes (Table 1) with the patients included in Step 0. Doses on the first day were decreased with each step. Step 1 doses were 20% less than those of Step 0. Step 2 doses were only 50% of Step 2. Further, 33% reductions were performed in Steps 3, 4, and 5, for whom there was no first-day antiemetic prophylaxis.

TABLE 3
Patient Characteristics

Step[a]	Sex	Age	Diagnosis	Stage	Sleep[b]	CDDP[c]
1/0	M	60	Small cell lung carcinoma	IV	7	182
2/0	M	70	Oesophagus (squamous)	IV	6	162
3/0	M	47	Adenocarcinoma pancreas	IV	7	190
4/1	M	47	Oropharynx (squamous)	III	9	170
5/1	M	66	Larynx (squamous)	IV	4	164
6/1	M	66	Larynx (squamous)	IV	6	163
7/2	M	68	Pharynx (squamous)	IV	10	148
8/2	M	58	Larynx (squamous)	IV	7	216
9/2	F	58	Mouth (squamous)	IV	8	180
10/3	M	67	Cavum (squamous)	III	7	195
11/3	F	72	Tongue (squamous)	IV	5	155
12/3	M	48	Tongue (squamous)	III	7	150
13/4	M	41	Oropharynx (squamous)	III	7	154
14/4	M	62	Oropharynx (squamous)	III	6	154
15/4	M	61	Oropharynx (squamous)	III	4	160
16/4	M	43	Tongue (squamous)	III	7	180
17/4	M	48	Oropharynx (squamous)	III	8	170
18/4	F	52	Small cell lung carcinoma	IV	6	205
19/5	M	66	Larynx (squamous)	III	7	170
20/5	M	57	Oropharynx (squamous)	IV	4	180
21/5	F	58	Ovarian adenocarcinoma	IIIc	5	174
Mean		57.9			6.5	172.5

[a] Patient/step.
[b] Duration in hours.
[c] Total dose in mg.

Number of Patients Included and End of the Study

Step 0 included 3 patients. If none of them presented emetic toxicity equal or superior to Grade 3, the next step also contained 3 patients. Every further step is formed by 6 patients if Grade 3 or 4 emesis is observed. If Grade 4 emesis happens in one or more patients out of a 3-subjects-step or in 2 or more patients out of a 6-subjects-step, that particular step is repeated and the study stopped if Grade 4 toxicity is observed again. The study also finishes if 2 consecutive patients present Grade 3 or 4 emesis at any point of it.

Chemotherapy Administration

Patients included in the trial were admitted to the hospital early in the morning to the night of cisplatin administration.

Standard prehydration lasted 12 hours and was scheduled to finish at bedtime.

Patients were lodged in individual rooms and asked to remain out of bed when possible and to avoid naps during the daytime. At bedtime, every individual took a 7.5 mg pill of zoplicon to induce sleep and the antiemetics and chemotherapy infusion bags were connected to the i.v. line but remained closed. The zoplicone is a cyclopyrollone, one of the rising generation of hypnotics with a monoexponential profile and a rapid elimination (mean elimination half-lives 5.3 $\pm$ 0.8) which acts binding to central omega receptors. Nurses checked at 15-minute intervals if the patient was asleep. When sleep was not achieved within the first 2 hours after prehydration end, chemotherapy was suspended and a new attempt was made the following night. Whether or not the patient was observed to be sleeping, antiemetics were administered followed by chemotherapy infusion.

Blinding

Patients and their attending physicians did not know the degree of antiemetic prophylaxis.

Data Collection and Toxicity Evaluation

Data were obtained 24 and 72 hours after cisplatin administration. We checked the presence of nausea or vomiting and the number of vomiting episodes before chemotherapy during the first 24 hours after chemotherapy and between 24 and 72 hours after chemotherapy.

The two main endpoints of this study are the degree of emetic toxicity and the number of vomiting episodes, both during the first 24 hours following the administration of cisplatin. The patients themselves provided the latter. For the standardization of the former we used the

TABLE 4
Results

	First 24 hours		24 to 72 hours	
Step[a]	Emesis grade	Vomiting	Emesis grade	Vomiting
1/0	0	—	0	—
2/0	0	—	0	—
3/0	0	—	1	—
4/1	0	—	0	—
5/1	0	—	1	—
6/1	0	—	0	—
7/2	0	—	0	—
8/2	0	—	1	—
9/2	1	1	2	3
10/3	3	6	0	—
11/3	0	—	0	—
12/3	1	—	2	4
13/4	0	—	1	1
14/4	0	—	0	—
15/4	1	1	0	—
16/4	1	1	0	—
17/4	0	—	0	—
18/4	0	—	1	1
19/5	0	—	1	1
20/5	3	9	2	2
21/5	4	12	1	—

[a] Patient/step.

National Cancer Institute (NCI) classification system (Table 2).

Ethical Considerations

The ethics committee of our institution approved all of the procedures which didn't contradict the 1983 revised Helsinki Declaration. Every participating individual signed an informed consent document.

RESULTS

Twenty-one patients were included in the trial. All of them were able to get to sleep in the first night within two hours after prehydration end and were therefore evaluable (Table 3). Sleep duration ranged between 4 and 10 hours with a mean of 6 hours and 48 minutes. In spite of two or three micturitions per night, due to the prehydration, the patients generally reported their sleep to be resumed promptly.

Most of the patients were males with advanced (Stage III or IV) squamous cell carcinoma of the head and neck area. None of them had anticipatory emesis. Cisplatin doses were always equal or superior to 100 mg per square meter of body surface.

Emesis superior to Grade 3 was not observed until the last step, making it possible to decrease the antiemetic dosage from 100% (Step 0) to 13% (Step 4), with

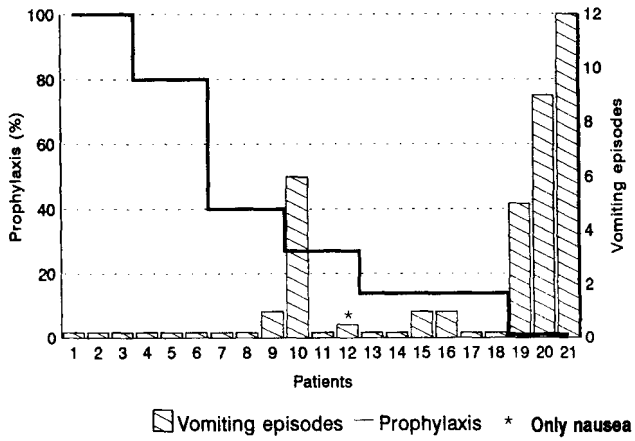

FIGURE 1. No linear increase in the number of vomiting episodes is observed as antiemetic prophylaxis is tapered. Significant emesis only occurs when antiemetic drugs are finally withdrawn.

4 groups of 3 patients each and a fifth of 6 patients. Out of these 18 first patients, only 4 experienced some vomiting during the first 24 hours. Three of them reported just one vomiting episode (Steps 2 and 4), and the other (Step 3) had 6 episodes. One additional patient (Step 3) experienced nausea without vomiting. The remaining 13 patients had neither vomiting nor nausea.

The last 2 patients receiving no first-day antiemetic prophylaxis at all (Step 5) experienced Grade 3 and 4 vomiting, reporting 9 and 12 episodes. We stopped the trial at that point following the safety measures stated.

During the subsequent 48 hours, 3 patients (Steps 0, 1, and 2) out of the initial 15 had nausea without vomiting and another 4 (Steps 2, 3, and 4) had, respectively, 3, 4, 1, and 1 vomiting episodes. One of the 3 last patients had only nausea on the following 48 hours, while others reported 2 additional vomiting episodes.

DISCUSSION

The goal of our research was to assess the hypothesis that chemotherapy related acute emesis is reduced when the patient receives the drugs while sleeping.

We chose cisplatin as a paradigm of highly emetogenic cytostatics and monitored nausea and vomiting as the antiemetic prophylaxis was reduced, step by step, following the reversed design of a Phase I clinical trial. As far as we know, the antiemetic role of sleep in oncology practice has never been addressed using this method.

There was no linear increase in emetic toxicity as ondansetron and dexamethason were tapered (Fig. 1). There were few emetic incidents. The ones that did occur were light and certainly not worse than those we are used to with ondansetron full protection. Some patients had no nausea in spite of pre-cisplatin ondansetron boluses

as low as 1 mg. We do not know what would have happened if those patients had had daytime cisplatin. As the emetic power of cisplatin is so well known, it would probably be unethical to perform such a trial. Nevertheless, experience based common sense as well as historical and current data make us suppose that, under normal circumstances, antiemetic prophylaxis can not be decreased to such a degree without significant emesis. We didn't find really disturbing emesis until cisplatin was infused without any prophylaxis. The trial ended at that point because of strict security measures designed to protect patients from being exposed to chemotherapy without the real protection of ondansetron or the hypothetical protection of sleep.

As far as we know, zopiclone has no proven antiemetic effect. Furthermore, it has been reported that nausea and vomiting follow sudden withdrawal.

Our data were not entirely consistent. Significant emesis was found at Step 3 but disappeared at Level 4. This indicates that a larger number of patients will be needed in subsequent studies to determine how effective sleep will be as an antiemetic.

We conclude that our results yield preliminary evidence supporting the objective reduction of chemotherapy induced acute emesis when cytostatics are given while patients are asleep.

It could be worthwhile to explore the role of sleeptime chemotherapy in certain unresolved settings like anticipatory emesis, late emesis, or ondansetron resistant emesis.

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