J Korean Med Sci 1999; 14: 688-92
ISSN 1011-8934

Neural Toxicity Induced by Accidental Intrathecal Vincristine Administration

Described here is a case of accidental intrathecal administration of vincristine with pathologic findings in the central nervous system. A 3-year-old boy with acute lymphoblastic leukemia, was given his ninth course chemotherapy. Vincristine was accidentally injected intrathecally. The clinical course was rapidly progressive (6-day course) and resulted in death. An autopsy was done. The brain and spinal cord was grossly edematous and congested without any specific feature. Histologically, profound loss of neuron was noted in the spinal cord. Remaining neurons in the spinal cord, particularly anterior horn cells were markedly swollen. The spinal nerves show diffuse axonal degeneration and myelin loss. The upstream portion of the spinal cord (brain stem, cerebellum, cerebrum) showed patchy loss of neurons, especially Purkinje cells and granular cells of the cerebellar cortex. Many neurons showed axonal reaction (chromatolysis) with swelling. Several neurons show intracytoplasmic eosinophilic inclusion body. Myelin loss, axonal swelling and enlargement of perivascular spaces were seen throughout the white matter of central nervous system.

Key Words: *Vincristine; Drug toxicity; Injection, spinal*

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Received: 22 March 1999
Accepted: 9 June 1999

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INTRODUCTION

In 1961, vincristine was released for clinical trials. It has proven to be the most effective regimen for childhood acute leukemia (1). It is an alkaloid, obtained from the Madagascan periwinkle. Vincristine exerts its oncolytic action by aggregating tubulins, which interferes with microtubule assembly causing metaphase arrest in the mitotic cycle (2-4). Neural tissue is particularly susceptible to the effects of vincristine which causes dissolution of neurotubules, and perhaps leads to the development of neurofibrillary tangles in animals (5). Vincristine has a narrow therapeutic index and is usually administered intravenously. When administered intravenously, the major side effects of vincristine are alopecia, hyponatremia and neurotoxicity. The most frequent neuropathic effects are chronic peripheral neuropathy, involving both sensory and motor nerves, and autonomic neuropathy. Reversible coma also have been reported (6). Vincristine toxicities are dose limited. Neuropathic effects caused by vincristine are all reversible and generally a complete recovery can be anticipated when the drug is withdrawn. Intrathecal vincristine causes same neurotoxic side effects as intravenous vincristine initial phase. But intrathecal vincristine is different from intravenous vincristine in respect to cause irreversible neuronal damage leading to death in the end, despite vigorous central nervous system (CNS) washout (7). During initial phase, meningism and back pain are prominent. Lower limb weakness, urinary retention (or frequency) and loss of lower limb myotatic reflexes develop, heralding progressive, ascending myeloencephalopathy. Respiratory failure and brain stem death are followed by a characteristic clinical course despite intensive efforts to support the patient's vital functions. Although, there are several previously reported cases of intrathecal vincristine neurotoxicity in foreign countries, we report the first case of accidental intrathecal injection of vincristine in Korea (7-12).

CASE REPORT

A 3-year-old boy with acute lymphoblastic leukemia, was given chemotherapy. Accidentally, vincristine was administered intrathecally. On the first day, leg pain with decreased motor activity developed. On the second day, meningitic symptoms, such as high fever and neck stiffness developed. Urinary retention due to bladder dysfunction was developed and heart rates increased. The boy was irritable and showed decreased sensory percep-

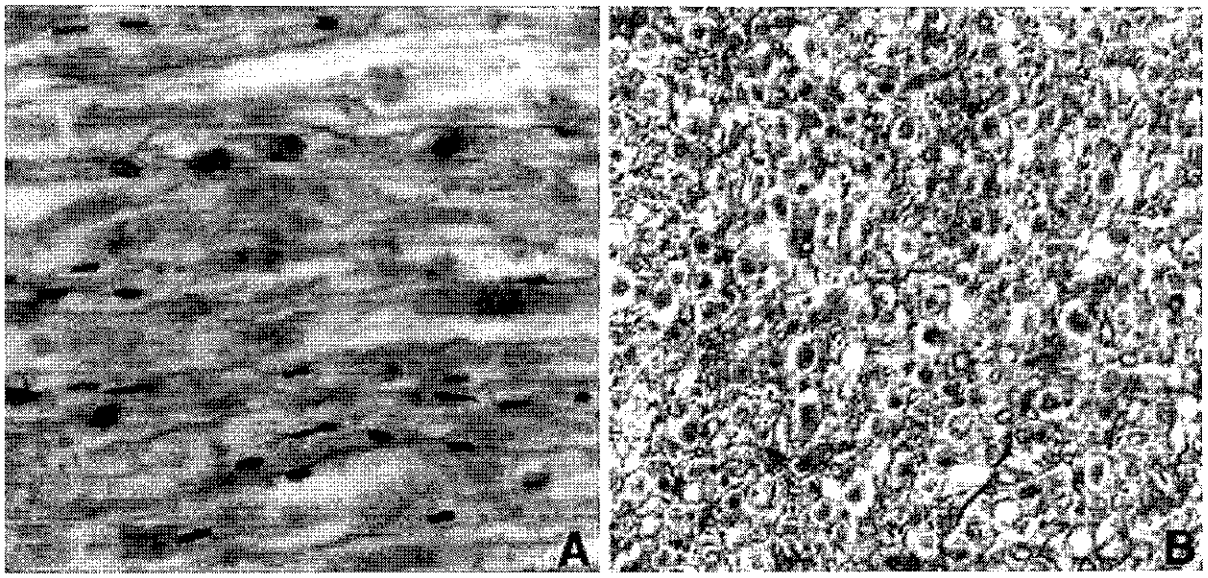

Fig. 1. Extensive axonal degeneration and myelin loss is noted in spinal nerve (A: longitudinal section, PAS, ×400, B: cross section, Luxol fast blue, ×200).

tion. On the third day, high fever and lower extremity paralysis with opisthotonus were noted. His consciousness level began to decline and confusion developed. On the fourth day, he was in a comatose state and respiratory arrest occurred. Two days later he died. An autopsy was performed and the specimen (brain and spinal cord) was examined.

Grossly, cerebrum, cerebellum and spinal cord showed mild edema with congestion. Sections were stained with hematoxylin and eosin, luxol fast blue, trichrome and Periodic acid-Schiff reaction. The most striking histologic changes occurred in the spinal cord and brain stem. Diffuse axonal degeneration with myelin loss was occurred in the spinal nerves (Fig. 1A-B). The spinal cord showed marked edema, axonal degeneration and destruction of both gray and white matters (Fig. 2A-B). Especially anterior horn motor neurons showed profoundly destructed features such as neuronal shrinkage, loss of nuclear mem-

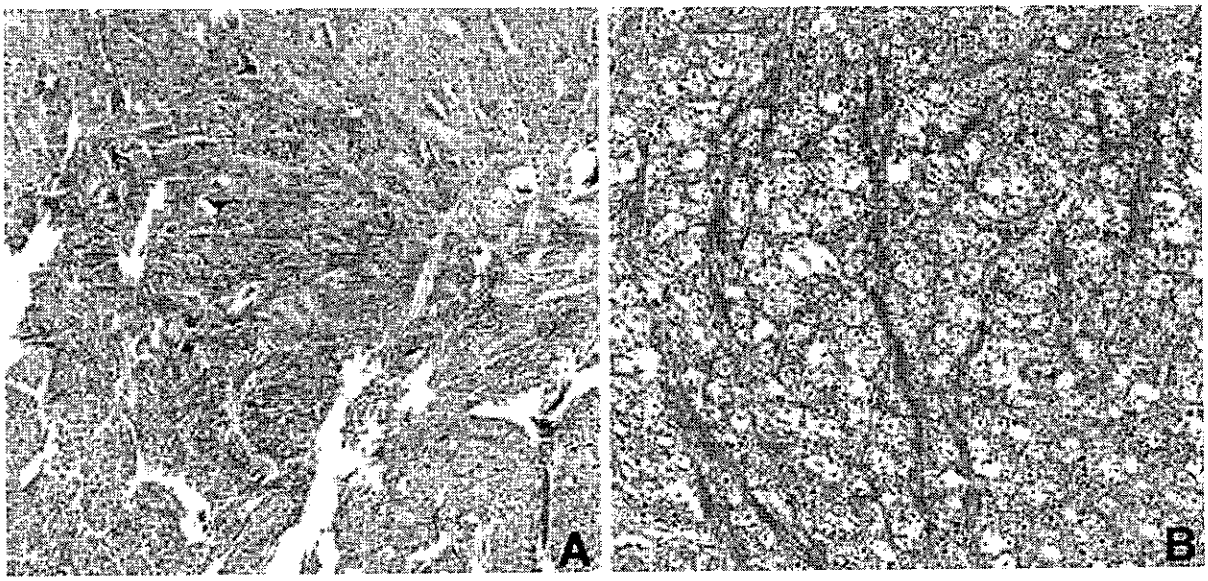

Fig. 2. A: Ventral horn of spinal cord shows interstitial edema with neuronal damage. Marked degeneration of anterior horn motor neurons is noted. B: The white matter of spinal cord shows diffuse axonal degeneration with myelin break down (Luxol fast blue, ×100).

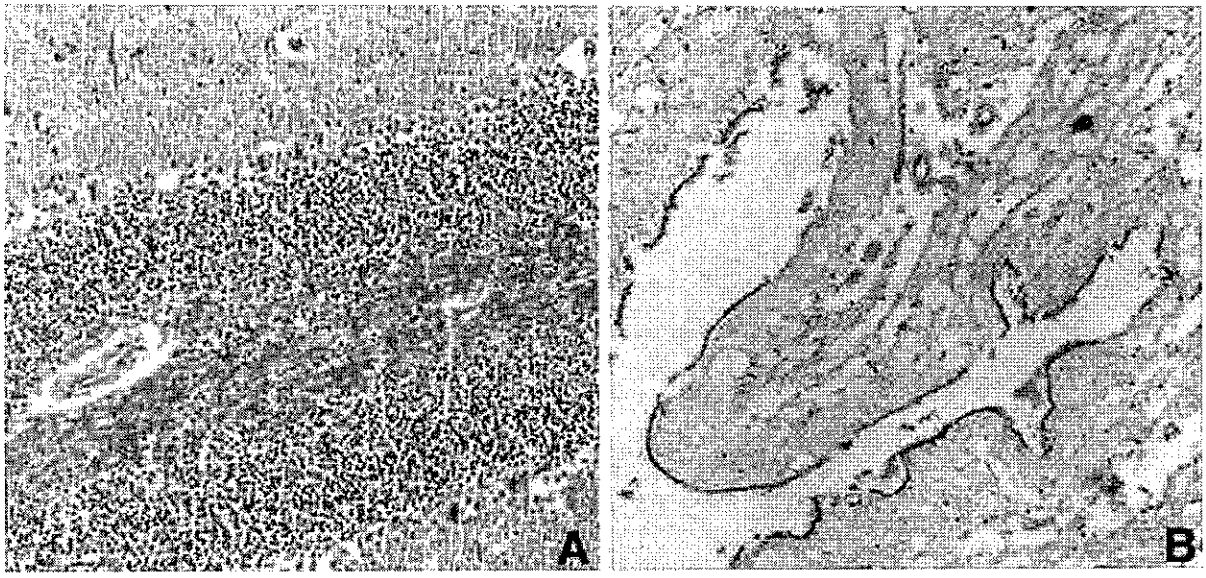

Fig. 3. A: Cerebellar cortex shows extensive loss of Purkinje cell. Perivascular edema is noted. B: Periventricular edema and focal ependymal denudation is present around the 4th ventricle (Luxol fast blue, ×100).

brane with a remaining clump of chromatin granule (Fig. 2A). Some of the neurons showed eccentrically displaced nuclei and clear cytoplasm with peripheral rimming of Nissl substance (central chromatolysis). The cerebellum and brain stem also showed extensively damaged features. The cerebellum showed loss of Purkinje cells and white matter edema (Fig. 3A). Diffuse edema and enlargement of perivascular spaces of the white matter was noted in the brain stem (Fig. 3B). Focal microcystic degeneration was also noted. Several neurons in the brain stem showed chromatolysis and swelling. The cerebrum showed diffuse edema of both gray and white matter, especially in the periventricular and perivascular areas. Focal denudation of ependymal cells of ventricles was also noted. The neurons of cerebral cortex and deep gray matter (basal ganglia and thalamus) revealed swelling and central chromatolysis (Fig. 4A). Some neurons showed pinkish round intracytoplasmic spheroids (Fig. 4B). The cerebral white matter showed marked periventricular interstitial edema compared with area distant from ven-

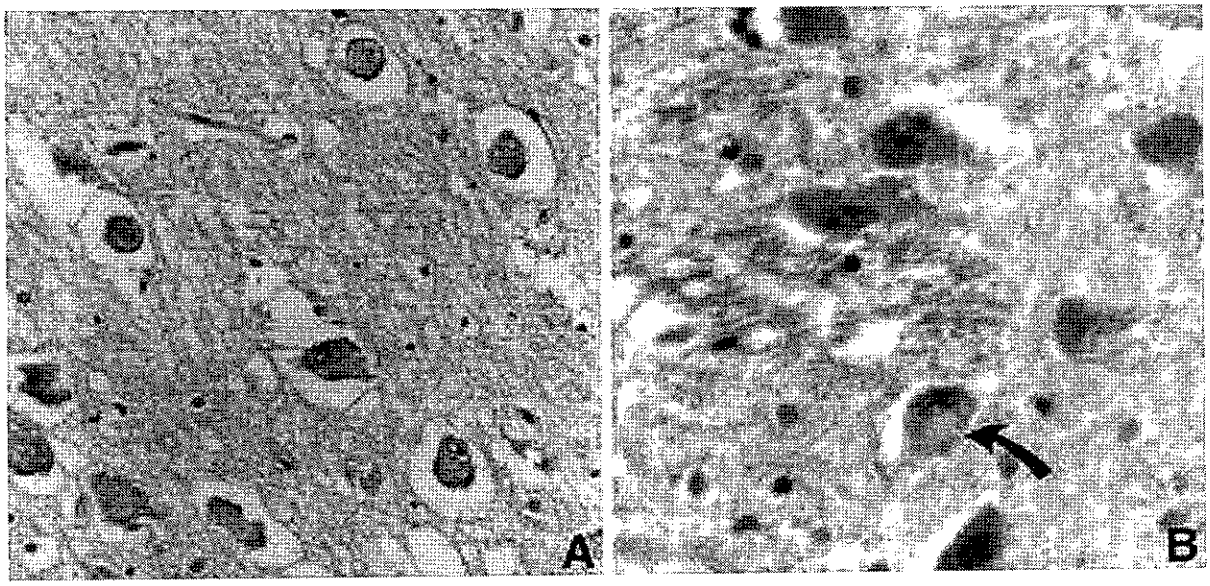

Fig. 4. A: The neurons of basal ganglia shows central chromatolysis. Perineuronal edema is noted (H&E, ×400). B: A neuron forms pinkish round intracytoplasmic spheroid structure (arrow) (Luxol fast blue, ×400).

tricle. Focal microcystic degeneration of white matter was also noted.

DISCUSSION

This case presents a clinicopathologic features of the effects of intrathecally administered vincristine. Clinically, the first sign was leg pain and motor weakness followed by meningism, urinary dysfunction, opisthotonus, progressive sensory loss and alteration of consious state. Subsequently comatose state and respiratory failure developed and resulted in death. Our case progressed the same course as previously reported cases (7-12) and those clinical findings suggests that intrathecal vincristine neurotoxicity is a progressive ascending myeloencephalopathy. The most frequent neuropathic effect, caused by intravenous vincristine injection is chronic peripheral neuropathy, involving both the motor and sensory nervous system (8-10). Intrathecal vincristine causes ascending neuropathy and chronic peripheral neuropathy (8). Ascending neuropathy is a result of direct toxic effect of vincristine. In this case, intrathecal vincristine caused leg pain with decreased motor activity followed by meningitic symptoms such as high fever and neck stiffness. Autonomic nervous system was also involved (8) and its manifestations were urinary retention due to bladder dysfunction, and increased heart rates. Finally, respiratory failure due to brain stem dysfunction developed.

Histologically, our case showed that extensive damage of the spinal cord, brain stem and cerebellum. The spinal cord showed extensive destruction of white matter with neuronal degeneration. Axonal degeneration and myelin loss was noted throughout the central and peripheral nervous system. Neurons in the pons, medulla, and cerebrum showed swollen cytoplasm, and central chromatolysis. The cerebellum showed diffuse loss of Purkinje cells. In the white matter of the cerebrum, microcysts formed by interstitial edema were frequently seen. Those findings are corresponded with the previous reports about the intrathecal vincristine toxicity. Manelis et al. described that striking pathologic changes were seen in the anterior horn cells of the spinal cord and in the motor nuclei of the medulla with enlarged neuron, clear zones among irregularly clumped aggregates of Nissl substance and acidophilic rhomboidal crystals (9). Bain et al. reported that cerebellar tissue was extensively damaged and proliferation of Bergmann glia and severe degeneration and necrosis of the cerebellar cortex were found (8). Histological changes of our case were prominent in spinal cord, cerebellum, and cerebrum in descending order. And neuronal derangements progressed from the injection site and ascended. Periventricular area was more profoundly affected. These findings imply that the severity of neuronal involvement appears to correlate with the concentration and amount of drug received.

In conclusion, intrathecal vincristine causes direct neurotoxicity and ascending neuropathy, which progresses to lethal neuronal damage and results in death in the acute phase of clinical course. Gaidys et al. reported that intravenous vincristine is bound to formed blood and tissue elements in within 20 min and once bound, vincristine and its metabolites are excreted slowly (7). When intrathecal vincristine gets across the blood brain barrier, CNS uptake is occurred rapidly and binding to tubulin is followed prior to the CNS washout (7). There have been no documented cases of survival after intrathecal vincristine injection despite of intensive care about maintenance of vital functions and other special therapies such as CSF exchange and intrathecal hydrocortisone (7-12).

The exact mechanism of vincristine toxicity is not yet known. Some authors proposed that the peripheral neurotoxicity of vincristine is caused by disruption of microtubules, which induce an inhibition of axonal transport of material from cell body to periphery (13, 14). Central neurotoxicity may be explained by the appearance of acidophilic intraneuronal crystals and clumped Nissl substances. In the cerebrum, intracytoplasmic spheroids, which are vincristine induced products and considered to be aggregates of neurofilaments, were found.

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Inadvertent intrathecal administration of vincristine

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This new feature is designed to help protect your patients with updates on adverse events related to various cancer treatments.

Despite its boxed label warning, there have been a number of cases in which vincristine was inadvertently administered intrathecally. When given in this way, vincristine causes central nervous system (CNS) toxicity, producing progressive ascending myeloencephalopathy. The first sign is evident in the neurons that innervate the distal lower extremity; it is characterized by leg weakness, leg pain, and loss of the tendo calcaneus reflex.[1] Autonomic dysfunction may follow with urinary retention. Symptoms of meningitis such as stiffness in the neck and high fevers may also occur. Generalized inflammation and dysfunction of the CNS lead to respiratory failure and death. Attempts to mitigate the toxic effects with cerebrospinal fluid lavage and glucocorticosteroids remain largely unsuccessful.[1]

Where reported

The first reported case of intrathecal administration of vincristine sulfate occurred in the United States in 1968 in a 23-month-old girl diagnosed with acute lymphocytic leukemia who was prescribed intrathecal methotrexate along with intravenous vincristine.[2] Inadvertently, 3 mg of vincristine was given intrathecally. This mistake was recognized a short time later, and 200 mL of cerebrospinal fluid was exchanged with 200 mL of saline as medical management. Despite these efforts, the patient displayed thrashing movements and an opisthotonic posture the following day. On day 3, the patient developed respiratory paralysis, became comatose, and died.

The reasons for this medication error are not clear, but contributing factors may have included premature removal of the drug from its overwrap packaging, unfamiliarity with cancer drugs and protocol, or failure to check physicians' orders by healthcare workers. The autopsy report revealed evidence of neuronal changes produced by the effects of intrathecal vincristine.[2]

The Research on Adverse Drug Events and Reports (RADAR) project of Northwestern University conducted a review of the literature published from 1968 to June 2006. Since 1968, 55 cases of inadvertent intrathecal vincristine have been reported worldwide. In addition to cases in the US, intrathecal administration of vincristine has occurred in the UK, Australia, Israel, Saudi Arabia, and Singapore. While 32 cases have been documented in the literature, only 13 have been reported to the FDA MedWatch. Of those 32 cases, 27 (84%) deaths have resulted (Table 1). Based on the literature findings, the three most frequently cited types of error were:

- physician/nurse and pharmacy error (69%);
- pharmacy error only (19%);
- physician-nurse error only (12%; Table 2).

In cases of physician/nurse and pharmacy error, reports show that intrathecal administration of vin-

Fast Facts

VINCRISTINE

Vincristine is an alkaloid isolated from the Madagascan periwinkle *(Catharanthus roseus)*. Because vincristine sulfate has low octanol:water solubility, it results in low oral bioavailability and poor penetration of the CNS. Therefore, it is labeled for intravenous administration. The drug is used in both children and adults to treat a variety of hematologic malignancies and solid tumors including acute lymphoblastic leukemia, Hodgkin's lymphoma, and non-Hodgkin's lymphoma. Vincristine exerts its cytostatic effects on mitotic spindle fibers causing cell cycle arrest during metaphase.

Common side effects associated with intravenous vincristine include abdominal cramps and constipation, a temporary change in taste, bruising/bleeding, and neurotoxicity, which may be irreversible.

Commun Oncol 2007;4:45–46

TABLE 1

Number of published case reports and deaths from inadvertent intrathecal administration of vincristine by region since 1968

Year	USA/ Canada	Europe	Australia	Asia	Total	Deaths
Prior to 1985	7	0	0	1	8	8 (100%)
1986–1990	1	0	1	0	2	1 (50%)
1991–1995	2	2	1	1	6	4 (66%)
1996–2000	4	1	0	3	8	6 (75%)
2001–2005	2	5	1	0	8	8 (100%)
Total	16	8	3	5	32	27 (84%)

cristine occurred most often because of inadequate communication between pharmacy and medical staff. In these situations, the pharmacy mistakenly delivered vincristine syringes with syringes containing intrathecal medications and physicians or nurses wrongly administered vincristine intrathecally. In cases of pharmacy error alone, the mislabeling of syringes was a common mistake, whereas physician/nurse error alone usually resulted from failure to read syringe labeling or to check physicians' orders.

TABLE 2

Number of cases of inadvertent intrathecal administration of vincristine attributed to each source of error reported since 1968

Year	Physician/ nurse + pharmacy	Pharmacy	Physician/ nurse
Prior to 1985	5	2	1
1986–1990	1	0	1
1991–1995	3	2	1
1996–2000	5	2	1
2001–2005	5	3	0
Total	19 (59%)	9 (28%)	4 (13%)

Additional errors that contributed to the inadvertent intrathecal administration of vincristine include:

- Administration of other chemotherapy agents in combination with vincristine;
- Premature removal of the drug's overwrap packaging;
- Lack of awareness regarding labeling and dispensing requirements;
- Lack of familiarity with chemotherapy drugs and protocols.

Recommendations

All of these cases involved a combination of human and system errors occurring in the medical, nursing, and pharmacy professions. Strategies and guidelines exist to prevent inadvertent intrathecal administration of vincristine. The most effective strategy is to sequester the intrathecal administration of chemotherapy drugs.[3] Thus, *intrathecal* administration of chemotherapy drugs should not occur at the same time or in the same location in the facility where *intravenous* administration of chemotherapy drugs occurs.

In the US, the recommendations for preventing this error include:

- Clearly labeling vincristine as "FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY. DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION."
- Properly training healthcare workers to prepare, deliver, and administer vincristine or any chemotherapy drug.
- Implementing a formal checking procedure or "time out" at each institution.[4]

Intrathecal administration of vincristine is a fatal yet preventable error that needs to be fully understood. With clear labeling, proper awareness, and training of pharmacists, physicians, and nurses, this medication misadventure can be avoided.

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