Inadvertent intrathecal vincristine administration: a neurosurgical emergency

Case report

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Vincristine has a high neurotoxicity level. If given intrathecally by accident, it can cause ascending radiculomyeloencephalopathy, which is almost always fatal. The authors report a rare case in which vincristine was accidentally injected intrathecally into a 32-year-old man. The patient, who had Burkitt lymphoma, was neurologically intact, and it is likely that his survival was made possible due to aggressive neurosurgical therapy. After immediate cerebrospinal fluid (CSF) aspiration, external ventricular and lumbar drains were placed for CSF irrigation, which was continued for 6 days. This CSF irrigation was combined with 1) the intrathecal administration of fresh-frozen plasma to bind the vincristine and 2) an intravenous antineurotoxic therapy involving pyridoxine, folic acid, and glutamic acid. The patient’s first sensorimotor deficits occurred after 2 days, led to an incomplete sensorimotor dysfunction below T-9 within the next 17 days, but progressed no further. Supported by the scarce data culled from the reviewed literature, the authors hypothesize that prolonged CSF irrigation combined with antineurotoxic therapy contributed to the patient’s satisfactory outcome. In conclusion, accidental intrathecal vincristine injection requires emergency and adequate neurosurgical therapy.

KEY WORDS • vincristine • intrathecal injection • paraplegia • external ventricular drainage

Intravenous vincristine sulfate is an alkaloid that is widely used as a chemotherapeutic agent to treat patients with leukemia, Ewing sarcoma, neuroblastoma, and other malignant conditions. It is administered intravenously, often in combination with other antineoplastic drugs. Vincristine is a microtubule-depolymerizing drug that exerts its antineoplastic properties by arresting the mitotic cycle in the metaphase. It similarly attacks neurotubules, which explains why, among others, peripheral motor and sensory neuropathy are common side effects. These neuropathic effects are dose dependent and reversible, if medication is stopped. Pyridoxine, glutamic acid, and folic acid are given in combination to alleviate the neuropathy, but the data supporting their efficacy are inconsistent.³,⁴,13–16

If administered intrathecally by accident, vincristine causes an ascending, progressive radiculomyeloencephalopathy.¹² Direct aspiration of the agent has been proposed to reduce the binding of vincristine to the neurotubules and, thereby, to prevent progressive neural destruction within the spinal cord and brain. Almost all patients, however, have died despite therapy, with a delay of several days.³,⁴,11,17,19,24–26

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History. At another institution, this 32-year-old man was oncologically treated for recurrent Burkitt lymphoma. Instead of methotrexate, vincristine was accidentally given intrathecally via lumbar puncture. After the injection of 1 mg vincristine, the mistake was noticed, 6 ml of CSF was aspirated, the supine patient was placed in a sitting position, and a bolus of 300 mg folic acid was given intravenously. Neurologically intact, the patient was transferred to the neurosurgical department.

Presentation and Treatment. On admission, we observed no focal neurological deficits. Immediately after admission the patient, while in the sitting position, was brought to our intensive care unit and an EVD and lumbar drain were placed. We continued the therapy with the patient in a minimum 45˚ upright position for at least 24 hours.

Through the EVD bag, which first was placed 20 cm above the level of the Monro foramen, the intrathecal compartment was irrigated using FFP-containing lactated Ringer solution (rate 50–80 ml/hour for 6 days). The levels of the EVD and lumbar drain bags were adapted hourly to ensure a 50– to 80–ml/hour in-and outflow to achieve an effective irrigation of the vincristine-loaded CSF.

On Day 6, the irrigation was stopped because the patient developed severe respiratory alkalosis, which was consid-
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ered to be caused by a lactated Ringer solution–mediated pH decrease in the CSF. After this was successfully treated, therapy was reinstituted on Day 7 in our standard care unit. The lumbar drain was left in place until Day 10.

During the period of CSF irrigation, four daily 25-mg doses of calcium folic acid per day, a 660-330-, and 660-mg daily dose of glutamic acid, and three daily 50-mg doses of pyridoxine were also given intravenously.

Clinical Course. On Day 2, the patient began experiencing urinary retention and loss of anal sphincter function. On Day 8, the patient developed a proximal and more left-sided lower-extremity paraparesis. He could move his lower limbs against gravity but not against added resistance.

In the following days, the deficits ascended and were progressive in intensity. On Day 14, dysesthesia of the dorsum of the feet and perianal hypesthesia appeared.

On Day 19, the paraparesis was exacerbated and there was visible muscle movement, but joint movement was absent. Dysesthesia and hypesthesia below the T-9 level were established.

Electromyographic and peripheral nerve conduction studies showed acute denervation in the muscles and sensorimotor polyneuropathic changes in the peripheral nerves of the lower extremities. The patient was seen again on Day 60, and a stable incomplete sensorimotor deficit below T-9 persisted. Magnetic resonance imaging of the brain and spinal cord revealed periradicular and perimedullary enhancement, but there was no evidence of gross neuronal destruction (Figs. 1 and 2).

Discussion

Twenty cases of inadvertent intrathecal vincristine administration have been reported in the literature (Table 1). Fourteen of these patients died, most of them within a few days. In all cases, death was caused by an ascending radiculomyeloencephalopathy. Histological and immunohistochemical investigations showed degeneration of myelin and axons and pseudocystic transformation resulting from the binding of vincristine to tubulin, neurofilament aggregation, and destruction of the cytoskeleton of neurons. These changes were most prominent in the lumbosacral region (the injection site in all but one case) and the thoracic cord; they were less pronounced in the cervical cord, brainstem, and cerebellum. This finding can be best explained by the physiological CSF circulation and a concentration dependency of the vincristine neurotoxicity: The vincristine-loaded CSF is progressively diluted while being transported from the lumbosacral injection site cranially to the basal cisterns. This physiological dilution, however, obviously fails to reduce the vincristine concentration substantially enough to prevent vincristine-induced upper myelon and brain damage.

If neuronal damage correlates with the concentration and
amount of the drug being received, it seems logical to reduce drug availability and to lower the rate of caudocranial CSF transport. Models of intrathecal methotrexate overdose have been used to show that aspiration alone, even if done repetitively, fails to retrieve substantial amounts of the drug. The same failure seems to be present in cases of intrathecal vincristine injection; none of the patients in whom only CSF aspiration was performed survived.\textsuperscript{4,6,22,23,25,26} Only removal of vincristine-loaded CSF and craniocaudal irrigation of the intrathecal compartment for a prolonged minimum period of 24 hours, removed via a lumbar drain and EVD, appears to be effective enough to lower the vincristine concentration and to avoid life-threatening vincristine-mediated neuronal damage. All five patients, in whom irrigation and external ventricular/lumbar drainage were performed for a minimum of 24 hours, survived the accidental intrathecal vincristine injection either with a sensorimotor deficit in the upper and lower extremities\textsuperscript{21,28} or in the lower extremities,\textsuperscript{3,9} whereas both patients in whom an EVD and lumbar drain were used for less than 24 hours died.\textsuperscript{10,11} Because most of the patients became symptomatic after 2 to 7 days and died after a median of 12.5 days, we decided to leave the EVD and the lumbar drain in place for 6 and 10 days, respectively. Compared with the neurological deficits suffered by the other four survivors, the outcome of our patient was very favorable, which in our opin-

### TABLE 1

**Summary of published cases in which vincristine was administered intrathecally**\textsuperscript{*}

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Vincristine Dose (mg)</th>
<th>Time of Recognition</th>
<th>Therapy</th>
<th>Survival (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schochet et al., 1968</td>
<td>2, F</td>
<td>3</td>
<td>shortly after</td>
<td>LD: 2400-ml CSF exchange by 0.9% saline in 24 hrs</td>
<td>3</td>
</tr>
<tr>
<td>Shepherd et al., 1978</td>
<td>5, ?</td>
<td>1.2</td>
<td>after 30 mins</td>
<td>20-ml CSF aspiration; hydrocortisone</td>
<td>12</td>
</tr>
<tr>
<td>Slyter et al., 1980</td>
<td>29, F</td>
<td>2</td>
<td>immediate</td>
<td>5-ml 0.9% saline injected; 10-ml CSF aspiration; 2 × 60-ml CSF exchange in 12 hrs; dexamethasone</td>
<td>14</td>
</tr>
<tr>
<td>Manelis et al., 1982</td>
<td>5, F</td>
<td>0.9</td>
<td>after 30 mins</td>
<td>none</td>
<td>17</td>
</tr>
<tr>
<td>Gaidys et al., 1983</td>
<td>2, F</td>
<td>0.68</td>
<td>immediate</td>
<td>EVD (Ommaya) &amp; LD: 645-ml CSF exchange by 0.9% saline in 90 mins; folic acid</td>
<td>6</td>
</tr>
<tr>
<td>Williams et al., 1983</td>
<td>16, M</td>
<td>2</td>
<td>after 48 hrs</td>
<td>folic acid; dexamethasone</td>
<td>36</td>
</tr>
<tr>
<td>Dyke, 1989</td>
<td>adult</td>
<td>2</td>
<td>immediate</td>
<td>EVD (Ommaya) &amp; LD; ? ml CSF exchange by Ringers lactate &amp; FFP in 24 hrs; dexamethasone</td>
<td>survived w/ tetraparesis</td>
</tr>
<tr>
<td>Bain et al., 1991</td>
<td>56, M</td>
<td>0.3</td>
<td>immediate</td>
<td>? ml CSF aspiration</td>
<td>30</td>
</tr>
<tr>
<td>Bleck &amp; Jacobsen, 1991</td>
<td>23, M</td>
<td>2</td>
<td>after 10 mins</td>
<td>110-ml CSF aspiration; dexamethasone, folic acid, vitamin B12, thiamine, pyridoxine</td>
<td>365 (in coma)</td>
</tr>
<tr>
<td>Al Fawaz, 1992</td>
<td>1.5, M</td>
<td>0.7</td>
<td>after 3 hrs</td>
<td>folic acid; hydrocortisone</td>
<td>75</td>
</tr>
<tr>
<td>Zaragoza et al., 1995</td>
<td>6, M</td>
<td>?</td>
<td>immediate</td>
<td>50-ml CSF aspiration; EVD &amp; LD; ? ml CSF exchange by Ringers lactate &amp; FFP in 24 hrs; dexamethasone</td>
<td>survived w/ tetraparesis</td>
</tr>
<tr>
<td>Lau, 1996</td>
<td>27, F</td>
<td>?</td>
<td>after 24 hrs</td>
<td>?</td>
<td>10</td>
</tr>
<tr>
<td>Michelagnoli et al., 1997</td>
<td>10, F</td>
<td>?</td>
<td>immediate</td>
<td>? ml CSF aspiration; LD &amp; EVD; ? ml CSF exchange by Ringers lactate &amp; FFP in 24 hrs; methylprednisolone</td>
<td>survived w/ tetraparesis</td>
</tr>
<tr>
<td>Fernandez et al., 1998</td>
<td>4, F</td>
<td>1.5</td>
<td>immediate</td>
<td>~ 60-ml CSF exchange by saline; LD &amp; EVD; ? ml CSF exchange by plasmalyte &amp; FFP for 12 hrs; folic acid, glutamic acid, dexamethasone</td>
<td>13</td>
</tr>
<tr>
<td>Meggs &amp; Hoffman, 1998</td>
<td>59, F</td>
<td>2</td>
<td>after 10 mins</td>
<td>?</td>
<td>40</td>
</tr>
<tr>
<td>Al Ferayan et al., 1999</td>
<td>7, M</td>
<td>0.5</td>
<td>immediate</td>
<td>75-ml CSF exchange by Ringers lactate; LD &amp; EVD: 1700-ml CSF exchange by Ringers lactate &amp; FFP for 24 hrs; glutamic acid</td>
<td>survived w/ para-paresis</td>
</tr>
<tr>
<td>Dettmeyer et al., 2001</td>
<td>5, F</td>
<td>?</td>
<td>immediate</td>
<td>?</td>
<td>7</td>
</tr>
<tr>
<td>present case</td>
<td>32, M</td>
<td>1</td>
<td>immediate</td>
<td>6-ml CSF exchange; EVD &amp; LD; ? ml CSF exchange by Ringers lactate &amp; FFP for 144 hrs; glutamic acid, folic acid, pyridoxine</td>
<td>survived w/ para-paresis</td>
</tr>
</tbody>
</table>

* LD = lumbar drain; ? = not stated.
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... supports our therapeutic concept.

More than 50% of vincristine, if given intravenously, binds to blood elements within 20 minutes. For this reason we chose to add FFP to the irrigation fluid. Because three of the four patients who received this combined therapy survived, we considered FFP in combination with irrigation fluid to be beneficial, but we are well aware that scientific proof is lacking.

We and most other authors additionally administer potentially neuroprotective and/or antineurotoxic medications (Table 1), such as corticosteroids, folic acid, glutamic acid, and pyridoxine, but scientific support for the empiric use of these drugs is weak.

The findings obtained in animal experiments suggest that there is a beneficial role for glutamic acid, folic acid, and pyridoxine, but in clinical trials only glutamic acid has been shown to reduce the neurotoxicity of vincristine if given in conventional doses intravenously. Furthermore, none of the patients in whom antineurotoxic therapy alone was used survived.

Conclusions

Vincristine-induced neuronal damage depends on the concentration of the drug. Aspiration of the CSF is not effective enough to substantially retrieve vincristine and to stop the fatal ascending radiculomyeloencephalopathy. The most important therapeutic step in treating a patient who has inadvertently been given an intrathecal dose of vincristine is early placement of an EVD and a lumbar drain to ensure prolonged CSF irrigation and craniocaudal vincristine washout.

An accidental intrathecal vincristine injection must be considered a neurosurgical emergency. The rapid binding of vincristine to blood components is the scientifically unproven rationale for adding FFP to the irrigation fluid. The beneficial role of additional antineurotoxic medication remains in question.

References


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