Transparency declarations

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References


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Safety of linezolid in patients with baseline thrombocytopenia

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Sir,

Thrombocytopenia (TCP) is a known risk factor (RF) associated with linezolid, most often manifesting after 2 weeks of therapy.1,2 The rate of TCP was 2.4% (range 0.3% to 10%) in clinical trials;1 however, post-marketing surveillance revealed an incidence of TCP [defined variably as platelet (PLT) counts of ≤100 000 to ≤150 000/μL] from 6% to 32%.3–6 The risk of severe TCP and bleeding complications (BCs) in patients administered linezolid in the setting of baseline (BL) TCP is unknown. Populations with high rates of drug-resistant Gram-positive infections are often cytopenic due to underlying diseases and/or therapeutic modalities. We sought to determine the effect of linezolid on PLT counts and bleeding risk in these patients.

Hospitalized patients ≥18 years receiving linezolid from 1 January 2001 to 31 December 2005 were identified and included if they had a PLT count ≤50 000/μL within 24 h prior to linezolid, received four or more consecutive doses of linezolid and had PLT values obtained after the receipt of linezolid. Only the first course of linezolid was included for patients with one or more courses of linezolid fulfilling inclusion criteria. Demographic, clinical and laboratory data were collected. Fisher’s exact, χ² or Student’s t-tests were used to compare the rates of RFs among patients who did and did not develop a ≥50% reduction in the PLT count after linezolid exposure. Statistical significance was defined as a P value of ≤0.05. Institutional Review Board approval was obtained.

Seven hundred and three courses of linezolid were administered to 315 patients; 45 patients (14%) received courses that met inclusion criteria. The mean age was 51 years (range 18–75), and 53% were male. Caucasians and African-Americans each accounted for 38% of the patients; 20% were Hispanic and 4% were Asian. The mean and median duration of linezolid therapy were 9.3 days (range 2–47) and 7 days, respectively. Co-morbid health conditions included: anaemia, 38 (84%); haematological malignancy, 20 (44%); sepsis, 15 (33%); cirrhosis, 14 (31%); solid organ transplantation, 13 (29%); receipt of chemotherapy within 30 days, 12 (27%); haemato poetic stem cell transplantation, 5 (11%); solid tumour, 3 (7%); end-stage renal disease (ESRD), 1 (2%); and heparin (HEP)-induced TCP, 1 (2%). All patients had at least one of these co-morbid conditions.

The median BL PLT count was 29 500/μL (range 5000–50 000). Fourteen (31%) had BL PLT values ≤20 000/μL. The median PLT nadir after linezolid initiation among all patients was 14 000/μL [range 0–57 000; some patients had nadir PLT counts >50 000/μL during the study period due to transfusions (TXs)]. The median and peak PLT values during linezolid therapy were determined for each patient. The median of the individual median PLT values was 34 000/μL, and the median peak was 58 000/μL (range 12 000–149 000). Thirty-five (78%) patients exhibited a reduction in the PLT count following the initiation of linezolid, with a median nadir PLT count of 11 000/μL and a median reduction of 42.5% (range 7–100). TX data were available for 30 of these patients; 24 received PLT TXs during linezolid therapy. Only two patients (4%) had no reduction in the PLT count during linezolid treatment. Eight patients (18%) had a PLT count nadir prior to linezolid (median 29 000/μL), and their PLT counts increased on linezolid therapy. Five of these eight patients underwent PLT TX, two did not undergo PLT TX and the TX record for one subject was unavailable. Twenty-four of the 35 (69%) patients experiencing a decline in the PLT count on linezolid therapy were receiving concomitant myelosuppressive medications; 10 received more than one such agent. The most commonly prescribed medications were piperacillin/tazobactam, 15 (43%); trimethoprim/sulfamethoxazole, 11 (31%); ganciclovir or valganciclovir, 5 (14%); and HEP or low-molecular weight HEP, 4 (11%). Linezolid was discontinued due to TCP in only 3 of the 850
35 (8.6%) patients who had a decline in the PLT count and in only 4 of the total 45 patients (8.9%).

Of the 35 patients who experienced a decline in the PLT count on linezolid therapy, 16 had a ≥50% reduction. These patients were compared with the rest of the patients who experienced no reduction or a moderate reduction in the PLT count to identify RFs that might predict significant worsening of TCP on linezolid. There were trends towards a longer median duration of linezolid exposure (8.5 versus 6 days, \( P = 0.275 \)) and receipt of chemotherapy within 30 days prior to linezolid (44% versus 17%, \( P = 0.08 \)) among patients with ≥50% decline in the PLT count, but neither of these variables reached statistical significance. The following characteristics were similar: BL haemoglobin and creatinine clearance, BL PLT and white blood cell counts, hospitalization in the intensive care unit (ICU) at the time of linezolid initiation and exposure to piperacillin/tazobactam, trimethoprim/sulfamethoxazole and HEP. Not unexpectedly, significantly more linezolid recipients with a PLT reduction of ≥50% required PLT TXs during or immediately following linezolid therapy (94% versus 59%, \( P = 0.016 \)).

There was only one BC during linezolid therapy and this led to linezolid discontinuation. A 58-year-old man with myelodysplasia developed a nosebleed requiring cauterization and intubation for airway protection. The patient had received 5 days of linezolid prior to this episode, and the PLT count at the time of the bleed was 36 000/µL. Significantly, the patient was also receiving HEP for possible pulmonary embolus until 12 h prior to the nosebleed when HEP was discontinued due to a partial thromboplastin time (PTT) of 203.5 s (normal 27.5–41.0). The international normalized ratio was 1.64 (normal 0.9–1.2), and PTT was 59.3 at the time of the nosebleed. No other BC occurred. Eleven of the 45 patients underwent surgery or invasive procedures after receiving at least 48 h of linezolid therapy. There were no BCs, although nine of these patients received concomitant PLT TX. Of note, there were no uniform criteria for PLT TX; PLTs were administered on the basis of the underlying disease, medical service and requirement for invasive procedures. It is unclear from this retrospective study whether PLT TX requirements would have been any different in the absence of linezolid therapy.

There are limited data regarding RFs for the development of TCP or BC during linezolid therapy. Grau et al.\(^7\) reported an incidence of TCP (PLT ≤100 000/µL) of 24.5% among 49 ICU patients and identified BL PLT value as an independent predictor of TCP (\( P = 0.034 \)). The authors postulated that the higher incidence of TCP than observed in clinical trials was due to more critically ill patients than clinical trial subjects. Disease severity score, central catheter-related infection and ESRD have also been noted as RFs for developing TCP.\(^8\) Also, although declines in PLT counts of almost 50% have been observed even after only 10 days of therapy,\(^3\) the duration of linezolid administration appears to influence the incidence of TCP.\(^1\) The present study was unable to confirm that the previously identified RFs correlated with a significant decline in the PLT count, although our sample size may have precluded our ability to detect this.

This is the first published report describing the use of linezolid in patients with marked BL TCP. This study suggests that it may be safe to prescribe linezolid for patients with very low PLT counts if TXs are given as required. Despite the occurrence of reductions in PLT counts during linezolid therapy, only one episode of non-life-threatening bleeding occurred, which could have been attributable to coagulopathy from HEP therapy.

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**References**