J Korean Med Sci 1998; 13: 334-8
ISSN 1011-8934

Overdose of Vincristine: Experience with a Patient

Vincristine, referred to as a vinka alkaloid, has been used as a component of the various chemotherapeutic regimens. The major side effects of the usual dosage of vincristine are bone marrow suppression, gastrointestinal disorder, and neurotoxicity. A 53-year-old cervical cancer patient received 14 mg (4 mg/m^2/day for 2 days) of vincristine instead of vinblastine because of the similarity between the two names. Then life threatening toxicities including paresthesias, bone marrow depression, severe oral mucositis, paralytic ileus, bladder atony, myalgia, muscle weakness, high fever, derangements of various organs (liver, heart), hypertension, and insomnia were encountered. But hypotension and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) were not observed. Other than paresthesias in the extremities, the patient recovered completely from toxic impairments with intensive symptomatic and supportive care. In order to prevent the administration of the overdosed drug, it would be advisable for chemotherapy to be administered only by an experienced physician who is able to check the dose and concentration.

Key Words : *Vincristine, overdose; Cervix neoplasm*

Lim Chae, Hye-Sung Moon, Seung-Cheol Kim

Department of Obstetrics and Gynecology, College of Medicine, Ewha Women's University, Seoul, Korea

Received : October 23, 1997
Accepted : January 14, 1998

Address for correspondence
Seung-Cheol Kim, M.D.
Department of Obstetrics and Gynecology, College of Medicine, Ewha Women's University, 911-1 Mok-dong, Yangcheon-gu, Seoul 158-056, Korea
Tel : (02) 650-5012, Fax : (02) 647-9860

INTRODUCTION

Vincristine has been widely used as a component of various chemotherapeutic regimens, although it has been reported that serious side effects that may results in fatality are likely to develop following overdosage. Several reports of accidental overdose of vincristine have been published (1-7). But more unreported cases may exist. We report a 53-year-old patient with invasive cervical cancer, accidentally given a vincristine overdose (4 mg/m^2/day for 2 days, 14 mg) instead of vinblastine because of the similarity between the two names. She revealed toxic effects including paresthesias, bone marrow depression, severe oral mucositis, paralytic ileus, bladder atony, myalgia, muscle weakness, high fever, derangements of various organs (liver, heart), hypertension, and insomnia. She completely recovered from toxic impairements except for parethesias in the extremities with intensive symptomatic and supportive care.

CASE REPORT

A 53-year-old woman, gravida 4, para 2, was admitted to the Department of Obstetrics and Gynecology of Ewha Women's University Mokdong Hospital for further evaluation and treatment of invasive uterine cervical cancer. She was diagnosed with invasive squamous cell carcinoma of stage IIb with tumor larger than 4 cm. We planned a neoadjuvant chemotherapy for this patient. She received the first cycle of neoadjuvant chemotherapy with vinblastine, bleomycin and cisplatin (VBP) without any problem. Laboratory examinations were done before the second cycle of neoadjuvant chemotherapy. CBC showed Hb 11.1 g/dl, Hct 31.4%, WBC 5,600/mm^3, platelet count 331,000/mm^3. Serum chemistry included sodium 140 mEq/L, blood urea nitrogen 18 mg/dl, creatinine 0.8 mg/dl, albumin 3.8 mg/dl, aspartate transaminase 18 U/L, and alanine transaminase 21 U/L. And also the pulmonary function test was normal. So, the second VBP regimen was scheduled to be given. But, by accident, instead of vinblastine, 14 mg of vincristine (4 mg/m^2/day for 2 days) was injected because of the similarity between the two names.

Initial symptoms of fever and nausea developed on day 2. Then, mild bone marrow toxicity was seen (platelet count 86,000/mm^3) on day 3. On day 4, she complained of tingling sensation on extremities and abdominal discomfort. On physical examination, slightly distended abdomen and oral mucositis were noted. On day 5, abdominal distension was prominent, a plain X-ray of the abdomen showed a gaseous distension of the large bowel

loops. Gastric decompression by nasogastric tube insertion was done and parenteral nutrition with supplemental elelctrolytes was started. Bone marrow toxicity was profound and lasted for 7 days. Platelet and WBC on day 6 recorded nadir counts of 33,000/mm^3, 400/mm^3 (P 0/mm^3), respectively (Fig. 1). 20 units of platelet-concentrates (10 units on day 5, 10 units on day 7) with G-CSF (150 μg/day IV for 7 days) were given for correction of myelotoxicity. High fever occurred on day 3 and lasted for 10 days, but the result of blood culture was negative. Patient gargled with betadine solution frequently and was isolated for prevention of infection. Prophylactic broad-spectrum antibiotics was also given. After being given, fever subsided spontaneously. Thirst developed, and evaluated serum sodium level was decreased (129 mEq/L) on day 5. Therefore, syndrome of inappropriate ADH secretion (SIADH) was suspected, but serum and urine osmolality were not compatible with it. Concentrations of serum electrolytes and fluid balance were monitored daily, and supplemental sodium was given in con-

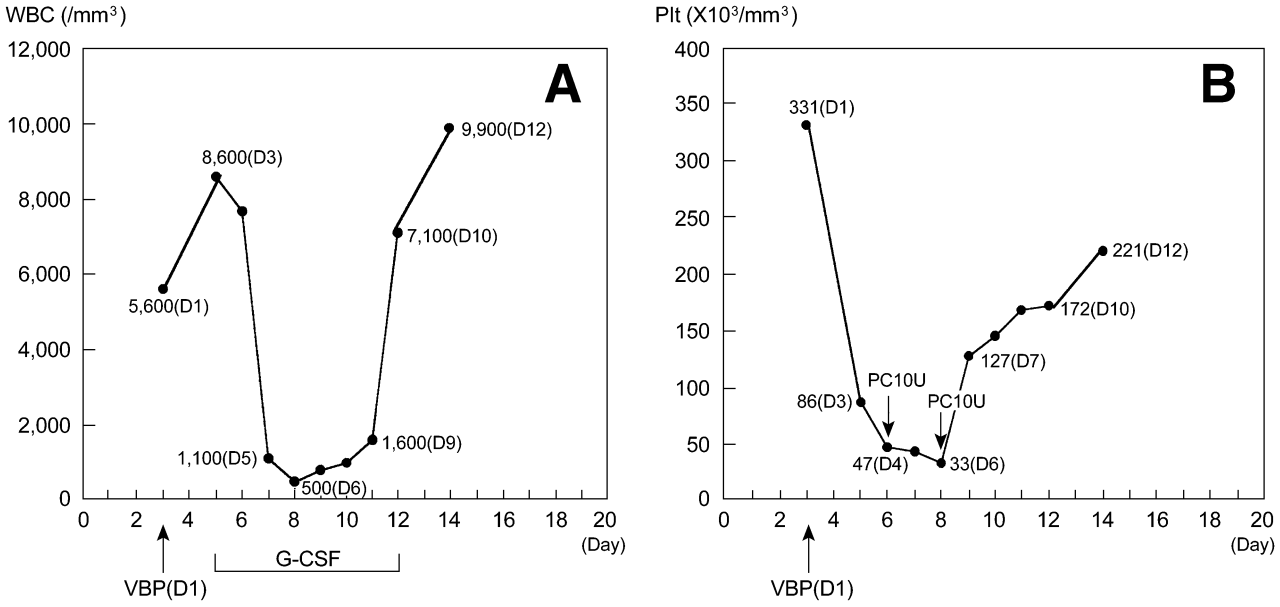

Fig. 1. A: The leukocyte counts during the VBP chemotherapy. VBP=vincristine, bleomycin, cisplatin, D=chemotherapy day. B: The platelet counts during the VBP chemotherapy. PC=platelet concentrate.

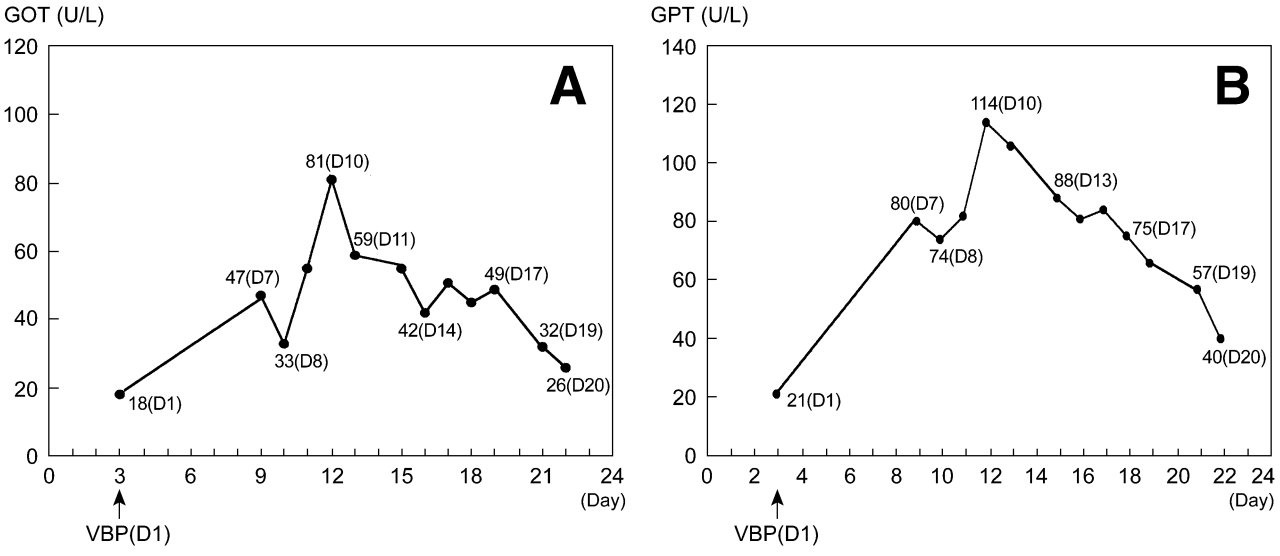

Fig. 2. A: The GOT levels during the VBP chemotherapy. VBP=vincristine, bleomycin, cisplatin, D=chemotherapy day, GOT=glutamate oxaloacetate transaminase. B: The GPT levels during the VBP chemotherapy. GPT=glutamate pyruvate transaminase.

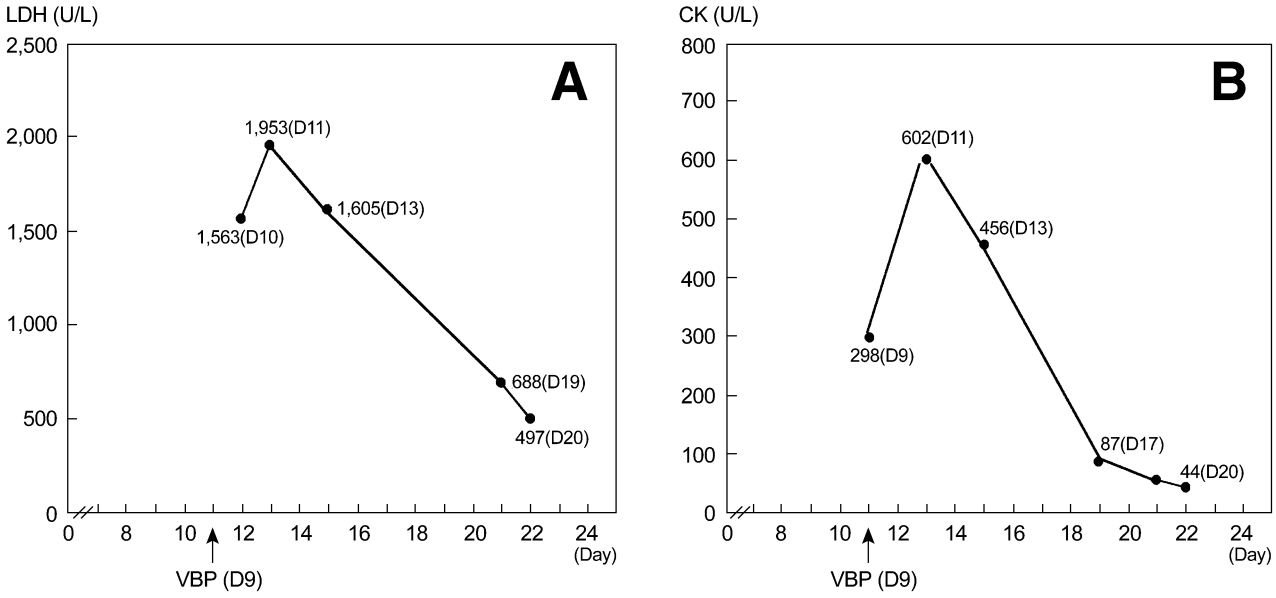

Fig. 3. A: The LDH levels during the VBP chemotherapy. VBP=vincristine, bleomycin, cisplatin, D=chemotherapy day, LDH=lactate dehydrogenase. B: The CK levels during the VBP chemotherapy. CK=creatine kinase.

sideration of SIADH. Hypertension of 170/110 mmHg occurred on day 7 and lasted for 10 days. Antihypertensives (nifedipine and amlodipine) were administered to control blood pressure. Involvements of various organs, including the liver and heart were also suggested from the study on blood chemistries as follows, GTP 114 U/L and GOT 81 U/L on day 10 (Fig. 2), and LDH 1,953 U/L and CK 602 U/L on day 11 (Fig. 3). Blood chemistries were monitored daily. Alopecia was prominent on day 10. By then, mild dysuria developed and Foley catheter was inserted. She complained of generalized myalgia on day 14, and decreased muscle power was noticed. At this point, cerebral dysfunction including insomnia developed. For a correction of insomnia and prophylactic control of seizure, flurazepam was given. In addition to the complications mentioned above, sinus tachycardia was noticed. We injected lidocaine when the heart rate reached 140/min (Table 1).

Folinic acid rescue (30 mg IV every 6 hours for 2 days) was given as an antidote. Vitamine B-complex and C with fluids were also given parenterally.

Abdominal discomfort and distension improved progressively from day 10. Liver and heart enzyme levels normalized at the time of discharge. The treatments for the preceding compromising state were essentially symptomatic and supportive and ended about 20 days later in success. But, vincristine-induced peripheral neuropathies, myopathies and cerebral dysfunction lasted to the time of discharge. Her general condition improved and she was discharged on foot on the 22nd hospital day with

Table 1. Toxic effect following vincristine overdose in the present case

Toxic effect	Onset*	Subsidence	Managements
Fever	D 2	D11	Antibiotics
Nausea / vomiting	D 2	D 6	
Bone marrow depression	D 3	D13	G-CSF / platelet transfusion / isolation
Neuropathies	D 4	-	
Oral mucositis	D 4	D15	Betadine gargling
Gastrointestinal effect	D 5	D15	NPO / fluid / hot pack
Hypertension	D 7	D16	Antihypertensives
Neurogenic bladder	D10	D20	Foley-catheter / anticholinergics
Myopathies	D14	-	
Cerebral dysfunction	D16	-	Flurazepam

* Onset from the start of chemotherapy

continuing paresthesias in the extremities.

DISCUSSION

Vincristine is a vinca alkaloid which is a cell-cycle specific agent. It blocks mitosis with metaphase arrest through disruption of microtubules of the mitotic apparatus (8), and it may affect various body systems. Half-life of the drug in the serum is extremely short because it rapidly binds to the tissue. Vincristine is metabolized and excreted by the liver.

The major toxic phenomena of vincristine involves neurotoxicity (9, 10). Vincristine-induced peripheral neuropathy occurs in almost every patient who receives the drug, and it is thought that vincristine may cause axonal damage by disruption of neurotubules and consequent impairment of axoplasmic transport mechanism (11, 12). The earlist manifestation is depression of the deep tendon reflex followed by paresthesias in fingers and toes (9). Autonomic neuropathy is frequently encountered in patients treated with vincristine and gastrointestinal symptoms occur most commonly (9). Orthostatic hypotension, as a complication of vincristine therapy, resulting from interruption of the sympathetic reflex arc which controls blood pressure, has been reported. The possibility of the effect of norepinephrine storage in postganglionic nerve terminals was studied. But until further clinical and experimental data are available, orthostatic hypotension cannot be considered as an established manifestation of vincristine toxicity (13). Cranial nerve palsies are seen less often than peripheral or autonomic neuropathies in patients receiving vincristine. Ocular findings occur most frequently (9). Vincristine apparently may exert a direct neurotoxic effect on the central nervous system. Cerebral dysfunction may result from vincristine overdose. Depression, agitation, insomnia, and hallucination have been reported with vincristine therapy (9). Generalized seizure may occur as a toxic side effect of vincristine administration and the incidence is said to be about 1 percent of patients receiving this drug. The precise mechanism is not known. They have been reported in association with hyponatremia secondary to SIADH and appear more frequently in patients with a previous history of seizure disorder (14). SIADH has been reported as a common side effect of vincristine therapy in patients receiving large doses. It may be due to vincristine acting on the hypothalamic nuclei to stimulate the release of antidiuretic hormone (9). Concentration of serum electrolytes and fluid balance should be monitored closely for at least ten days. Fever has also been reported after large doses of vincristine. The mechanism of this is not known but it may involve direct hypothalamic stimulation (2) or SIADH may be the reason for fever. Because vincristine binds to the tissues rapidly and it is mainly excreted via the biliary system and the liver, hepatic function may be an indicator of outcome (7). Also a considerable increase in serum CPK with LDH was reported which we also experienced. It may be an indication of some sort of effect on the myocardium. Sinus tachycardia could have been related to the myocardial damage. There has been no publications commenting on vincristine toxicity to the myocardium (6).

Most therapy-related overdoses are attributed to miscalculation. In our experience, vincristine (1.5 mg/m^2) was administered instead of scheduled vinblastine according to the common dose of vinblastine (4 mg/m^2) because of the similarity between the two names. Nearly identical experience was reported by Koutarou et al. (6), in which they administered vincristine instead of vinblastine because of the similarity between the two names. Because normal dose of vincristine is very small, approximately 1.5 mg/m^2 (0.06 mg/kg), overdose of this drug can be very traumatic, sometimes fatal. We were unware of the mistake until the patient complained of abdominal distension and severe myelotoxicity developed. Management was only symptomatic and supportive. No specific antidote has been found for treating vincristine overdose, but folinic acid was proposed. Helen et al. (7) reported three cases treated by folinic acid rescue and plasmapheresis. They claimed that folinic acid resulted in earliest onset and shorter duration of toxic effect. But Lamber et al. (4) did not find a more rapid recovery from the serious side effects among those administered amino acid. Don et al. (15) reported 42 patients who were assigned to receive glutamic acid 500 mg orally three times daily plus vincristine (1.0 mg/m^2 weekly for six days). They concluded that the administration of glutamic acid has decreased vincristine induced neurotoxicity without any attendant side effects. The mechanisms are unknown but, one possibility is the ability of glutamate to interact with tubulin, and another is inhibition of the uptake of vinblastine into human leukocyte (15). Trials of thiamine, pyridoxine and B12 were unsuccessful. Sincalide, metoclopramide have been found to be helpful in the treatment of vincristine-induced ileus. In Helen et al's cases (8), double-volume exchange transfusion in which post-exchange drug levels decreased by more than 50% in the two surviving children whereas in the child who succumbed they remained unchanged which contributed to a favorable outcome. Pierga et al. (16) reported one case treated by plasmapheresis for vincristine overdose. Plasmapheresis of 1.5 times the plasma volume was done and the clinical course was favorable. But its beneficial effect remains to be established.

The most important consideration in regard to vin-

cristine overdose is prevention (2). All personnels involved in handling chemotherapeutic agents should be fully aware of the potential dangers, and chemotherapy should be given only by an experienced physician who can check the dosage and concentration before it is administered. Charts of normal doses of chemotherapeutic agents should be available in all nursing stations and wherever drugs are prepared or administered. All chemotherapeutic doses should be fully calculated and recorded in the chart by a member of the hematology-oncology service. And stock only small dose vials of vincristne (10 ml=1 mg). The following must be considered. First, currently, the evidence is too meager to provide even a relative contraindication in the usage of vincristine in patients with neurologic disease or in those receiving other neurotoxic drugs or radiaton therapy to the neuraxis (9). Second, seizures attributable to vincristine do not appear to be an indicator for discontinuing administration of the drug. There are some reported cases in which vincristine was continued without occurrence of further seizure (14). Third, the occurrence of syndrome of inappropriate antidiuretic hormone following vincristine does not preclude a further safe usage of this drug (17). Marie et al. (17) observed a further occurrence of recurrent elevation in antidiuretic hormone excretion 8-10 days following a repeated treatment with vincristine. However, syndrome of antidiuretic hormone was prevented by prophylactic rigorous fluid restriction

REFERENCES

1. Berenson MP. *Recovery after inadvertent massive overdosage of vincristine (NSC 67674). Cancer Chemother Rep 1971; 55: 525-6.*
2. Kaufman IA, Kung FH, Koernig HM, Commander (MC), USN, Giammona ST. *Overdosage with vincristine. J Pediatr 1976; 89: 671-4.*
3. Barna P. *Vincristine overdose [letter to editor]. Clin Pediatr 1980; 19: 440.*
4. Lamber LT, Paul CB, Reinier S, Robert G. *Massive vincristine overdose: failure of leucovorin to reduce toxicity. Cancer Treat Rep 1982; 65: 1967-9.*
5. Beer M, Cavalli F. *Vincristine overdose: Treatment with and without leukovorin rescue. Cancer Treat Rep 1983; 67: 746-7.*
6. Koutarou M, Masaaki U, Hitoshi O, Yoshimasa K, Masahiro O, Hiroshi M. *A massive dose of vincristine. Jpn J Clin Oncol 1987; 17: 247-53.*
7. Helen VK, Bouhoutsou, Varvoutsi MC, Papadatos J, Stefanidis CG, Vlachos P, Scardoutsou A, Kostakis A. *Vincristine overdose: experience with 3 patients. Pediatr Hematol Oncol 1991; 8: 171-8.*
8. Johnson IS, Armstrong JC, Gorman M. *The vinca alkaloids: a new class of oncolytic agents. Cancer Res 1963; 23: 1390-427.*
9. Susan R, Sheldon K. *Vincristine neurotoxicity. Ann Int Med 1974; 80: 733-7.*
10. Weiss HD, Walker MD, Wiernik PH. *Neurotoxicity of commonly used antineoplastic agents. N Engl J Med 1974; 291: 75-81 and 127-33.*
11. Wisniewski H, Terry RD, Hirano A. *Neurofibrillary pathology. J Neuropathol Exp Neurol 1970; 29: 163-76.*
12. Schlaepfer WN. *Vincristine-induced axonal alteration in rat peripheral nerve. J Neuropathol Exp Neurol 1971; 30: 488-505.*
13. Sumter MC, Lanie E, Carlos RA, Daniel M. *Orthostatic hypotension during vincristine therapy. Arch Intern Med 1970; 126: 290-3.*
14. Johnson FL, Irwin D, Bernstein ID, Hartmann JR, Ronald LS Jr. *Seizures associated with vincristine sulfate therapy. J Pediatr 1973; 82: 699-702.*
15. Don VJ, Wells HB, Atkins JN, Zekan PJ, White DR, Richards F, Cruz JM, Muss HB. *Amelioration of vincristine neurotoxicity by glutamic acid. Am J Med 1988; 84: 1016-21.*
16. Pierga JY, Philippe B, Pahierry D, Thao P, Pierr P. *Favorable outcome after plasmapheresis for vincristine overdose. Lancet 1992; 340: 185.*
17. Marie JS, Charles C, Myron M, Frank AO. *Syndrome of recurrent increased secretion of antidiuretic hormone following multiple doses of vincristine. Blood 1975; 45: 315-9.*