Thrombocytopenia Secondary to Linezolid Administration: What Is the Risk?

SIR—Attassi et al. [1] raise concerns that the incidence of thrombocytopenia associated with administration of linezolid may be higher than the 3% incidence previously reported by the manufacturer [2]. In addition, the authors propose that the risk for thrombocytopenia may occur earlier than the 2-week time frame after which the manufacturer recommends monitoring of platelet counts in patients who do not have other risk factors for thrombocytopenia. We would like to describe our experience with treating patients with linezolid, because we have also seen a higher-than-reported incidence of thrombocytopenia.

Shands Hospital at the University of Florida is a 576-bed university teaching hospital in Gainesville. Since linezolid received US Food and Drug Administration approval, the use of this drug has been restricted at our institution, and all use requires prior approval of the Infectious Diseases Service. Linezolid use is limited to the treatment of serious infections caused by gram-positive organisms that are resistant to other therapies (e.g., vancomycin-resistant enterococci) and treatment of patients who are intolerant to other drugs (e.g., patients infected with methicillin-resistant <i>Staphylococcus aureus</i> who cannot tolerate vancomycin).

Since May 2000, a total of 71 patients at our institution have received linezolid for durations ranging from 1 to 44 days. Forty-eight patients received therapy for ≥5 days. Thrombocytopenia, defined as a decrease in platelet count of ≥30%, occurred in 23 (48%) of 48 patients, with a range of decrease of 32%–89%. This incidence of thrombocytopenia is similar to the 47% incidence reported by Attassi et al. [1]. In our patients, a decrease in platelet count to <100,000 cells/mm³ occurred in 9 (19%) of 48 patients, compared with the 32% incidence reported by Attassi et al. [1].

In contrast to Attassi et al. [1], we have seen a similar median duration of therapy for patients who developed thrombocytopenia (median, 12 days; range, 5–34 days) and patients who did not develop thrombocytopenia (median, 12 days; range, 5–44 days). Attassi et al. [1] reported a longer duration of therapy for patients who developed thrombocytopenia (median, 19.1 days; range, 10–42 days) than for patients who did not develop thrombocytopenia (median, 7.7 days; range, 5–11 days).

It is clear that the incidence of thrombocytopenia associated with linezolid therapy is much higher than the 3% incidence found in clinical trials reported by the manufacturer in the product information [2]. It is likely that restricting the use of this agent has resulted in selection of a population of patients who are inherently sicker, and thus more prone to hematologic abnormalities, than those included in the clinical trials. Because thrombocytopenia has occurred with a median duration of therapy of <14 days, clinicians should begin monitoring platelet counts <14 days after initiation of treat-

References


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Safety of Lactobacillus Strains as Probiotic Agents

Str—Although I agree with Sipsas et al. [1] that any report of organisms causing disease needs to be taken seriously, I disagree with many of the points they make in their letter. First of all, the original review that they cite [2], although laudable, included several important inaccuracies, starting with a definition for probiotics that the authors of the review appear to have made up. Probiotics should be defined as “live microorganisms which when administered in adequate amounts confer a health benefit on the host” [3, p. 2]. The original review [2] wrongly stated that probiotic products used in Europe differ from those used in the United States, because, for example, Lactobacillus rhamnosus GG is used on both continents. Furthermore, the authors of that review [2] and Sipsas et al. [1] missed a critical point: for a strain of Lactobacillus to be considered a probiotic, it first must have been shown to confer health benefits on the host [3]. Unfortunately, countless numbers of “probiotic” products on the market—and too many organisms cited in the literature as “probiotics”—have never been shown to confer any health benefits on the host. At best, there are a handful of strains for which there is evidence of an associated health benefit [4]. Yet, even with so many pseudobiological products available, which often have unreliable contents [5], very few case reports of side effects have been reported [6].

The case report [7] cited by Sipsas et al. [1] lacks essential details necessary for useful conclusions to be made. The patient consumed “heavy daily” amounts of undisclosed dairy products that may or may not have contained a probiotic strain (probably they did not, given that few such strains are available). There is no mention of the patient being uncompromised, as stated by Sipsas et al. [1]. The patient had constipation, but we do not know whether it resolved because the patient ate dairy products or whether it was caused by excessive eating. Did the patient sustain a selective intestinal lesion as a result of the constipation or coloscopy? Did the laxative preparation given before colonscopy include an antibiotic? Either way, the intestinal flora was disrupted. Because the isolates did not undergo molecular identification, and because no attempt was made to determine whether they were the same as the strains in the yogurt ingested by the patient, it is a stretch to say there is any evidence of a correlation between the endocarditis and the patient’s diet, never mind the ingestion of a true probiotic.

It is difficult to determine how many people use probiotics safely on a daily basis. The manufacturer of the product Yakult, which contains Lactobacillus casei strain Shirota, claims sales of >9 billion bottles per year. Sales by Danone, Valio, and other manufacturers of products that contain probiotics for which there is evidence of health benefit likely increase that figure to >20 billion doses per year. To raise fears of endocarditis on the basis of 4 cases (yogurt is not a probiotic, so I have discounted 6 of the cases mentioned by Sipsas et al. [1]) that have occurred in 10 years, after perhaps 200 billion doses of probiotic products have been ingested around the globe, is to exaggerate and misrepresent the true risks of probiotic therapy.

With respect to safety, credible scientists in the field of probiotics have long cautioned that use of any therapy, including administration of lactobacilli, foods, or pharmaceuticals, should take into account the condition of the patient or end user. For some immunocompromised patients and patients with intestinal bleeding, probiotic ingestion may or may not have beneficial results. Because probiotic products are readily available over the counter, there is an onus on the consumer to understand what they are buying.

Sipsas and colleagues, citing a 2001 study [8] in which the infecting organism could not be correlated with that isolated from yogurt ingested by the patient, have failed to show an “increasing number of reports that suggest a pathogenic role for the lactobacilli used as probiotic agents” [1, p. 1284]. Rather, they have raised false alarms on the basis of personal perceptions. If they describe pathogenic virulence factors produced by well-proven probiotic organisms in highly reliable product formulations and then show that these are expressed in patients with disease, then we will gladly take notice. Until then, there is good evidence that properly tested probiotics have an enormous potential to prevent disease and, in some cases, treat it. Until this message is taken seriously by health care professionals, governments, and industry, rumormongering is not constructive. Pick up any pharmaceutical compendium and you will find many reasons why we should be more concerned.

References
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