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Adverse Interactions between Antifungal Azoles and Vincristine: Review and Analysis of Cases

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Summary

Triazole and imidazole antifungal agents inhibit metabolism of vincristine, leading to excess vinca alkaloid exposure and severe neurotoxicity. Recent reports of debilitating interactions between vincristine and itraconazole, as well as posaconazole, voriconazole and ketoconazole underscore the need to improve medical awareness of this adverse combination. We therefore undertook a comprehensive analysis of reports of adverse drug interactions (ADIs) with the combination of vincristine and azole antifungal agents, established a new classification, and provided a detailed summary of these toxicities. In patients who had sufficient data for analysis, forty-seven individuals were identified who had an ADI with the combination of vincristine and antifungal azoles. Median age was 8 years (1.3–68 years) with 33(70%) having a diagnosis of acute lymphoblastic leukemia. Median time to ADI with vincristine was 9.5 days with itraconazole, 13.5 days posaconazole, and 30 days voriconazole. The median number of vincristine doses preceding the ADI was 2 doses with itraconazole, 3 doses posaconazole, and 2 doses voriconazole. The most common severe ADIs included gastrointestinal toxicity, peripheral neuropathy, hyponatremia/SIADH, autonomic neuropathy, and seizures. Recovery from these ADIs occurred in 80.6% of patients. We recommend using alternative antifungal agents if possible in patients receiving vincristine to avoid this serious and potentially life-threatening drug interaction.

Keywords

azole antifungal; vincristine; drug interactions

Introduction

Metabolism of vincristine has been shown to be mediated by the CYP3A subfamily and this vinca alkaloid is a substrate for the efflux transporter P-glycoprotein (P-gp) [1,2]. Triazole and imidazole antifungal agents inhibit the metabolism of vincristine through cytochrome P450 (CYP) 3A4, leading to excess vinca alkaloid exposure and severe neurotoxicity. In addition, ketoconazole, itraconazole, and posaconazole inhibit vincristine transport by P-gp.

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Given continued reports of severe neurotoxicity with the combination of vincristine and antifungal azoles, there remains a lack of appreciation of this adverse drug interaction. For example, while potentiation of vincristine neurotoxicity by itraconazole was first described by Murphy and colleagues in 1995, case reports and case series of this severe drug interaction with itraconazole continue to be reported [3–8]. In addition, new cases have been recently reported with the second generation triazoles posaconazole and voriconazole [9–12]. Moreover, in resource challenged clinical settings where ketoconazole is still used for antifungal prophylaxis, severe vincristine neurotoxicity in children with acute lymphoblastic leukemia (ALL) also occurs [13]. Despite what appears to be continued reporting of this deleterious combination, little is known about the recognition, clinical manifestations, prevention, and management of this drug interaction. Moreover, none of the previous reports provide a detailed analysis for comparison of the relative frequencies with which different toxicities from this interaction occur. We therefore performed a comprehensive review of the literature. We then analyzed the demographics, introduced a new classification and provided a detailed summary of clinical manifestations and toxicities, and documented outcomes of these interactions between vincristine and antifungal azoles.

Methods

A review of all reports of adverse drug interactions with the combination of vincristine and azole antifungals was performed with a MEDLINE search (1947 – November 2010) using the keywords “vincristine” and “fluconazole”, “itraconazole”, “posaconazole”, “voriconazole”, or “ketoconazole.” The bibliographies of pertinent articles were also reviewed for relevant reports. Other databases, MICROMEDEX, Drug Interactions Analysis and Management, and Drug Interaction Facts, were also reviewed for reports of adverse drug interactions between vincristine and antifungal azoles. An evaluable case was defined as one in which sufficient demographic, clinical, and/or outcome data were available for descriptive statistics. Results were limited to the English-language literature and to reports in humans. Variables included age, gender, primary diagnosis, reason for azole antifungal therapy (as defined elsewhere [14]), azole antifungal and vincristine dosage regimen, time to adverse drug interaction with the azole-vincristine combination, number of vincristine doses given, use of nifedipine, adverse drug reaction, and patient outcome. As there were no consistent toxicity scales used in the published reports, we were not able to assign a quantitative assessment of severity of the adverse drug interactions. Recovery from the adverse drug interaction was defined as resolution of clinical manifestations of the vincristine azole interaction as reported by the individual publications. All data were extracted and reviewed by two of the authors. Toxicity data were classified and reviewed by four of the authors.

Results

A total of 47 patients were identified as meeting the case definition described above [3–13,15–20]. Interactions with vincristine were reported for the following antifungal azoles: itraconazole (N=35); posaconazole (N=3);voriconazole (N=1), and ketoconazole (N=8). There were no evaluable cases of adverse drug interaction reports with the combination of vincristine and fluconazole.

The demographics of these patients are summarized in Table 1. The median age for all patients was 8 years, with 43.2% of patients ≤ 5 years, 25% of patients 6 to 12 years, 6.8% of patients 13 to 18 years, and 25% of patients > 18 years, reflecting the predominance of lymphoid malignancies, particularly pediatric ALL. These adverse interactions occurred at standard dosages of vincristine and antifungal agents.

The median time to clinical manifestations of side effects due to a vincristine azole interaction was 9.5 days (range, 2–28 days) with itraconazole, 13.5 days (range, 12–15 days) with posaconazole, and 30 days with voriconazole. The median number of vincristine doses administered after which the adverse drug interaction occurred was 2 doses (range, 1–4 doses) for itraconazole, 3 doses (range, 2–3 doses) for posaconazole, and 2 doses for voriconazole. There was no mortality associated with the vincristine and antifungal azole drug interaction. Recovery from these adverse drug interactions occurred in 80.6% of patients.

The major types of adverse drug interactions reported in patients receiving vincristine with antifungal triazoles and imidazoles are summarized in Tables 2 and 3. The most common adverse effects included gastrointestinal toxicity in 31 patients (66%), peripheral neuropathy in 28 patients (59.6%), electrolyte abnormalities (hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH)) in 21 patients (44.7%), and autonomic neuropathy in 18 patients (38.3%). Seizures occurred in 11 patients (23.4%).

The major types of adverse drug interactions reported in patients receiving vincristine with itraconazole were also analyzed by age. In pediatric patients (< 18 yo) the most common side effects in declining order included gastrointestinal toxicity (85.7%), electrolyte abnormalities (61.9%), autonomic neuropathy (61.9%), peripheral neuropathy (47.6%), and cranial neuropathy (23.8%). By comparison in adult patients (≥ 18 yo) the most common side effects in declining order included gastrointestinal toxicity (81.8%), peripheral neuropathy (81.8%), electrolyte abnormalities (45.5%), autonomic neuropathy (36.4%), and cranial neuropathy (9.1%). Seizures occurred in 38.1% of the pediatric patients and in 0% of the adult patients.

Specific types of neuropathic, gastrointestinal, and renal adverse effects are summarized in Tables 2 and 3. Neuropathic toxicity is categorized as autonomic, cranial, and peripheral neuropathies. The most common manifestation of autonomic neuropathy was hypertension, while the most common finding of cranial neuropathy was ptosis. Signs and symptoms of peripheral neuropathy commonly included loss of deep tendon reflexes and neuropathic pain/paresthesia. Other manifestations of peripheral neuropathies included difficulty walking or standing, diffuse muscle weakness, and weakness in the extremities. The most common gastrointestinal symptoms were ileus, constipation, abdominal pain, and abdominal distension.

Discussion

This report describes the demographics and toxicities when vincristine is administered concomitantly with antifungal azoles. We describe a wide range of severe toxicities with the combination of antifungal azoles and vincristine including autonomic neuropathy, cranial neuropathy, peripheral neuropathy, gastrointestinal side effects, electrolyte abnormalities, and seizures. While the drug interaction between vincristine and itraconazole has been widely reported, new cases continued to be published 16 years after the initial description of this interaction [21]. Cases have also been recently published with the newer antifungal triazoles posaconazole and voriconazole. The median time to an adverse drug interaction with itraconazole, posaconazole, and voriconazole was 9.5 days, 13.5 days, and 30 days, respectively. The median number of vincristine doses given after which the adverse drug interaction occurred with itraconazole, posaconazole, and voriconazole was 2 doses, 3 doses, and 2 doses, respectively. However, an adverse drug interaction may occur even after one dose of vincristine administered simultaneously with an antifungal azole [4,8]. For example, Sathiapalan et al. described a patient who developed debilitating neurotoxicity including pain in extremities, sweating, abdominal distension, constipation, hypertension, and

hyponatremia/SIADH five days after a single vincristine dose was administered simultaneously with itraconazole [4]. In addition, Takahashi and colleagues reported five patients receiving CHOP chemotherapy (vincristine administered every three weeks) who developed vincristine neurotoxicity with concomitant itraconazole [8].

We attempted to understand the potential role of cumulative doses of vincristine. Among the 13 cases where a vincristine dose was specified, 10 patients had no previous dose of vinca therapy. However, we speculate that higher previous doses of vincristine therapy may lead to more severe toxicity following an interaction with an antifungal triazole.

Although there were no lethalities, toxicity is still debilitating requiring substantial supportive measures to assist in recovery from neurotoxicity, as well as withholding an important antineoplastic agent. In addition, three patients in the itraconazole group experienced only a partial recovery as did three patients in the ketoconazole group. One patient in the posaconazole group had no recovery from the adverse drug interaction. This patient sustained bilateral foot paresthesias, foot drop, generalized loss of deep tendon reflexes, profound muscle weakness, and inability to walk, which did not resolve after five months of discontinuation of vincristine.

The adverse drug interaction between vincristine and antifungal triazoles has been previously reported [7,16,22]. However, this review is unique in that it classifies and analyzes in detail the frequency of specific types of autonomic, cranial, and peripheral neuropathies, gastrointestinal side effects, and electrolyte abnormalities reported in patients receiving the combination of vincristine and antifungal triazoles and imidazoles (Tables 2 and 3). This drug interaction is also unique in that most patients were < 18 years old, reflecting the more frequent use of vincristine in common pediatric malignancies especially ALL.

Vincristine is an alkaloid obtained from the periwinkle plant that was first marketed in the early 1960's as Oncovin® by Eli Lilly and Company for use in acute leukemia. It has since been incorporated into a wide variety of chemotherapy regimens for other disorders in which antifungal azoles will be used for the treatment and prophylaxis of invasive mycoses. These include Hodgkins and non-Hodgkins lymphoma, chronic myeloid leukemia, neuroblastoma, brain tumors, Kaposi Sarcoma, and multiple myeloma. A number of these diseases predominantly affect children and it is particularly noteworthy that a number of these childhood regimens give vincristine in weekly doses for four to six uninterrupted weeks.

The predominant mechanism of cytotoxicity is believed to be related to the inhibition of microtubule formation resulting in an arrest of cells in metaphase (cell-cycle-specific agent). Vincristine is typically given intravenously in bolus doses of 1.5 to 2 mg/m^2 often capped at 2 mg (especially in children) either every seven days or once per cycle, but has also been given as a continuous infusion of up to five days [23].

Studies in cancer patients have shown vincristine to have a triphasic elimination when given as a bolus injection. The distribution, middle, and terminal half-lifes were found to be 5 minutes, 2.3 hours, and 85 hours respectively, however the terminal half-life has ranged from 19 to 155 hours representing the initial distribution in the serum, distribution to the tissues, and tissue sequestration respectively [24]. Approximately 70% of an injected dose is eliminated in the feces with the remaining 10% eliminated in the urine [23].

Triazole antifungal agents interact with vincristine by inhibiting its metabolism through CYP3A4 and its transport by P-gp [1,2,25]. Both itraconazole and posaconazole are inhibitors of CYP3A4 and P-gp [25,26]. These molecules share a common structure of a long hydrophobic arylaliphatic side chain. In contrast, fluconazole and voriconazole are

inhibitors of CYP3A4, CYP2C9, and CYP2C19 but do not inhibit P-gp [25,26]. These molecules share a similar structure of a substituted isopropyl core. Fluconazole is a weaker CYP3A4 inhibitor than itraconazole and demonstrates dose dependent CYP3A4 inhibition over a wider range [27,28], which may explain the paucity of drug interaction reports with this combination [21, 29].

The imidazole ketoconazole is an inhibitor of CYP3A4 and P-gp [27] and therefore a likely inhibitor of vincristine metabolism. Ketoconazole is structurally similar to the triazoles itraconazole and posaconazole in that it has a long hydrophobic arylaliphatic side chain on the asymmetric carbon atom. While vincristine neurotoxicity reported by Gomber and colleagues in 8 patients was attributed to malnutrition [13], the more plausible explanation was inhibition of vincristine metabolism by ketoconazole.

Adverse events reported with the concomitant administration of itraconazole and vincristine included common vincristine side effects such as peripheral neuropathy and gastrointestinal side effects. However, rare side effects such as autonomic neuropathies, cranial neuropathies and electrolyte abnormalities [30] were also frequently reported with an acute onset. Hypertension was an unexpected frequent manifestation of vincristine-associated autonomic neuropathy, occurring in 40% of patients. In three early publications, patients also received nifedipine which may have potentiated vincristine neurotoxicity [3,16,17]. Nifedipine is a P-gp inhibitor and has been reported to decrease vincristine total plasma clearance and increase the area under the concentration versus time curve [31]. Nifedipine should be avoided in combination with vincristine and for the treatment of hypertension from acute vincristine toxicity. No other medications were described in the published reports that inhibited CYP3A4 or transport by P-gp. Bladder dysfunction also was reported in 11.4% of patients in the itraconazole group. Ptosis, which is a rare neuropathy associated with vincristine [30], occurred in 14.3% of patients. In addition, uncommon electrolyte abnormalities such as the SIADH [2,30] occurred in 37.1% of patients. While seizures are an uncommon complication of vincristine therapy, they occurred in nearly 23% of patients (N=8) in this review. Hyponatremia was a plausible explanation for seizure activity in 5 of these patients, while direct neurotoxicity appeared to explain seizures in the other 3 patients.

In the posaconazole treated patients, reported side effects included peripheral neuropathy, gastrointestinal side effects, electrolyte abnormalities, and seizures. Hyponatremia, SIADH, and seizures were frequently reported in patients receiving the combination of vincristine and posaconazole. Only peripheral neuropathy was reported in the one published case report with voriconazole [9]. Other reports describing vincristine’s interaction between voriconazole or posaconazole and for which there were insufficient data for detailed analysis are summarized in Table 4.

In the ketoconazole treated patients, reported side effects included autonomic, cranial, and peripheral neuropathies, gastrointestinal side effects, and seizures [13]. A retrospective chart review by Harnicar and colleagues reported decreased peristalsis defined as abdominal pain, constipation, or ileus in patients receiving vincristine and fluconazole (N = 5) concomitantly [29]. A retrospective review by van Schie and colleagues reported constipation and peripheral neuropathy in one patient receiving vincristine and fluconazole [21]. However, we did not include these studies in our analysis as they did not provide detailed information on individual patients.

There are several possible strategies for managing the serious potentially life-threatening drug interaction between vincristine and the antifungal azoles. These include the use of an alternative non-azole antifungal agent, reduction of the vincristine dose, and discontinuation of the antifungal azole before vincristine chemotherapy [2,25,29]. In patients receiving

antifungal azoles for prophylactic, preemptive, or empirical therapy, we recommend using another class of antifungal agents such as the echinocandins or lipid formulations of amphotericin B. Due to its injurious effect on renal clearance, amphotericin B should not be given concomitantly with high-dose methotrexate. Dose reduction of vincristine is another approach [29], but may not be acceptable in most cancer chemotherapy protocols and may lead to a reduction in vincristine dose intensity. In the absence of vincristine drug level monitoring and of pharmacokinetic studies between vincristine and antifungal azoles we do not recommend this strategy. Withholding the antifungal azole before vincristine chemotherapy and using a non-azole antifungal agent during the withholding period is another approach that may be considered; however, this may be logistically difficult with triazoles that possess long half-lives ($t_{1/2}$) such as those seen in pediatric and adult pharmacokinetic studies of itraconazole (28.3 – 47.4 h), posaconazole (35 h), or fluconazole (16.8 – 18.1 h) [32–34]. Withholding voriconazole before vincristine chemotherapy may also be problematic in patients who are CYP2C19 homozygous poor metabolizers, as the half-life of voriconazole is prolonged in these patients [35–38]. We recently described a patient with a prolonged $t_{1/2}$ of voriconazole of 24 to 30 hours due to *CYP2C19*2/*2* poor metabolizer genotype. Voriconazole was discontinued three days before vincristine chemotherapy to avoid this serious drug interaction [39].

For patients requiring treatment for invasive fungal infections while receiving vincristine chemotherapy, we also recommend using a non-azole antifungal agent if possible. If treatment with an antifungal triazole is essential we recommend consulting an infectious diseases physician and clinical pharmacist [39].

In conclusion, severe neurotoxicity has been described with the concomitant administration of vincristine and antifungal azoles including itraconazole, posaconazole, voriconazole, and ketoconazole. We recommend using alternative antifungal agents if possible in patients receiving vincristine chemotherapy to avoid this serious and potentially life-threatening drug interaction.

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Table 1

Demographics of 47 patients with toxicity caused by vincristine in combination with antifungal azoles.

	n	Itra	Keto	Posa	Vori
Total N	47	35	8	3	1
Age (median years) (range)	44[1]	8 (1 – 68)	8.5 (2 –12)	9 (4 – 21)	5
Age ≤ 5 years, N (%)		14 (43.8)	3 (37.5)	1 (33.3)	1 (100)
Age 6 – 12 years, N (%)		5 (15.6)	5 (62.5)	1 (33.3)	0 (0)
Age 13 – 18 years, N (%)		3 (9.4)	0 (0)	0 (0)	0 (0)
Age > 18 years, N (%)		10 (31.3)	0 (0)	1 (33.3)	0 (0)
Male/Female, N	35[1]	11/12	7/1	2/1	0/1
Primary diagnosis	44[1]				
ALL, N (%)		24 (68.6)	5 (62.5)	3 (100)	1 (100)
Anaplastic large cell lymphoma, N (%)		1 (2.9)			
Diffuse large B-cell lymphoma, N (%)		3 (8.6)			
Follicular lymphoma, N (%)		1 (2.9)			
Multiple myeloma, N (%)		1 (2.9)			
B cell NHL, N (%)		1 (2.9)			
T cell NHL, N (%)		1 (2.9)			
Lymphoblastic NHL, N (%)			3 (37.5)		
Not reported, N (%)		3 (8.6)			
Reason for antifungal therapy					
Primary prophylaxis, N (%)		31 (88.6)	8 (100)		
Secondary prophylaxis, N (%)		1 (2.9)		2 (66.7)	
Treatment, N (%)		3 (8.6)		1 (33.3)	1 (100)
Azole dosage regimen					
Pediatric patients (< 18 yo)	29[1]	2.5 mg/kg/day[2] to 8 mg/kg/day IV	5 to 8 mg/kg/day[2]	7 mg/kg/day po to 50 mg po TID	Not reported
Adult patients (≥ 18 yo)	11[1]	200 mg po day to 200 mg po BID		400 mg po BID	

	n	Itra	Keto	Posa	Vori
Vincristine dosage regimen	21[1]	1.5 mg/m^2 qmonth to 2 mg qweek	1.4 mg/m^2 qweek	1.8 mg (1.5 mg/m^2) day 1 and 6 to 2 mg qweek	Not reported
Received nifedipine, N (%)	11[1]	11 (31.4)	0 (0)	0 (0)	0 (0)
Received nifedipine before starting vincristine, N (%)		0 (0)			
Received nifedipine after starting vincristine, N (%)		11 (100)			
Time to adverse drug interaction[3], median days (range)	29[1]	9.5 (2 – 28)		13.5 (12 – 15)	30
Number of vincristine doses given[4], median (range)	29[1]	2 (1 – 4)		3 (2 – 3)	2
Resolution of adverse drug interaction	36[1]				
Recovery, N (%)		23 (65.7)	3 (37.5)	2 (66.7)	1 (100)
Partial recovery, N (%)		3 (8.6)	3 (37.5)	0 (0)	0 (0)
No recovery, N (%)		0 (0)	0 (0)	1 (33.3)	0 (0)
Not reported, N (%)		9 (25.7)	2 (25)[5]	0 (0)	0 (0)

[1] number of cases with available data.

[2] route not specified.

[3] time to adverse drug interaction with the concomitant administration of vincristine and antifungal azole.

[4] number of vincristine doses given with the concomitant administration of antifungal azole after which adverse drug interaction occurred.

[5] two patients “not reported” were found to have died from fever, neutropenia, and sepsis.

itra = itraconazole;keto=ketoconazole;posa = posaconazole;vori = voriconazole;N = number of patients;ALL = acute lymphoblastic leukemia;NHL = non-Hodgkin’s lymphoma.

Table 2

Autonomic, cranial, and peripheral neuropathies reported in patients receiving the combination of vincristine and antifungal azoles.

Adverse Event	Signs and Symptoms	All Azoles N = 47 (%)	Itra N = 35 (%)	Keto N = 8 (%)	Posa N = 3 (%)	Vori N = 1 (%)
Autonomic neuropathy		**18 (38.3)**	**17 (48.6)**	**1 (12.5)**	**0 (0)**	**0 (0)**
	Hypertension		14 (40)			
	Inability to pass urine		1 (2.9)			
	Incontinence		1 (2.9)			
	Neurogenic bladder		1 (2.9)	1 (12.5)		
	Orthostatic hypotension		1 (2.9)			
	Palpable bladder		1 (2.9)			
	Sweating		1 (2.9)			
	Decrease in anal tone		1 (2.9)			
Cranial neuropathy		**11 (23.4)**	**6 (17.1)**	**5 (62.5)**	**0 (0)**	**0 (0)**
	Jaw pain		1 (2.9)	3 (37.5)		
	Opthalmoplegia		1 (2.9)			
	Ptosis		5 (14.3)			
	Transient visual loss			1 (12.5)		
	Weak gag reflex			1 (12.5)		
Peripheral neuropathy		**28 (59.6)**	**19 (54.3)**	**6 (75)**	**2 (66.7)**	**1 (100)**
	Loss of deep tendon reflexes		8 (22.9)	1 (12.5)	2 (66.7)	1 (100)
	Severe foot drop/steppage gait		2 (5.7)		1 (33.3)	1 (100)
	Areflexia		2 (5.7)	5 (62.5)		
	Arthralgia		2 (5.7)			
	Back pain		1 (2.9)	1 (12.5)		
	Difficult/inability to walk or stand up		3 (8.6)		1 (33.3)	
	Diffuse muscle weakness		2 (5.7)		1 (33.3)	
	Hypothenar and thenar wasting		1 (2.9)			
	Muscle cramps		1 (2.9)			
	Myalgia		4 (11.4)			
	Neurotoxicity of extremities		4 (11.4)		1 (33.3)	

Adverse Event	Signs and Symptoms	All Azoles N = 47 (%)	Itra N = 35 (%)	Keto N = 8 (%)	Posa N = 3 (%)	Vori N = 1 (%)
	Neuropathic pain/paresthesia		5 (14.3)	1 (12.5)	1 (33.3)	
	Paralysis of extremities		2 (5.7)			
	Weakness of extremities		3 (8.6)	5 (62.5)		

itra = itraconazole;keto=ketoconazole;posa = posaconazole;vori = voriconazole;N = total number of patients.

Table 3

Gastrointestinal, renal, and other adverse events reported in patients receiving the combination of vincristine and antifungal azoles.

Adverse Event	Signs and Symptoms	All Azoles N = 47 (%)	Itra N = 35 (%)	Keto N = 8 (%)	Posa N = 3 (%)	Vori N = 1 (%)
Gastrointestinal		**31 (66)**	**29 (82.9)**	**1 (12.5)**	**1 (33.3)**	**0 (0)**
	Abdominal distension		6 (17.1)			
	Abdominal pain		15 (42.9)		1 (33.3)	
	Constipation		16 (45.7)	1 (12.5)	1 (33.3)	
	Ileus		18 (51.4)			
	Nausea		2 (5.7)			
	Non alcoholic steatohepatitis		2 (5.7)			
	Perforation		1 (2.9)			
	Vomiting		1 (2.9)			
Renal (electrolyte abnormalities)		**21 (44.7)**	**19 (54.3)**	**0 (0)**	**2 (66.7)**	**0 (0)**
	Hyponatremia		19 (54.3)		2 (66.7)	
	SIADH		13 (37.1)		2 (66.7)	
Other		**16 (34)**	**12 (34.3)**	**2 (25)**	**2 (66.7)**	**0 (0)**
	Agitation		1 (2.9)	1 (12.5)	1 (33.3)	
	Depression		6 (17.1)			
	Seizure		8 (22.9)	1 (12.5)	2 (66.7)	
	Cerebral edema				1 (33.3)	

itra = itraconazole;keto=ketoconazole; posa = posaconazole;vori = voriconazole;N = total number of patients;SIADH = syndrome of inappropriate antidiuretic hormone secretion.

Table 4

Other reports of vincristine drug interactions with voriconazole and posaconazole.

Age Gender	Primary Diagnosis	Triazole Antifungal Dosage Regimen	Adverse Drug Reaction	Reference
Pediatric	ALL	voriconazole 7 mg/kg IV BID (N = 2)	constipation, peripheral neuropathy	21
Adults (≥ 18 yo)	ALL	voriconazole (N= 12) posaconazole 400 mg po BID (N = 2)	decreased peristalsis (abdominal pain, constipation, or ileus)	29

ALL = acute lymphoblastic leukemia