Risk of serotonin syndrome in acutely ill patients receiving linezolid and opioids concomitantly: A retrospective cohort study

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Abstract

Introduction: Linezolid is an oxazolidinone antibiotic with a reversible, non-selective monoamine oxidase inhibitory effect. Combining linezolid with serotonergic agents may increase serotonin syndrome (SS) risk.

Secondary to its high tissue penetration, linezolid is recommended in patients with suspected or confirmed resistant gram-positive bacterial infections, as pneumonia, and skin-soft tissue infections, especially if vancomycin cannot be used. However, it is unclear whether co-administration of linezolid with opioids increases the risk of serotonin syndrome.

Research objective: Whether combing linezolid with opioids will increase the incidence of SS in acutely ill patients.

Methods: This was a retrospective observational study. All adult patients admitted to Hamad Medical Corporation facilities in Qatar and received linezolid between March 2020 and September 2020 were included in the study.

The primary outcome was the prevalence of SS defined by Hunter's criteria. SS was confirmed if the patient had spontaneous clonus; inducible clonus plus agitation or diaphoresis; ocular clonus plus agitation or diaphoresis; tremor plus hyperreflexia; or hypertonia plus fever plus ocular clonus or inducible clonus.

Results: We included 106 patients, most of the patients were males (91.5%). More than half of the cohort (56.6%) received a concomitant opioid agent. Morphine and fentanyl were the most prescribed opioids (37.7% and 34%, respectively). Among patients who received opioids, only one patient (1.6%) had spontaneous clonus. However, this patient developed spontaneous clonus post cardiac arrest, which made the association with the linezolid-opioids combination doubtful.

Conclusion: In this study, the incidence of SS was low in acutely ill patients who received concomitant linezolid and opioids. However, larger prospective studies are required to confirm this finding.

Introduction

Serotonin syndrome is a drug-induced life-threatening adverse drug reaction that has been characterized by a triad of neuro-excitatory features due to excess serotonergic activity at central receptor[1]. The characteristic symptoms fall into three main features; neuromuscular hyperactivity, autonomic hyperactivity, and altered mental status[2]. Clinical features can range from mild to life-threatening, and the onset is usually rapid within hours of drug combinations, although there have been reported cases with delayed reactions[3]. Serotonergic drug classes include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, MAOIs, opioids, and triptans[1]. The most common drug combination that can cause this syndrome is a monoamine oxidase inhibitors (MAOIs) drug combined with any serotonin re-uptake inhibitor (SRI)[2]. Thus, the use of opioids in combination with MAOI or within two weeks period following the discontinuation of an irreversible MAOI should be avoided when possible[4].

Linezolid is an oxazolidinone antibiotic with a weak, reversible, non-selective MAOI[5]. It is predicted that combinations of linezolid with various SRIs, such as opioids, might precipitate serotonin syndrome[6]. There is limited evidence on the interaction between linezolid and opioids; only a few cases were reported; thus, it is difficult to draw any definite conclusions[6–8]. Nonetheless, there is conflicting clinical evidence in the literature about the degree and risk of the interaction between linezolid and opioids such as fentanyl and morphine, as some reviews suggested that fentanyl is safe when co-administered with MAOIs[9,10].

Linezolid is a commonly used therapeutic option in managing bacterial infections with multi-drug resistant gram positive-organisms, especially soft tissue infections, hospital and ventilator-associated pneumonia with proven or suspected methicillin-resistant staphylococcus aureus (MRSA)[11]. Linezolid may be the drug of choice in treating patients with vancomycin-resistant enterococcus infections or patients with MRSA infections and renal insufficiency, where administration of nephrotoxic medication as vancomycin may worsen the kidney injury, especially if co-administered with another nephrotoxic drug[12].

Both linezolid and opioids are essential medications, especially for acutely or critically ill patients, and the concomitant administration of both agents may be of significant clinical importance. To our knowledge, there has been no study done to evaluate the risk of interaction between linezolid and opioids in acutely ill patients.

Objective

The purpose of this study is to evaluate the incidence of serotonin syndrome among acutely ill patients who received concomitant opioids and linezolid.

Patients And Methods

Study design and population

We conducted a retrospective cohort study that included adult patients (> 18 years of age) admitted to one of the Hamad Medical Corporation (HMC) COVID-19 facilities, hospitalized between the period of March 2020 and September 2020, and received concomitant linezolid and opioids. Patients were excluded if they received linezolid for less than one day. Patients were followed up for two weeks after the start of linezolid.

Data collection

The following information was collected from the electronic medical records for eligible patients: patients' demographics, comorbid diseases, spontaneous clonus, temperature > 38ºC, tremor and hyper-reflexia, intubation status, intensive care unit (ICU) admission and discharge dates, mortality, other medications that can cause serotonin syndrome based on Lexicomp drug information handbook. We included all opioids approved in our hospitals: morphine, fentanyl, remifentanil, and tramadol.

Assessment of outcomes

The primary outcome was the incidence of serotonin syndrome (SS) according to patients' clinical findings. Serotonin syndrome was defined by the Hunter's criteria.

According to Hunter's criteria: for a patient to be diagnosed with Serotonin syndrome, the patient should be receiving a serotonergic agent and develops one of the following: spontaneous clonus, inducible clonus PLUS agitation or diaphoresis, ocular clonus PLUS agitation or diaphoresis, tremor PLUS hyperreflexia, or hypertonia PLUS temperature above 38ºC PLUS ocular clonus or inducible clonus.

Statistical analysis

The primary outcome of serotonin syndrome incidence was presented as frequency and percentage. The patients' characteristics were presented as frequencies with percentages for categorical characteristics and means with standard deviations for continuous characteristics. All statistical analyzes were performed using the Statistical Package for Social Sciences (SPSS) program version 25 (IBM Corp., Armonk, NY).

Results

A total of 106 acutely ill patients were included. The majority of patients were males (91.5%) with a mean age (± SD) of 53 ± 16.2. Diabetes, hypertension, and chronic kidney disease were the most common comorbidities (51.9%; 44.3%; 19.8%, respectively). Table 1 describes the demographic characteristics of the study population. Most patients were under ICU care (88.67%), with more than half of them (53.8%) requiring invasive mechanical ventilation. Thirty days mortality was 36.8%, which reflects how critically these patients were. All patients who received concomitant linezolid and opioids were in ICU.

Table 1
Patient's demographic

Characteristic	N = 106
Age, mean ± SD	53 ± 16.2
Male sex, n (%)	97 (91.5)
Diabetes mellitus, n (%)	55 (51.9)
Hypertension, n (%)	47 (44.3)
Chronic Kidney disease, n (%)	21 (19.8)
Chronic liver disease, n (%)	5 (4.7)
Chronic respiratory disease, n (%)	19 (17.9)
Malignancy, n (%)	9 (8.5)
ICU admission, n (%)	94 (88.67)
Invasive mechanical ventilation, n (%)	57 (53.8)
Mortality, n (%)	39 (36.8)
Route of linezolid administration, n (%)	
Oral/NG	35 (33)
Intravenous	69 (65.1)
Oral/NG/IV	2 (1.9)
Number of serotonergic medications received during linezolid therapy, n (%)	
0	38 (35.8)
1	43 (40.6)
2	17 (16)
3	8 (7.5)
Concomitant medications, n (%)	
Any opioids	60 (56.6)
Morphine	40 (37.7)
Fentanyl	36 (34)
Dextromethorphan	11 (10.4)
Remifentanil	11 (10.4)
Ondansetron	2 (1.9)
Amitriptyline	1 (0.9)
SD: standard deviation, ICU: intensive care unit, NG: nasogastric, IV: intravenous.	

Linezolid was administered intravenously for most patients (65.1%). About 64% of the cohort were prescribed concomitant linezolid and serotonergic agents. Sixty patients received a combination of linezolid and opioids (56.6%). Morphine and fentanyl were the two commonly prescribed opioids (37.7% and 34% of the total serotonergic drugs, respectively). Other serotonergic drugs were ondansetron (1.9%) and amitriptyline (0.9%), (Table 1).

Among patients who received opioids, only one patient met the SS criteria (1.6%), manifested as spontaneous clonus. However, this patient developed spontaneous clonus post-cardiac arrest, which made the association between SS and the linezolid-opioids combination doubtful (Table 2).

Table 2
Hunter's criteria for patients received concomitant linezolid and opioids

Criteria	n (%)
Spontaneous clonus	1 (1.66)
Inducible clonus and agitation or diaphoresis	0 (0)
Ocular clonus and agitation or diaphoresis	0 (0)
Tremor and hyperreflexia	0 (0)
Temperature of 38°C and ocular clonus or inducible clonus	0 (0)

Discussion

The purpose of this study was to evaluate the incidence of serotonin syndrome among acutely ill patients who received concomitant linezolid and opioids. The incidence of SS was very low; among 60 patients who received concomitant linezolid and opioids, only one patient met Hunter's criteria. Despite that this patient received concomitant linezolid and fentanyl, the patient had spontaneous myoclonus after cardiac arrest, which makes the association with SS and linezolid-opioid drug interaction less likely.

Severe life-threatening serotonin syndrome may be associated with high-grade fever > 41°C, seizures, coma, arrhythmia, rhabdomyolysis, metabolic acidosis, respiratory failure, and death[1,13]. Although mild, undetected forms of serotonin syndrome cannot be ruled out in this study, we could say that severe serotonin syndrome secondary to the opioids-linezolid combination was not observed in this patient's cohort. In this study, we used Hunter's criteria to evaluate the incidence of serotonin syndrome. Hunter's criteria became the gold standard tool for diagnosing serotonin syndrome as it was more sensitive than Sternbach Criteria (84% versus 75%, respectively)[14].

Serotonin syndrome observed due to a combination of linezolid and opioids was reported in a few cases[15,16]. One case reported a high suspicion of serotonin syndrome due to the co-administration of linezolid and methadone[15]. Another case report showed that the combination of linezolid, fentanyl, and amitriptyline resulted in serotonin syndrome. However, in this case, there was an administration of a third serotonergic agent, which may augment the incidence of SS[16].

Butterfield et al. conducted an analysis of phase III and IV randomized clinical trials data evaluating the serotonin toxicity with concomitant use of either linezolid or comparators and serotonergic agents[17]. Three patients fulfilled Hunter's criteria (0.14%) in the linezolid group. Although 22% of patients in each arm received analgesics, including opioids and non-opioid agents, the authors did not specify whether these three patients received concomitant opioids or not. Additionally, most patients had co-morbidities that may contribute to the adverse events reports.

The warry of serotonin syndrome induced by opioids-linezolid drug-drug interaction may be a reason to deprive the acutely ill patients of a safe and effective therapeutic option as linezolid. On the other hand, opioids are commonly required for sedation and analgesia, especially for intubated patients or patients undergoing invasive procedures. Evaluating the incidence and severity of this drug-drug interaction was crucial for a better understanding of linezolid safety in acutely ill patients receiving opioids.

To the best of our knowledge, this study is the first study aimed to evaluate the incidence of serotonin syndrome among acutely ill patients who received concomitant linezolid and opioids. This study has some limitations. One of the limitations is the observational study design, as all required data were collected retrospectively from the patient's electronic files, as the patient may develop SS signs or symptoms but missed to be documented by the physician or the bedside nurse. Another limitation is the sample size; as this study included 106 patients, only 60 patients received concomitant linezolid and opioids. Additionally, this study was conducted in COVID-19 facilities during the COVID-19 pandemic. However, we believe that this should not restrict the generalizability of the results to non-COVID-19 acutely ill patients.

Conclusion

Based on this study, the incidence of serotonin syndrome among acutely ill patients who received concomitant opioids and linezolid is very low, and the use of this combination is probably safe. Further prospective studies with a larger sample size are needed to confirm these findings.

Declarations

Ethical approval and consent to participate

This study was approved by HMC medical research center, under Number: MRC-01-21-699. Consent to participate was waived for this study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors contributions

Hassan Mitwally, Mohamed Saad, Dania Alkhiyami, Amr Fahmi, Sara Mahmoud, Eman Al Hamoud, and Rasha El Enany contributed in conception and design of the study. Hassan Younis, Shaban Mohammed, Palli Abdul Rouf, Binny Thomas, and Moza Al Hail contributed in data acquisition. Mohamed Saad and Hassan Mitwally contributed in data analysis and data interpretation. All authors contributed in drafting and approving the final manuscript.

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