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ORIGINAL ARTICLE

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Antidote studies of vinorelbine-induced skin ulceration in the mouse

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Abstract: The new cantharanthine-modified vinca alkaloid vinorelbine (Navelbine) was administered intradermally (ID) to dehaired BALB/c mice. Dose-dependent skin lesions were produced over the range 0.01–0.5 mg/ mouse, with complete healing after 9–35 days. Local (ID) injections of hydrocortisone and saline were ineffective at blocking vinorelbine-induced skin ulceration. Topical skin heating to 43°C or cooling to 10°C were also ineffective. In contrast, hyaluronidase, 15 Units ID, following vinorelbine significantly reduced skin lesions. These results show that vinorelbine is a vesicant and that inadvertent extravasations may be managed with subcutaneous injection of the spreading factor enzyme, hyaluronidase.

Key words Extravasation · Vinca alkaloid

Introduction

Vinorelbine (Navelbine) is a semisynthetic derivative of vinblastine with the systematic name 3′,4′-didehydro-4′-deoxy-C′ norvincaleukoblastine bitartrate. It is marketed in Europe for the treatment of non-small cell lung cancer (NSCLC) under the trade name Navelbine (Pierre Fabre Oncology, Paris, France) and has been recently approved for use in NSCLC in the United States (Burroughs Wellcome Company) [12]. Whereas other clinically used vinca alka-loids vincristine, vinblastine and vindesine have substitutions on the vindoline portion of the molecule, vinorelbine differs in the catharanthine portion of the molecule [13]. Like the other vinca alkaloids, vinorelbine binds to tubulin to halt polymerization into microtubules and, to an extent less than other vincas, causes the formation of spiral tubulin paracrystals [8]. Vinorelbine also appears to bind less effectively to axonal microtubules than other vincas, perhaps explaining its lower degree of neurotoxicity [1].

The drug has been shown to possess broad antitumor activity in preclinical systems [4] and produces reversible neutropenia as the dose-limiting side effect in humans [13]. Neurotoxicity is not seen in the monkey [13], but approximately one-third of human patients with solid tumors may experience low-grade paresthesias [3, 14, 15]. Other typical vinca alkaloid toxicities are also produced by vinorelbine but at greatly reduced intensity and incidence. These include nausea and vomiting, stomatitis and alopecia. It is not known whether vinorelbine produces local necrosis if inadvertently extravasated, as is the case with vincristine [10, 11], vinblastine [2] and vindesine [6]. However, vinorelbine has been reported to induce local reactions at the injection site in up to 10% of patients [12].

In this report we describe the local ulcerogenic effects of vinorelbine given intradermally into mouse skin. In addition, several local treatments were evaluated to identify a potential antidote to inadvertent vinorelbine extravasations in the clinic.

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Materials and methods

A model using dehaired, adult BALB/c female mice (Jackson Laboratories, Bar Harbor, Me. was used as described previously for vinblastine, vincristine and vindesine [5]. The mice were housed four or five per cage and had access to food and water ad libitum under a protocol approved by the medical center IACUC Committee. Briefly, the mice (25–30 g each) were dehaired over a 2-cm^2 dorsal area using the topical depilatory agent, Neet Lotion (Whitehall Laboratories, New York, N.Y.). The mice were anesthetized 1 day

later with sodium pentobarbital 20 mg/kg intramuscularly, and given an intradermal (ID) injection of vinorelbine (Navelbine) 10 mg/ml solution in saline (Burroughs Wellcome Company, Research Triangle Park, N.C.). Doses ranged from 0.05 to 0.5 mg, representing approximately 7.14 to 71.4 mg/m^2 using a body surface area conversion for mice described previously [9]. For reference, the recommended dose in phase II/III clinical studies is 30 mg/m^2 [13].

Each mouse was uniquely identified and had any visible skin lesions measured using a micrometer every other day. Ulceration was defined as complete desquamation of skin visible to the naked eye. The perpendicular borders were measured and a simple area was computed. These areas were converted to a cumulative toxicity index, which is the integrated lesion size × time area in cm^2 · days for the entire time period that an ulcer was visible (between 20 and 27 days).

Adjuvant studies

Potential pharmacologic antidotes (adjuvants) were injected ID (0.05 ml) immediately adjacent to the vinorelbine injection site taking care not to directly admix the two solutions. Pharmacologic adjuvants included sodium chloride for injection, USP (Abbott Laboratories, North Chicago, Ill.), hyaluronidase 15 Units (Wydase; Wyeth Laboratories, Philadelphia, Pa.), and hydrocortisone sodium succinate (Solu-Cortef; Upjohn Company, Kalamazoo, Mich.). Topical heating to 43–44°C or cooling of the skin to approximately 10°C was accomplished with flexible plastic containers placed over the skin site for 30 min after ID vinorelbine injection. The mice were immobilized in Plexiglass tube restraints for this period as described previously [7].

Statistical analyses

Analyses were carried out on the ulceration results for each treatment group. Each group included three to five mice from two experiments for a total of eight mice per group. The peak lesion size and area under the lesion versus time curve were analyzed by an initial analysis of variance followed by a multiple range test, the Student Newman Keuls procedure. The latter test segregates different treatments into subsets. A statistically significant treatment ($P < 0.05$) is found in a unique subset.

Results

Vinorelbine produced dose-dependent skin ulcers in the mice (Table 1). The AUCs for ulceration were statistically distinct for the 0.01, 0.1 and 0.5 mg doses, but not for the 0.05 dose which was segregated to a subset also containing the 0.1 mg dose. Vinorelbine-induced lesions were characterized by central ulcerated areas with minimal surrounding swelling or erythema. Skin lesions peaked in size between 3 and 5 days after injection and were completely healed after 35, 25, 17 and 9 days for the 0.5, 0.1, 0.05 and 0.01 mg ID doses, respectively.

Antidote studies showed that hyaluronidase, 15 Units ID, consistently reduced the size of skin ulcers at both ID vinorelbine test doses of 0.1 and 0.5 mg (Table 2). These results are graphically displayed for the 0.5 mg vinorelbine dose in Fig. 1. There was a trend toward lower ulceration with saline and hydrocortisone but these results did not achieve statistical significance, and there was no benefit for either heating or cooling.

Discussion

Vinorelbine appears to be a vesicant agent in the mouse skin model. This complements prior studies in this same model with vinblastine, vincristine and vindesine [5]. However, lesions produced by vinorelbine are smaller than with the same dose of any of the other three vinca alkaloids. For example, a 0.1 mg ID dose of vincristine produces a mean ulcer AUC of 10.85 [5]

Table 1 Dose-response for intradermal vinorelbine-induced skin ulceration in BALB/c mice. Values are means (SD); $n = 8$

Vinorelbine dose (mg)	Peak lesion		Lesion × time area (cm^2 · days)
	Day	Area (cm^2)	
0.01	3	0.08 (0.07)	0.15 (0.16)
0.05	5	0.19 (0.10)	0.91 (0.17)
0.1	5	0.53 (0.27)	1.59 (0.71)
0.5	4	1.64 (0.47)	16.73 (5.79)

Table 2 Effect of local adjuvants on vinorelbine skin ulceration after intradermal injection. Values are means (SD) $n = 8$ mice per treatment group from two experiments using 3–5 mice per experiment

Navelbine ID dose (mg)	Peak lesion			Lesion × time area (cm^2 · days)
	Adjuvant (mg)	Days	Area (cm^2)	
0.5	None	4	1.82 (1.19)	16.73 (5.79)
0.5	Saline	6	1.89 (1.39)	13.55 (4.92)
0.5	Hyaluronidase	3	0.38 (0.21)	4.37 (1.47)*
0.5	Heat	4	1.73 (1.16)	17.78 (6.93)
0.5	Cold	8	1.38 (0.77)	15.06 (6.10)
0.5	Hydrocortisone	5	0.76 (0.54)	8.55 (3.97)
0.1	None	6	0.53 (0.31)	1.59 (0.71)
0.1	Saline	3	0.18 (0.11)	0.85 (0.51)
0.1	Hyaluronidase	2	0.08 (0.06)*	0.31 (0.29)*
0.1	Heat	3	0.67 (0.39)	1.89 (0.92)
0.1	Cold	5	0.52 (0.43)	1.29 (1.11)
0.1	Hydrocortisone	1	0.11 (0.54)	0.72 (0.61)

*$P < 0.05$ by Student Neuman Keuls test following analysis of variance

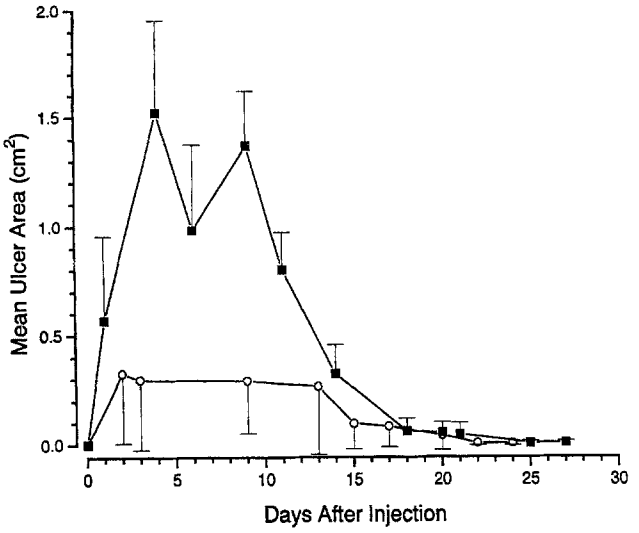

Fig. 1 A comparison of mean ulcer areas ($n = 8$/point) for mice receiving 0.5 mg vinorelbine ID (■) or the same dose plus 15 Units hyaluronidase ID immediately afterwards (○). *Vertical bars* indicate one standard deviation

compared to 1.59 for vinorelbine (present results). A 0.5 mg ID dose of vinblastine or other vincas could not be tested in the prior study owing to acute lethality at that dose level. This was not a problem with vinorelbine in the current trial and, except for skin ulcers, the mice tolerated the 0.5 mg vinorelbine dose without difficulty. However, since the clinical dose of vinorelbine is 30 mg/m^2, which is higher than other vincas, the likelihood of extravasating a toxic volume of infusate before recognition is probably similar.

As with the other vincas, hyaluronidase proved to be effective for vinorelbine-induced skin ulcers. Hyaluronidase is a mucolytic enzyme which depolymerizes hyaluronic acid to open interstitial spaces allowing enhanced systemic uptake of subcutaneous fluid [16]. It has previously been used therapeutically to enhance fluid uptake and to reduce the local toxicity of nafcillin extravasations in infants [17]. In a prior study, the systemic uptake of radiolabelled vinblastine from an ID injection was significantly enhanced by ID hyaluronidase [5]. Local heating was also beneficial in the prior study whereas it was ineffective against vinorelbine.

Overall, these studies suggest that vinorelbine extravasations could be managed with subcutaneous hyaluronidase at the standard dose of 150 Units diluted in 1–2 ml saline. There is no indication that topical heating would be effective with vinorelbine. Finally, since this new vinca consistently produces dose-dependent skin ulcers with ID injection in mice, every effort should be made to avoid inadvertent extravasation in patients receiving intravenous vinorelbine injections.

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