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Intravenous Voriconazole after Toxic Oral Administration▽

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In a male patient with rhinocerebral invasive aspergillosis, prolonged high-dosage oral administration of voriconazole led to hepatotoxicity combined with a severe cutaneous reaction while intravenous administration in the same patient did not. High concentrations in the portal blood precipitate liver enzyme abnormalities, and therefore, oral administration of voriconazole may have a hepatotoxicity profile different from that of intravenous (i.v.) administration. Intravenously administered voriconazole might still be an option after oral-voriconazole-induced toxicity has resolved.

Oral administration of voriconazole may have a hepatotoxicity profile different from that of intravenous (i.v.) administration, presumably because high concentrations in the portal blood precipitate liver enzyme abnormalities (4, 5). We routinely measure voriconazole serum levels in patients with invasive aspergillosis to monitor drug exposure in these highly vulnerable patients (1, 7). Serum samples are measured by liquid chromatography tandem mass spectrometry with a validated method of analysis.

A 58-year-old male patient (80 kg) with a history of a transsphenoidal resection of a microadenoma of the pituitary gland presented 6 years later with right-sided headache and ptosis of the right eye. Initially diagnosed with a cluster headache, the patient was treated with high-dose prednisolone at 80 mg once daily. Since he did not respond to treatment, a computed tomography (CT) scan of the sinuses and magnetic resonance imaging (MRI) scan of the brain were performed. The imaging studies showed opacification of the right sphenoidal sinus, an enlarged sella, and invasion of the right cavernous sinus. Histopathology and culture of tissue from the sphenoid sinus revealed *Aspergillus fumigatus*; rhinocerebral aspergillosis was diagnosed. During this work-up, asymptomatic Philadelphia-chromosome-positive chronic myeloid leukemia was also diagnosed and was treated with imatinib.

Voriconazole was started in a dose of 400 mg two times a day given orally (p.o.), followed by 200 mg p.o. two times a day. Since low voriconazole serum levels were detected during visits at our outpatient clinic, the dosage was increased stepwise up to 300 mg four times daily to reach a trough level between 1.5 and 2.0 mg/liter (Fig. 1) (1, 7). No CYP2C19 or 2C9 polymorphism for ultrarapid metabolism was detected. Comedication at this time consisted of imatinib (100 mg once a day p.o., started 2 weeks earlier), pregabalin (150 mg twice a day p.o., started 2 months earlier), methadone (20 mg three times a day p.o.), fentanyl patches (200 μg), and oxycodon (10 mg) on demand. During the next month of therapy, liver enzymes gradually increased to values of 10 times the upper level of normal (ULN) despite nontoxic serum levels of voriconazole. Besides, the patient developed a cutaneous reaction (Fig. 2), with red striae, blisters, and erythema, which was aggravated by exposure to sunlight. Biopsy of the lesions showed extended interface dermatitis with vacuolar alteration of the basilar epidermis and superficial edema without inflammatory infiltrate. No apoptotic or necrotizing keratinocytes were observed. Based on these observations, pseudoporphyria, epidermolysis bullosa acquisita, and erythema multiforme could be ruled out, and a lichenoid drug reaction was diagnosed.

Oral administration of voriconazole was discontinued after 8 weeks of therapy. After discontinuation of voriconazole, the liver enzymes normalized, and the cutaneous reaction disappeared within the next 2 weeks. During this period, the patient received liposomal amphotericin B (400 mg once a day) and earlier-described comedication, but he deteriorated clinically, with expansion of the lesion visible by MRI, presumably due to low cerebral penetration of liposomal amphotericin B. Voriconazole was now reinstated intravenously in a dosage of 480 mg two times a day, followed by 320 mg two times a day. Routine serum monitoring again revealed low concentrations in serum. A dosage increase to 500 mg two times a day resulted in serum trough concentrations of about 1.5 mg/liter. Liver enzymes and the voriconazole serum trough concentration were measured once weekly to monitor hepatotoxicity. As therapy continued, only mild liver enzyme elevations were observed in the following 8 weeks, without a recurrence of the cutaneous reaction. Treatment was continued with intravenous voriconazole, and stable disease was achieved.

To our knowledge, this is the first report of prolonged voriconazole administration at a high dosage within a patient in whom oral administration led to hepatotoxicity combined with a severe cutaneous reaction while intravenous administration did not. Since there seems to be no clear-cut dose effect on the occurrence of adverse reactions to voriconazole and since urticaria, Stevens-Johnson syndrome, discoid lupus, and allergic

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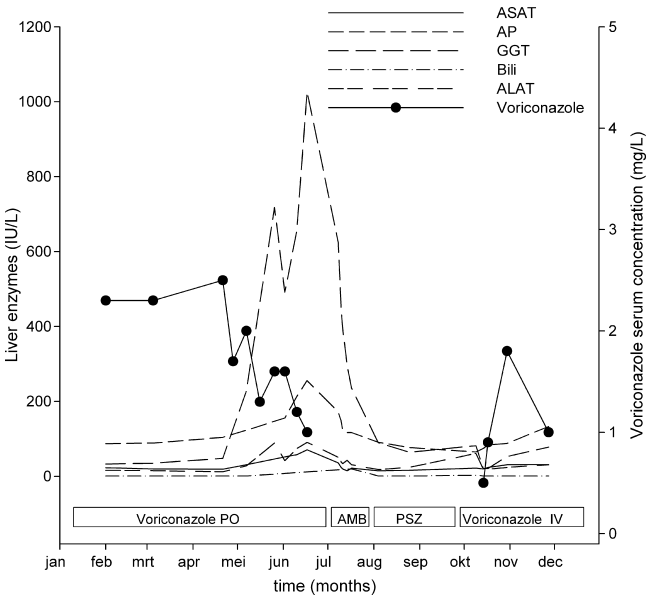

FIG. 1. Hepatic function, voriconazole dosage, and serum concentration during therapy. AMB, liposomal amphotericin B; PSZ, posaconazole; ASAT, aspartate transaminase (10 to 40 U/liter); AP, alkaline phosphatase (30 to 120 U/liter); GGT, gamma glutamyl transpeptidase (0 to 51 U/liter); ALAT, alanine transaminase (5 to 40 U/liter); Bili, bilirubin (2 to 14 μmol/liter).

infusion reactions have been described, an immunologic mechanism could also be considered. In that case, desensitization during i.v. administration might have occurred, as has been recently reported as a tolerance-inducing procedure for several types of adverse drug reactions (2). Alternatively, this observation within a single patient supports the hypothesis that a high concentration in the portal venous blood may damage the liver (4). Other explanations of the hepatotoxicity, like viral hepatitis, bile duct obstruction, or drug-induced hepatotoxicity by pregabalin or imatinib, could be ruled out. Moreover, high oral doses of voriconazole may lead to higher levels of circulating toxic metabolites as a result of a first-pass effect, and we speculate that these metabolites resulted in cutaneous toxicity. The primary route of voriconazole metabolism involves fluoropyrimidine *N*-oxidation to form UK-121,265 and eventually conjugation with glucuronic acid, which is considered a detoxifying mechanism facilitating excretion (6). In this patient, the hepatic glucuronidation capacity might be compromised due to the increased voriconazole dosage of up to 30 mg/kg of body weight divided in four dosages, which may be aggravated by other coadministered drugs that needed glucuronidation, resulting in accumulation of UK-121,265. Absorption of light by this metabolite in the skin, inducing free radicals, might have

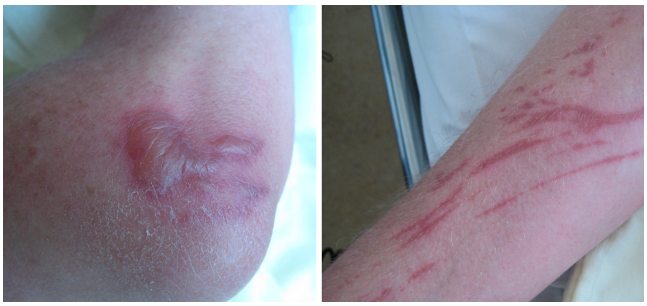

FIG. 2. Cutaneous reaction. Dorsal part of the right forearm with well-circumscribed linear maculae (right) and left elbow showing a 1.5-cm-diameter bulla with an erythematous base (left).

caused the cutaneous reaction, as has been described for N-oxide metabolites of phenothiazines (3).

We conclude that intravenously administered voriconazole might still be an option in case of a mild adverse reaction when liver enzymes have normalized and dermatitis has resolved after oral voriconazole-induced toxicity. Cautiousness is warranted, and we don't advise this in case of a severe adverse or allergic reaction. The introduction of intravenous voriconazole should be performed in a clinical setting with appropriate safety measures and only when other antifungal agents are not an option.

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