Real-life incidence of hypoglycemia and thrombocytopenia due to linezolid

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Background

- Thrombocytopenia is a well recognized adverse effect of linezolid, however the incidence ranges from 15-50% in the literature
- Hypoglycemia is not a widely known adverse effect of linezolid and is not routinely monitored for
- There is increasing evidence to support the relationship between linezolid and hypoglycemia, including case reports and reports in the FDA Adverse Event Reporting System
- There is no consensus on the real-life incidence of linezolid-induced thrombocytopenia and hypoglycemia
- The safety concerns of these adverse effects warranted further exploration into incidence and associated risk factors

Objectives

- To quantify the real-life incidence of thrombocytopenia and hypoglycemia in patients receiving linezolid (LZD) for a minimum of 5 days, and to evaluate potential associated risk factors for these adverse effects.

Methods

- **Study Design:** Retrospective chart review
- **Inclusion criteria:** Patients who received LZD for a minimum of 5 days at St. Paul's Hospital between Jan. 2013 and Aug. 2017
- **Exclusion criteria:** Hematological disorder causing decreased platelets (PLT), PLT < 100 x 10^9 cells/L at LZD initiation, chemotherapy within 2 weeks, diagnosis of disseminated intravascular coagulopathy, hemorrhage not caused by thrombocytopenia requiring blood transfusion, insulin-dependent DM, on sulfonylureas or meglitinides, acute liver failure, adrenal insufficiency, endogenous hyperinsulinism
- **Primary Endpoints:**
  - Incidence of thrombocytopenia & hypoglycemia
- **Secondary Endpoints:**
  - Risk factors associated with linezolid-induced thrombocytopenia or hypoglycemia
- **Statistical Analysis:** Chi Squared and Student's T-test

Patient Characteristics (No. (%) or mean ± SD)	Patients with TP N = 18	Patients without TP N = 84	P Value
Female	5 (28)	33 (39)	0.36
Age, years	58 ± 17	49 ± 22	0.07
Weight, kg	69 ± 16	65 ± 21	0.32
Linezolid route			
Oral	11 (61)	56 (66)	0.65
Intravenous	2 (11)	10 (12)	0.92
Oral & Intravenous	5 (28)	18 (21)	0.56
Mg/kg per dose	9.1 ± 2.1	10.1 ± 2.8	0.10
Linezolid dose			
600 mg BID	17 (94)	82 (98)	0.47
600 mg BID to once daily	1 (6)	2 (2)	0.47
Duration of linezolid, days	22 ± 18	12 ± 7	0.023
Vancomycin within 2 weeks	7 (39)	31 (37)	0.87
Concurrent LMWH	8 (44)	33 (39)	0.69
Concurrent UFH	9 (50)	18 (21)	0.013
Concurrent Piperacillin	3 (17)	10 (12)	0.58
Renal replacement therapy	3 (17)	3 (4)	0.032
Renal impairment	11 (61)	27 (32)	0.021

Table 1: Characteristics of patients with and without thrombocytopenia (TP)

*Statistically significant

Variables No. (%)	Patients with TP N = 18	Patients without TP N = 84	P Value
Baseline Value			
SCr elevated (F > 90 umol/L, M > 100 umol/L)	9/18 (50)	23/84 (27)	0.061
Platelets < 150 x 10^9/L	3/18 (17)	5/84 (6)	0.12
Albumin < 35 g/L	12/12 (100)	43/56 (77)	0.063
CRP > 3.1 mg/L	5/6 (83)	52/53 (98)	0.058
Total bilirubin > 20 umol/L	0/15 (0)	5/65 (8)	0.27
Most Aberrant Value			
SCr elevated (F > 90 umol/L, M > 100 umol/L)	11/18 (61)	27/84 (32)	0.021
Platelets < 150 x 10^9/L	15/18 (83)	10/84 (12)	< 0.001
CRP > 3.1 mg/L	9/10 (90)	31/33 (94)	0.67
Total bilirubin > 20 umol/L	2/10 (20)	2/28 (7)	0.26

Table 2: Laboratory data of the patients with and without thrombocytopenia (TP)

*Statistically significant

Results

- 102 patients (38 females; mean age 50 ± 21) were included
- Mean duration of LZD = 14 ± 10 days
- **Primary Endpoints:**
  - Incidence of Thrombocytopenia = 17.6% (18/102)
  - Incidence of Hypoglycemia = 0% (0/102)
- **Secondary Endpoints:**
  - Risk factors for thrombocytopenia included duration of LZD treatment, renal impairment, renal replacement therapy, concurrent UFH
  - Risk factors for hypoglycemia not assessed
- PLT declined from baseline in 76% (64/84) of non-thrombocytopenic patients

Variables (No. (%) or mean ± SD)	**Patients with TP N = 18**
Time to first thrombocytopenic PLT value	16 ± 12 days
Time to most aberrant PLT value	21 ± 15 days
Time to first normal PLT value after LZD stopped	6 ± 5 days in 9 patients (data unavailable for 9 patients)
TP within 14 days of starting LZD	9/18 (50)
LZD discontinued due to TP	11/18 (61)
PLT transfusion	1/18 (6)

Table 3: PLT characteristics and TP management in patients with TP

Limitations

- Small sample size
- Many patients were on LMWH or UFH
- Data on all risk factors not available for all patients
- Blood glucose measurements were not readily available to assess hypoglycemia
- Did not measure serum linezolid concentrations

Conclusions

- The real-life incidence of thrombocytopenia in patients receiving linezolid for a minimum of 5 days was 17.6%
- There were no cases of hypoglycemia, suggesting a low real-life incidence of this adverse effect
- Clinicians should monitor patients for linezolid-induced thrombocytopenia, especially in those with renal impairment or longer treatment durations