

Vincristine induced severe SIADH: potentiation with itraconazole

Case Report

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Abbreviations: multiple myeloma (MM); Syndrome of inappropriate antidiuretic hormone secretion, (SIADH); vincristine, (VCR)

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Summary

This study reports on a 50 year-old woman with multiple myeloma who developed severe syndrome of inappropriate antidiuretic hormone secretion (SIADH) when antifungal drugs and vincristine (VCR) were concomitantly administered. Moderate hyponatremia was observed after a second course of VCR without clinical symptoms. Neuropathy, bone marrow toxicity, and severe SIADH appeared during the third chemotherapy course when VCR was administered with itraconazole. Therefore we suggest that itraconazole has potentiated the severity of VCR neurotoxicity. Some 20 cases of drug interaction with VCR enhancing SIADH severity have been reported in the literature. In those patients, a single dose of VCR could induce severe neurotoxicity, which was in contrast with common VCR toxicity features that are usually dose-dependent and correlated with administration frequency. VCR metabolism involves the hepatic cytochrome P450 3A. Substrates and inhibitors of CYP3A enzymes may thus impair VCR metabolism.

I. Introduction

The first case of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was reported by Schwartz (1957) based on the following cardinal findings: (1) hyponatremia with corresponding hypoosmolality of the serum and extracellular fluid, (2) continued renal excretion of sodium, (3) absence of clinical evidence for fluid volume depletion, (4) increased urine osmolality as compared to concomitant osmolality of the plasma, and (5) normal function of the kidneys, suprarenal glands and thyroid glands. SIADH may be caused by various conditions including cytotoxic drugs such as vincristine (VCR). Around 76 cases of hyponatremia and/or SIADH associated with VCR have been reported. In addition, it has been recently reported that drug-drug interactions may also be responsible for VCR-induced hyponatremia and neurotoxicity. We report here the case of a 50 year-old woman with multiple myeloma who developed a severe SIADH when concomitantly administering an antifungal drug and VCR.

II. Case report

A 50 year-old white woman was admitted for medullary compression secondary to multiple myeloma

(MM) which had been diagnosed in August 2003. Chemotherapy with dexamethasone, VCR and adriamycin was started. The first course was held in September 2003 with a sodium level at 142 mmol/L before treatment. No complication was reported at that time. On the second course (October 2003), sodium level was 134 mmol/l and decreased to 129 mmol/l on November 17th (D22 after the second administration) without any symptom. Normalisation at 136 mmol/l occurred on November 20th. At that time, the patient presented as an emergency with fever, inflammatory syndrome and an interstitial syndrome of the lung. Triple antibiotic therapy was started with macrolide, trimethoprim-sulfamethoxazole and cephalosporin. An antifungal treatment with itraconazole was also initiated. Serum sodium level continued to increase until 145 mmol/L before the third VCR course was (November 25th). Seven days later, she developed paralytic ileus (abdominal distension and constipation) and fever. Chest and abdominal plain X-ray showed a pulmonary interstitial edema and apparent redistribution of pulmonary blood volume, normal heart size and gaseous distension of the large bowel loops. Blood examination showed sodium level at 126 mmol/l, potassium 2.7 mmol/l, bicarbonates 16 mmol/l, creatinine 60 µmol/l, blood urea nitrogen 3 mmol/l, hemoglobin 11.3 mmol/l, red blood

cells 16000, C-reactive protein 5 mg/L. Electrocardiography was normal, echocardiography showed normal ejection fraction and wall motion. The pulmonary wedge pressure was below the normal. A gastric decompression by nasogastric tube insertion and parenteral nutrition with electrolytes supplementation was started. Abdominal discomfort and distension improved progressively within 15 days. At the same time, she developed generalised paresthesia, respiratory distress, headaches, nausea, agitation and somnolence without seizures or focal neurologic deficit. Laboratory values revealed: sodium 108 mmol/L, potassium 3.2 mmol/L, and bicarbonates 16 mmol/L. She was treated with 3% saline solution infusion and necessitated several days of mechanical ventilation. Serial blood, bronchoalveolar fluid and lumbar cerebrospinal fluid cultures were negative. She was then transferred to our department with a serum sodium level of 119 mmol/L.

Clinically, there was no sign of edema or volume depletion. Blood pressure was 145/85 mmHg. Laboratory values revealed: serum sodium 117 mmol/L, potassium 3.7 mmol/L, blood urea nitrogen 1.7 mmol/L, creatinine 50 μ mol/L, uric acid 84 μ mol/L, glucose 4.94 mmol/L, protein 74 g/L, plasma osmolality 251.6 mOsm/L, urine osmolality 535 mOsm/L, urine sodium 209 mmol/24 h, urine potassium 8 mmol/24 h. no glycosuria. Thyroid, adrenal and hepatic function tests were normal. Antidiuretic hormone level was in the normal range (2.2 pg/ml, N 2-3 pg/ml) but inappropriately high for the serum osmolality. The diagnosis of SIADH was made and total water intake was restricted. VCR and antimicrobial agents were stopped. The patient was discharged on day 10 with a serum sodium level at 138 mmol/L. Two months later, a fourth chemotherapy course excluding VCR was administered without any changes in serum sodium levels.

III. Discussion

In our patient, hyponatremia appeared 7 days after VCR was started and improved after 10 days on fluid restriction. Furthermore, serum sodium level gradually improved to 140 mmol/l. There was no recurrence of hyponatremia with the reintroduction of chemotherapy excluding VCR. All the cardinal signs for SIADH were present: hyponatremia, serum hypo-osmolality, continued renal excretion of sodium, absence of clinical evidence of fluid volume depletion, osmolality of the urine greater than that appropriate for the concomitant osmolality of the plasma, normal function of kidneys, suprarenal and thyroid glands. For these reasons, hyponatremia was attributed to VCR.

The overall reported rate of SIADH associated with VCR is very low, around 1.3/100 000 treated patients. The first case reported of SIADH in VCR therapy was reported by Fine et al, in 1966. The average age of the patients who present this side effect is 35.6 +/- 28.3 years, 62% are males and racial distribution is predominantly Asians patients (Hammond et al, 2002). SIADH usually occurs between 4 to 10 days after VCR administration and improves 1 week after starting symptomatic treatment (Stuart et al, 1975). The severity and frequency of SIADH is correlated with the frequency of VCR administration as

well as the doses (Kosmidis et al, 1991; Sathiapalan and El-Solh, 2001). Clinically, patients may complain for fatigue, anorexia, nausea, diarrhoea and headaches. When the serum sodium falls below 115, altered mental status, confusion, lethargy, psychosis, seizures, coma and occasionally death may occur. Rarely, focal neurologic signs are present. Some risk factors have been reported for the development of VCR-induced SIADH including Asian patients (Hammond et al, 2002), patients with liver disease (Nishihori et al, 2000), HIV patients (Othieno-Abinya and Nyabola, 2001) and old patients (Langfeldt and Cooley, 2003).

The pathogenesis of VCR-induced SIADH is not clear. It seems to be a multifactorial direct toxicity on central nervous system (inhibitory mechanism of the supraoptic nucleus neurosecretion) (Rufener et al, 1972; Tomiwa et al, 1983) and renal tubules (Philip et al, 1979). Miller and Moses suggested that VCR may induce potentiation of vasopressin action in the kidney. Furthermore, VCR interfere with cells microtubules assemblage and can disturb the transfer of H₂O and blood urea nitrogen across distal and collecting tubules cells (Philip et al, 1979).

There have been approximately 20 cases reported in the literature of drug-drug interaction between azole antifungals and VCR enhancing severity of SIADH (Fine et al, 1966; Fedeli et al, 1989; Kivisto et al, 1995; Gillies et al, 1998; Jeng and Feusner, 2001; Kamaluddin et al, 2001; Sathiapalan and El-Solh, 2001; Sathiapalan et al, 2002). The first cases between VCR and itraconazole were reported in children by Murphy et al, in 1995 and then in adults by Bohme et al, the same year. In those patients, seizures, SIADH and severe paralytic ileus (with one case of bowel perforation) occurred more frequently with the association than when VCR administered alone (Kamaluddin et al, 2001). Furthermore, a single dose of VCR may also induce severe neurotoxicity, which contrasts with common toxicity features of VCR that are usually dose-dependent and correlate with administration frequency (Sathiapalan et al, 2002). Usually neurotoxicity occurs five days after administration of VCR and 2 to 4 weeks after starting itraconazole. SIADH persists for about 10 days after fluid restriction and discontinuation of itraconazole. No recurrence of SIADH after treatment with VCR without itraconazole and with concomitant fluid restriction is usually observed (Gillies et al, 1998; Sathiapalan and El-Solh, 2001). VCR metabolism involves hepatic cytochrome P450 3A subfamily (CYP3A). Indeed, all substrates and/or inhibitors or inducers of CYP3A such as azole antifungals (Gillies et al, 1998; Jeng and Feusner, 2001; Kamaluddin et al, 2001; Sathiapalan and El-Solh, 2001; Sathiapalan et al, 2002), nifedipine (Fedeli et al, 1989; Sathiapalan and El-Solh, 2001), cyclosporine (Kivisto et al, 1995), or isoniazid may thus impair VCR metabolism. Another mechanism of interaction is by an inhibition of P-glycoprotein-mediated drug efflux, resulting in high intracellular VCR levels. Nifedipine, which inhibits P-glycoprotein, may thus block the efflux of VCR from intracellular sites, resulting in prolonged VCR half-life and increased area under the curve (Nishihori et al, 2000).

In our case, neuropathy, bone marrow toxicity and hyponatremia appeared when VCR and an azole antifungal were administered together. Since only moderate hyponatremia with no clinical symptoms was observed after the second course when VCR was administered alone, we therefore suggest that itraconazole has potentiated the severity of VCR neurotoxicity.

Symptomatic treatment of SIADH associated with VCR is mainly based on fluid restriction that may be associated with administration of hypertonic saline solution and intravenous furosemide diuresis.

There are no specific treatments of VCR neurotoxicity. However, an attempt of increased plasma clearance of the drug with exchange transfusions has been performed with favourable outcome in most cases. Pierga et al, also reported one case of favorable outcome with plasmapheresis for VCR overdose (Pierga et al, 1992). Acid folinic was also shown to protect mice from a lethal dose of VCR. Glutamic acid, which was tried by Jackson et al, (Jackson et al, 1988), may decrease VCR-induced neurotoxicity without side effects. Trials with aminoacid, pyridoxine and B12 were unsuccessful.

In conclusion, this case outlines the importance of drug-drug interactions that may result in increased VCR neurotoxicity. Caution is mandatory when using drugs that potentially interact with CYP or P-glycoprotein pumps. The occurrence of SIADH following VCR does not preclude a further safe usage of this drug if prevention by prophylactic rigorous fluid restriction and appropriate association of drugs are respected.

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