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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Vinca Alkaloids. [Updated 2013 Dec 3].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Vinca Alkaloids

Updated: December 3, 2013.

VINBLASTINE, VINCRISTINE, VINORELBINE

OVERVIEW

Introduction

The vinca alkaloids include vincristine, vinblastine and vinorelbine which are important antineoplastic agents used in many chemotherapeutic regimens for a wide variety of cancers. Despite their cytotoxic activity against cancer cells, the vinca alkaloids have rarely been implicated in causing clinically apparent acute liver injury.

Background

The vinca alkaloids are antineoplastic agents that act by binding to intracellular tubulin, the basic protein subunit of microtubules which are important in many intracellular processes including mitosis and cell division. The vinca alkaloids inhibit cell division by blocking mitosis; they also inhibit purine and RNA synthesis causing death of rapidly dividing cells. Vincristine and vinblastine were initially isolated from periwinkle (vinca rosea), extracts of which were found to have antitumor activity. Subsequently, they have been synthesized, although their structure is quite complex. Vinorelbine is a semisynthetic derivative of extracts of periwinkle. Vincristine (vin kris' teen) was approved for use in cancer chemotherapy in 1963, vinblastine (vin blas' teen) in 1965 and vinrelbine (vin or' el been) in 1994. They have become major components of many combination anticancer regimens, used particularly in treatment of acute leukemia, Hodgkin disease and other lymphomas, various sarcomas, Wilms tumor, neuroblastoma, and breast and lung cancer. The vinca alkaloids are given intravenously, typically at one or two week intervals in cycles with other agents. The vinca alkaloids are available in generic forms and under the trade names Oncovin (vincristine), Velban (vinblastine) and Navelbine (Vinorelbine). Side effects are common and include nausea, vomiting, fatigue, headache, dizziness, peripheral neuropathy, hoarseness, ataxia, dysphagia, urinary retention, constipation, diarrhea, bone marrow suppression, alopecia and phlebitis at the infusion site.

Hepatotoxicity

Despite being cytotoxic for cancer cells and metabolized actively by the liver, the vinca alkaloids have only rarely been associated with significant hepatic toxicity. Because they are usually given with other anticancer agents and/or radiotherapy, which may also be hepatotoxic, the role that they play in causing liver injury is not always clear. When given on their own, the vinca alkaloids are associated with transient and asymptomatic elevations in serum aminotransferase levels in 5% to 10% of patients. However, clinically apparent liver injury attributed to the vinca alkaloids has been rare and not well defined. Both vincristine and vinblastine may increase the risk of sinusoidal obstruction syndrome, also known as venoocclusive disease of the liver, caused by radiation, dactinomycin or the alkylating agents, but not when given on their own. In these situations, the risk of sinusoidal

obstruction syndrome is greater with higher doses of radiation, dactinomycin or cyclophosphamide and younger age (in children).

Mechanism of Injury

The reason why the vinca alkaloids are not particularly toxic to liver cells is not known, but cell division and mitosis (the major targets of vincristine and vinblastine) are rare in the resting liver. Both agents are extensively metabolized in the liver and excreted in bile.

Outcome and Management

Serum enzyme elevations are not uncommon during cancer chemotherapy and may occasionally be dose limiting; however, the vinca alkaloids are rarely the sole or major reason for significant or persistent enzyme elevations or clinically apparent liver injury. Patients who develop sinusoidal obstruction syndrome, but recover, can be safely treated with further courses of vincristine alone or combined with reduced doses of the alkylating agent or dactinomycin.

Drug Class: Antineoplastic Agents

CASE REPORT

Case 1. Fatal sinusoidal obstruction syndrome after abdominal irradiation and vincristine therapy.

[Modified from: Hansen MM, Ranek L, Walbom S, Nissen NI. Fatal hepatitis following irradiation and vincristine. Acta Med Scand 1982; 212: 171-4. PubMed Citation]

A 30 year old woman with poorly differentiated lymphocytic nodular lymphoma was treated with prednisone and weekly infusions of vincristine and once weekly oral streptonigrin (an antibiotic and bioreductive antineoplastic agent). Vincristine was withdrawn after 4 cycles because of neuropathy. After 6 cycles of chemotherapy, she underwent mediastinal (2000 rads) and abdominal (2225 rads) irradiation over a two month period with another cycle of vincristine (day 88). On day 111, which was 10 days after finishing radiation therapy and 33 days after the fifth and last infusion of vincristine, she developed pancytopenia, fever, abdominal pain, ascites and jaundice. Serum aminotransferase levels were markedly elevated with only modest increases in alkaline phosphatase. The fever and pancytopenia resolved with antibiotic therapy, but she developed progressive jaundice and hepatic failure and died 4 weeks later. Autopsy showed an enlarged, congested liver with sinusoidal obstruction and severe centrilobular necrosis. The autopsy showed no residual evidence of lymphoma.

Key Points

Medication:	Vincristine, hepatic irradiation
Pattern:	Hepatocellular (R=~100)
Severity:	5+ (hepatic failure and death)
Latency:	111 days after starting vincristine, 10 days after irradiation
Recovery:	None
Other medications:	Prednisone, streptonigrin

Laboratory Values

Days After Starting	Chemo Therapy	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
1	Started oral prednisone and weekly doses of vincristine and streptonigrin				

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Days After Starting	Chemo Therapy	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
11	V & S	9	105	0.8	
17	V & S	10	100		
24	V & S	11	105		
31	S	13	90		
38	S	11	90		
53	Rad	15	135		
88	Rad & V	25	140		
111	Admission	4000	255	5.8	Jaundice, ascites, fever
113	Day 2	1550	230	6.0	
117	Day 6	185	265	10.0	
122	Day 11	88	405	20.0	
131	Day 20	62	340	20.5	
141	Day 30	Died of hepatic failure			
Normal Values		**<30**	**<275**	**<1.2**	

* ABBREVIATIONS: V=vincristine infusion, S=oral streptonigrin, Rad=radiation therapy.

Comment

The clinical presentation with weight gain, abdominal pain, ascites and jaundice is typical of sinusoidal obstruction syndrome. Hepatic irradiation, dactinomycin, and the alkylating agents (dacarbazine, cyclophosphamide, myleran and busulfan) are most frequently associated with this form of liver injury. The injury is probably due to direct toxicity to sinusoidal lining cells with their subsequent necrosis and extrusion into the sinusoidal spaces, which causes obstruction, hemorrhage and local ischemia to hepatocytes. Signs of portal hypertension appear early, followed (in severe cases) by jaundice and hepatic failure. The dose of radiation used in this patient (<3000 rads) was not considered adequate to cause sinusoidal obstruction syndrome on its own, which suggested that vincristine might have increased the risk of this complication.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Vinblastine – Generic, Velban®

Vincristine – Generic, Oncovin®

Vinorelbine – Generic, Navelbine®

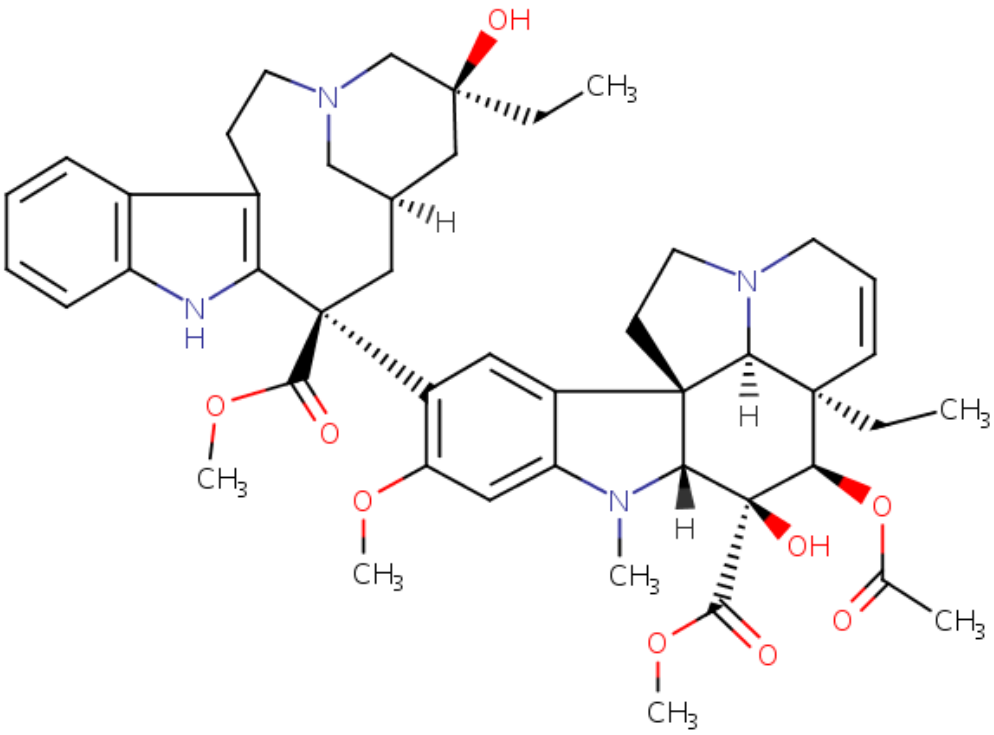
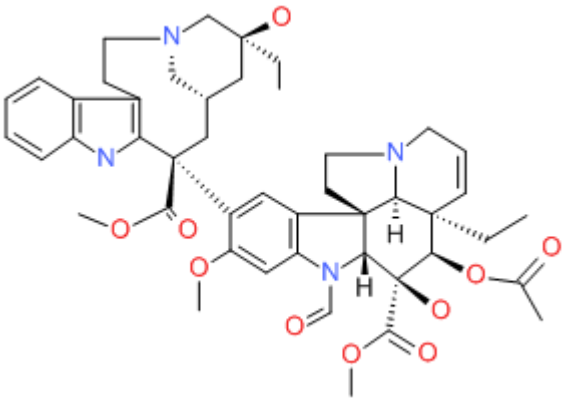
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Vinblastine	865-21-4	C46-H58-N4-O9	
Vincristine	57-22-7	C46-H56-N4-O10	

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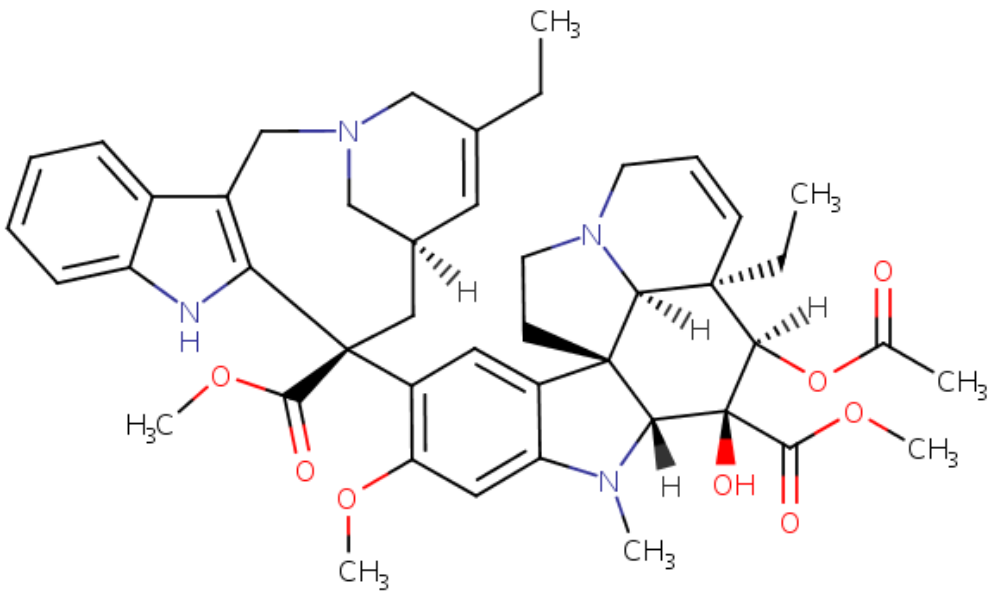
DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Vinorelbine	71486-22-1	C45-H54-N4-O8	

ANNOTATED BIBLIOGRAPHY

References updated: 03 December 2013

Zimmerman HJ. The vinca alkaloids. Oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 692-4.

(Expert review of hepatotoxicity published in 1999 mentions that vincristine and vinblastine appear to cause little hepatic injury in humans or experimental animals).

DeLeve LD. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 549-68.

(Review of hepatotoxicity of published in 2007; mentions that vincristine may increase the risk of sinusoidal obstruction syndrome caused by dactinomycin).

Chabner BA, Bertino J, Clearly J, Ortiz T, Lane A, Supko JG, Ryan DP. Cytotoxic agents. Chemotherapy of neoplastic diseases. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1677-730.

(Textbook of pharmacology and therapeutics).

Costa G, Hreshchyshyn MM, Holland JF. Initial clinical studies with vincristine. Cancer Chemother Rep 1962; 24: 39-44. PubMed PMID: 14023264.

(Preliminary studies of vincristine against various cancers; dose limiting side effects included peripheral neuropathy and bone marrow suppression; 5 of 12 patients had patchy hepatic necrosis on autopsy despite having no abnormalities of liver tests before death).

Bohannon RA, Miller DG, Diamond HD. Vincristine in the treatment of lymphomas and leukemias. Cancer Res 1963; 23: 613-21. PubMed PMID: 13968454.

(Review of mechanism of action, clinical efficacy and toxicity of vincristine; AST elevations occurred in a small proportion of patients, but were not dose-limiting).

Raine J, Bowman A, Wallendszus K, Pritchard J. Hepatopathy-thrombocytopenia syndrome–a complication of dactinomycin therapy for Wilms' tumor: a report from the United Kingdom Childrens Cancer Study Group. J Clin Oncol 1991; 9: 268-73. PubMed PMID: 1846405.

(Among 355 children with Wilms tumor who received the combination of dactinomycin and vincristine, 5 developed "hepatopathy-thrombocytopenia syndrome" [bilirubin 1.3-6.1 mg/dL, ALT 335-5723 U/L], but none of 146 given vincristine alone developed this syndrome).

Hansen MM, Ranek L, Walbom S, Nissen NI. Fatal hepatitis following irradiation and vincristine. Acta Med Scand 1982; 212: 171-4. PubMed PMID: 7148508.

(30 year old woman with lymphoma developed sinusoidal obstruction syndrome after liver irradiation and chemotherapy with vincristine [bilirubin 6.0 rising to 21.0 mg/dL, AST 4000 U/L, Alk P 250 U/L], with progressive multiorgan failure and death 4 weeks later: Case 1).

el Saghir NS, Hawkins KA. Hepatotoxicity following vincristine therapy. Cancer 1984; 54: 2006-8. PubMed PMID: 6090004.

(49 year old woman with lung cancer treated with VP-16, cyclophosphamide and vincristine developed ALT elevations [2 to 6 times ULN] a week after chemotherapy with normal bilirubin levels and liver biopsy; ALT elevations recurred when vincristine was given alone).

Green DM, Finklestein JZ, Norkool P, D'Angio GJ. Severe hepatic toxicity after treatment with single-dose dactinomycin and vincristine. A report of the National Wilms' Tumor Study. Cancer 1988; 62: 270-3. PubMed PMID: 2838151.

(5 children, ages 1 to 8 years, developed severe hepatic injury [sinusoidal obstruction syndrome] 2-9 days after the 2nd or 3rd course of dactinomycin and vincristine, and 1 died; no recurrence when vincristine was restarted alone or with reduced and split doses of dactinomycin).

Green DM, Norkool P, Breslow NE, Finklestein JZ, D'Angio GJ. Severe hepatic toxicity after treatment with vincristine and dactinomycin using single-dose or divided-dose schedules: a report from the National Wilms' Tumor Study. J Clin Oncol 1990; 8: 1525-30. PubMed PMID: 2167951.

(Retrospective analysis of 154 children with Wilms tumor treated with dactinomycin and vincristine found higher rate of hepatotoxicity with higher single dose dactinomycin [14%] than with lower [4%] or split doses [3%]; clinical presentation with ascites, elevated AST [529 to 8208 U/L] and 50% with jaundice).

Zhou XJ, Rahmani R. Preclinical and clinical pharmacology of vinca alkaloids. Drugs. 1992; 44 Suppl 4: 1-16; discussion 66-9. PubMed PMID: 1283846.

(Review of structure, mechanism of action, pharmacology, clinical efficacy and toxicities of vinca alkaloids; hepatotoxicity not discussed).

Bisogno G, de Kraker J, Weirich A, Masiero L, Ludwig R, Tournade MF, Carli M. Veno-occlusive disease of the liver in children treated for Wilms tumor. Med Pediatr Oncol 1997; 29: 245-51. PubMed PMID: 9251728.

(Among 511 children with Wilms tumor treated with dactinomycin and vincristine with or without other agents or irradiation, 64 [12%] had hepatotoxicity including 41 [8%] with sinusoidal obstruction syndrome [all with hepatomegaly, 83% ascites, 28% jaundice, 6% fatal]; rates higher in children <1 years of age and those who received irradiation [12% vs 7%]).

Ortega JA, Donaldson SS, Ivy SP, Pappo A, Maurer HM. Venoocclusive disease of the liver after chemotherapy with vincristine, actinomycin D, and cyclophosphamide for the treatment of rhabdomyosarcoma. A report of the Intergroup Rhabdomyosarcoma Study Group. Childrens Cancer Group, the Pediatric Oncology Group, and the Pediatric Intergroup Statistical Center. Cancer 1997; 79: 2435-9. PubMed PMID: 9191535.

(Among 821 children [ages 2-15 years] with rhabdomyosarcoma treated with vincristine, dactinomycin and cyclophosphamide, 10 [1.2%] developed sinusoidal obstruction syndrome and 1 died; single major risk factor was higher doses of cyclophosphamide).

Nishihori Y, Yamauchi N, Kuribayashi K, Sato Y, Morii K, Hirayama Y, Sakamaki S, et al. [Severe hemolysis and SIADH-like symptoms induced by vincristine in an ALL patient with liver cirrhosis]. Rinsho Ketsueki 2000; 41: 1231-7. Japanese. PubMed PMID: 11193445.

(Abstract only: 11 year old boy with leukemia and chronic hepatitis C developed severe hemolysis and died of hepatic failure while being treated with vincristine).

van der Hul RL, Seynaeve C, van Geel BN, Verweij J. Low dose methotrexate and vinblastine, given weekly to patients with desmoid tumours, is associated with major toxicity. Sarcoma 2003; 7: 153-7. PubMed PMID: 18521380.

(Among 10 patients with desmoid tumors given methotrexate [50 mg/week] and vinblastine [10 mg/week], severe side effects were common and 2 developed transient ALT elevations [3 to 10 times ULN] without jaundice).

Arndt C, Hawkins D, Anderson JR, Breitfeld P, Womer R, Meyer W. Age is a risk factor for chemotherapy-induced hepatopathy with vincristine, dactinomycin, and cyclophosphamide. J Clin Oncol 2004; 22: 1894-901. PubMed PMID: 15143082.

(Among 339 children with rhabdomyosarcoma treated with vincristine, dactinomycin and cyclophosphamide, 18 [6%] developed hepatotoxicity and 3 died [1%]; risk of liver injury was greater in children <3 years of age [15% vs 4%]).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury and 2 to antineoplastic agents [melphalan and gemtuzumab], but none to vincristine or vinblastine).

Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol 2010; 70: 721-8. (Worldwide pharmacovigilance database contains 9036 hepatic adverse drug reactions in children, vincristine accounted for 46 instances, ranking 26th). PubMed PMID: 21039766.

Langholz B, Skolnik JM, Barrett JS, Renbarger J, Seibel NL, Zajicek A, Arndt CAs. Dactinomycin and vincristine toxicity in the treatment of childhood cancer: a retrospective study from the Children's Oncology Group. Pediatr Blood Cancer 2011; 57: 252-7. PubMed PMID: 21671362.

(Retrospective review of six pediatric cancer clinical trials, comprising 4567 patients; the review found an overall risk for hepatotoxicity due to dactinomycin to be between 10-15%, depending upon age and type of tumor being treated; patients <1 year of age were at greater hepatotoxicity risk; vincristine was not associated with liver injury in this review).