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Vinblastine and erythromycin: an unrecognized serious drug interaction

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Abstract Vinblastine and erythromycin are among the most commonly used chemotherapeutic and antimicrobial agents, respectively. No interaction between the two has ever been reported. Towards the end of a phase I study of vinblastine plus oral cyclosporin (to reverse multidrug resistance), three patients also received erythromycin to raise their cyclosporin levels. All developed severe toxicity consistent with a much higher vinblastine dose than was actually given. This apparent potentiation of vinblastine toxicity has not been previously described.

Key words Vinblastine · Erythromycin · Interaction

Introduction

The vinca alkaloid vinblastine is used in combination with other cytotoxic agents in the curative treatment of Hodgkin's disease and germ cell tumours, and for palliation in cancers of the breast, lung, bladder, and kidney, cancers with unknown primary, and Kaposi's sarcoma. The macrolide antibiotic erythromycin is the drug of choice for community-acquired pneumonia, Legionnaire's disease, *Campylobacter enterocolitis* and many gram-positive infections in individuals who are allergic to penicillin. Although there are undoubtedly patients who have received erythromycin and vinblastine simultaneously, no reports of any interaction appear in the literature, including papers that can be accessed through MEDLINE (1966+), or have been reported to the adverse drug report databases at the Health Protection Branch (Ottawa, Canada) or the Federal Drug Agency (Rockville, Md.).

In the context of a phase I–II study of cyclosporin A (CyA) as a modifier of multidrug resistance [13, 14], four patients received vinblastine in combination with oral CyA and erythromycin. The latter was used to maintain high cyclosporin blood levels (≥1000 μg/l whole blood) at lower oral doses in an attempt to reduce CyA-induced gastrointestinal (GI) toxicity. All patients developed severe toxicity characteristic of a much higher dose of vinblastine than was actually given. One patient received only one course of chemotherapy and is not described, because of the possibility that this was an idiosyncratic reaction. The other three received at least one additional course of chemotherapy with the same dose of vinblastine with deletion of either erythromycin or CyA.

Case reports

The three patients were white, non-smokers, taking no regular medications and with normal haematological, hepatic, and renal profiles prior to treatment. All had metastatic renal cell carcinoma. Oral CyA (Sandoz Canada) was given for 3 days in four divided doses daily and vinblastine was given by i. v. push on the 3rd day. Oral erythromycin was started 24 h before first dose of CyA and continued until CyA was discontinued on the evening of day 3. Surfak (docusate calcium; Hoechst Canada) 100–200 mg daily, Stemetil (prochloropherazine; Rhone-Poulenc Rorer Canada) 10 mg up to four times daily, Sulcrate (sulcralfate; Nordic Laboratories) 1 g four times daily and Zofran (ondansetron; Glaxo Canada) were administered as necessary for the first 5 days.

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Patient 1

A 49-year-old man (ht. 178 cm, wt. 73 kg) with metastases to the supraclavicular lymph nodes received three monthly courses of chemotherapy with CyA and vinblastine sulphate 10 mg/m^2 (David Bull Laboratories Canada). The CyA dose for the first course was 17 mg/kg per day, and the CyA trough whole blood level on the 3rd day was 531 μg/l. The CyA dose for the second course was 21 mg/kg per day, and the 3rd day CyA trough was 880 μg/l. The patient received a third course at the same dosages, but CyA levels were not measured. He tolerated each course well except for severe nausea and vomiting during the 3 days of CyA administration. Following each course he developed constipation for 6 days and mild neutropenia (nadir 0.25–0.53×10^9/l) with no trend towards progressive symptoms or nadir depth over the three courses. Muscle pains did not occur. Following his 3rd course, complete radiological restaging showed no metastases aside from stable supraclavicular nodes. One month after the third course, by which time all toxicity had resolved, he received a fourth cycle of vinblastine 10 mg/m^2, this time with only 10 mg/kg of CyA per day to reduce GI toxicity, and erythromycin 333 mg t.i.d. (Abbott Laboratories) to boost blood CyA levels. The CyA trough level on the 3rd day was 578 μg/l. Constipation lasted 6 days, and on the 13th day the patient required admission because of back pain and muscle spasms. He developed severe neutropenia (nadir 0.03×10^9/l). No connection was made between the new symptoms, the severity of the neutropenia and the use of erythromycin.

Patient 2

A 68-year-old man, (ht. 181 cm, wt. 83 kg) with rapidly enlarging paraaortic lymph nodes received erythromycin base (Upjohn Canada) 250 mg p.o. q.i.d. and CyA 13 mg/kg per day for 3 days and vinblastine 9 mg/m^2 on the 3rd day. The 3rd-day CyA trough was 330 μg/l. On the 11th day, the patient was admitted with 48 h of severe bilateral shoulder pain requiring morphine analgesia (5 mg/h i.v.) for 4 days. Admission was complicated by severe constipation and febrile neutropenia from day 10 to day 16 (nadir 0.05×10^9/l). Peak CyA levels as high as 1712 μg/l 2 h after CyA were presumed to have caused the severity of his symptoms by interacting with vinblastine.

In his second course, 6 weeks later, this patient received vinblastine 9 mg/m^2 after 3 days of oral erythromycin without CyA in order to "prove" that the latter had caused the severe toxicity. On the 9th day, the patient was again hospitalized for severe bilateral shoulder pain requiring i.v. morphine for 9 days. On the 11th day, the patient developed febrile neutropenia similar in severity (nadir 0.11×10^9/l) and duration (5 days) to the previous course.

Patient 3

One month after patient 2 had received his first course of chemotherapy, a 66-year-old man (ht. 180 cm, wt. 64 kg) with lung metastases was treated with CyA 10 mg/kg per day, vinblastine sulphate 7 mg/m^2 and erythromycin base 333 mg t.i.d. The 3rd-day CyA trough was 546 μg/l. The patient was admitted to hospital on the 14th day with a 5-day history of severe pain involving upper arms, forearms and shins. The following day he developed febrile neutropenia (nadir 0.02×10^9/l), which lasted for 3 days. After recovery he elected to continue chemotherapy. Six weeks after the first course of chemotherapy, he received vinblastine 7 mg/m^2 by i.v. push alone. One week later he complained of a mild ache in both shoulders but was otherwise well, with no constipation and no neutropenia (nadir 1.45×10^9/l). The drug combinations and corresponding toxicity profile for each of the three patients are summarized in Table 1.

Discussion

Neutropenia, constipation, and myositis are all well-documented side effects of high-dose vinblastine [1, 12]. In our previous work, in the course of which vinblastine and oral CyA were administered to 16 patients without erythromycin [13, 14], moderate neutropenia and severe constipation were seen in most patients, but myalgia did not develop. To boost CyA blood levels while lowering the CyA dose in the next cohort of patients, erythromycin was added to the regimen. Erythromycin has previously been shown to increase CyA absorption, probably due to the inhibition of intestinal cytochrome P450 enzymes, as well as to decrease CyA metabolism [4, 6]. All three of our patients who received vinblastine and CyA with erythromycin experienced severe neutropenia and severe myalgia, which did not occur when erythromycin was omitted (patients 1, 3) but did recur when erythromycin was administered without CyA (patient 2).

Patient 1 experienced more profound neutropenia and the new onset of severe myalgia with the addition of erythromycin to his last course of chemotherapy. The excessive toxicity was initially attributed to CyA. A preliminary report by Samuels et al. [9] indicated that high doses of intravenous CyA enhanced vinblastine toxicity when both vinblastine and CyA were given continuously for 5 days. Although, with the concomitant dose reduction of CyA and addition of erythromycin, trough CyA blood levels were no higher than during previous courses of therapy, erythromycin might still have increased the area under the plasma concentration-time curve, thereby increasing overall exposure to CyA and potentiating vinblastine toxicity. Were this the case, however, patient 2 would have been expected to experience some reduction in toxicity with the omission of CyA, but this did not occur. The recurrence of severe toxicity in patient 2 despite the deletion of CyA from the second course strongly suggests that this toxicity was not caused by an interaction between CyA and vinblastine. Similarly, in the study of Rodenburg

Table 1 Vinblastine toxicity with and without CyA and erythromycin (*CyA* cyclosporine; *VBL* vinblastine)

Patient	VBL dose (mg/m^2)	Treatment		Toxicity		
		CyA	Erythromycin	Myalgia	Neutropenia	Constipation
1	10	Yes	No	None	Mild	Severe
	10	Yes	Yes	Severe	Severe	Severe
2	9	Yes	Yes	Severe	Severe	Severe
	9	No	Yes	Severe	Severe	Severe
3	7	Yes	Yes	Severe	Severe	Severe
	7	No	No	Mild	Mild	None

et al. [8], toxicity from bolus vinblastine was not enhanced by CyA administered at a lower dose than used by Samuels et al. However, the possibility cannot entirely be ruled out that patient 2 was extremely sensitive to vinblastine and that his toxicity was due to that drug alone rather than to the interaction with erythromycin.

In the absence of detailed pharmacokinetic studies only speculation about the mechanism of interaction between erythromycin and vinblastine is possible. Vinblastine is extensively metabolized in the liver to the biologically active derivative desacetylvinblastine. Only about 15% is detected unchanged in the urine and 10% in bile [5]. Aside from apparent synergistic activity with methotrexate, no other drug interactions have been described for vinblastine [1, 12]. Because of the large inter-patient variability in vinblastine toxicity for a given dose [12] it is quite possible that significant drug interactions have been missed. Erythromycin has been reported to potentiate the effects of several drugs in addition to CyA, including carbamazepine, corticosteroids, theophylline, benzodiazepines and warfarin, probably by interfering with their cytochrome P450-mediated metabolism [3, 4, 10]. This is the most likely explanation for the interaction with vinblastine. The mechanism may be more complex, however, as haemorrhage after the addition of erythromycin to warfarin has been reported in several cases despite only a modest pharmacokinetic interaction. Erythromycin also increases digoxin plasma concentrations but the mechanism is not clear. It has been recommended that empiric dose reductions be made when these drugs are administered with erythromycin [6].

The interaction between vinblastine and erythromycin is particularly noteworthy in that both drugs are likely to be prescribed with increasing frequency. Chemotherapeutic regimens containing vinblastine have recently demonstrated promising activity in the neo-adjuvant therapy of stage III A non-small-cell lung cancer [11] and resectable bladder cancer [7]. In the case of lung cancer, significantly increased resectability and survival rates compared with historical controls have been achieved with combinations such as vinblastine, mitomycin C, and cisplatin. Randomized studies are currently under way. For bladder cancer, such regimens as M-VAC (methotrexate, vinblastine, Adriamycin and cisplatin) have allowed bladder preservation in over 50% of patients who would otherwise have had to undergo cystectomy [2]. With respect to erythromycin, delayed-release preparations have been recently introduced, which have improved patient acceptability.

In summary, the three patients presented, who received vinblastine while taking erythromycin, experienced severe toxicity typical of much higher doses of vinblastine. Patients receiving chemotherapy with vinblastine should avoid taking erythromycin at the time of vinblastine infusion. Pharmacokinetic studies are needed to confirm this interaction and also to determine its mechanism.

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