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SHORT REPORT

Co-prescribing of linezolid and serotonergic agents in a general hospital setting

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Background. Co-prescription of linezolid and serotonergic agents (SSRIs, SNRIs, NaSSA, TCAs) can lead to serotonin syndrome, this study seeks to identify prescribing practise of these agents.

Methods. Study of all general hospital inpatients prescribed intravenous linezolid in a 3-month period, using drug charts and clinical notes.

Results. Co-prescription occurred in 20% with SSRIs most frequently concurrently used. There were no cases of serotonin syndrome. There was no evidence in clinical notes of vigilance for potential interaction.

Conclusion. Co-prescription is common; awareness of potentially serious interaction is not evident in current practice.

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Key words: Drug interaction, linezolid, serotonin syndrome, SSRI.

Background

Linezolid, an oxazolidinedone antimicrobial, has a spectrum of activity against Gram-positive bacteria, including multi-drug resistant Gram-positive cocci, which are significant pathogens of community and hospital acquired infections (Falagas & Vardakas 2008). Linezolid's adventitious pharmacokinetics allow for extensive absorption, absolute oral bioavailability at 100% and peak plasma concentrations after 1–2 hours. Its unique mechanism of action makes cross resistance with other agents unlikely. Its use in the general hospital setting is increasing because of its adventitious pharmacokinetic and pharmacodynamic profiles that allow early change from intravenous to oral administration (Vardakas *et al*. 2007).

Pharmacologically, linezolid is a reversible non-selective inhibitor of MAOI, with similar potency to moclobemide in tyramine pressor tests (Cantarini *et al*. 2004). Therefore, there exists a risk of dangerous interaction with serotonergic, dopaminergic and noradrenergic drugs. In the case of serotonergic drugs, there is a potential for development of serotonin syndrome, which carries a mortality of up to 11%. The hyperserotonergic state is defined by a triad of altered mental status, autonomic instability and neuromuscular excitation (Lawrence *et al*. 2006). Despite no evidence of problematic interactions in the initial phases 1, 2 and 3 clinical studies, there have been post-marketing case reports of serotonin syndrome. Given this risk, the FDA advises against co-prescription of linezolid and serotonergic drugs, unless urgent emergency situations may necessitate immediate linezolid treatment (Pfizer Healthcare Ireland 2012). Evidence is inconclusive of comparable risk associated with linezolid and other drugs with lesser degrees of serotonergic activity, for example, tramadol. Irish manufacturers of linezolid clearly outline in the Summary of Product Characteristics that co-prescription with serotonin re-uptake inhibitors, tricyclic antidepressants and serotonin 5-HT1 receptor agonists is contraindicated (Farrell 2007).

To date, serotonin syndrome has been described with linezolid and fluoxetine, venlafaxine, citalopram, paroxetine and sertraline. Current evidence recommends avoidance of concurrent prescribing where possible, or cautious risk-benefit analysis before co-prescription of SSRIs and linezolid, otherwise safe practice dictates employment of a 14-day washout period before the commencement of linezolid, as well as vigilance for hyperserotonergic symptoms. Where symptoms suggest possible serotonin syndrome, best practice involves measurement of creatine kinase (CK) and use of objective symptom rating scales, for example, those of Boyer or Sternbach (Quinn & Stern 2009).

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Table 1. *Boyer and Sternbach criteria for serotonin syndrome*

Boyer's criteria for serotonin syndrome	Sternbach's criteria for serotonin syndrome
Including administration of serotonergic agent in preceeding 5 weeks	Recent addition or increase in a serotonergic agent Absence of other possible aetiologies (e.g. infections) No recent addition or increase of neuroleptic agent
Any one of the following symptoms required	Any three of the following symptoms required
Tremor and hyperflexia	Mental state changes
Spontaneous clonus	Agitation
Muscle rigidity, > 38°C and ocular or inducible clonus	Myoclonus
	Hyperreflexia
	Diaphoresis
	Tremor
	Diarrhoea
	In-coordination
	Fever

Aim

The primary aim was to study prescribing practice by examining the frequency of co-prescription of linezolid with serotonergic agents, whether a washout period was applied, and which SSRI agents were used. We also aimed to study outcome by finding whether any cases of serotonin syndrome were recorded. Finally, we recorded the application of objective symptom rating scales, measurement of CK and reference to examination for these in clinical notes in vigilance of hyperserotonergic symptoms.

Method

This is a retrospective audit of clinical practice in a 960 bed tertiary referral hospital and regional cancer centre. A total of 70 acutely unwell inpatients prescribed intravenous linezolid, over a 3-month period, were included. Following approval from the Medical Risk Management Department and liaising with the Departments of Pharmacy & Clinical Microbiology, a retrospective list was generated of all patients prescribed intravenous linezolid over a 3-month period from August until October 2012. Drug charts and clinical notes were obtained to ascertain if patients were co-prescribed serotonergic agents, specifically SSRIs, SNRIs, NaSSA and TCAs within 14 days of commencing intravenous linezolid (600 mg BD). The parameters noted on reviewing these charts included the timeframe of co-administration, number and class of antidepressants prescribed. We reviewed clinical notes for reference to evidence-based best practise in the documentation of clinical examination for hyperserotonergic symptoms using rating scales of Boyer or Sternbach criteria (Quinn & Stern 2009; Table 1). We also specifically checked for the presence of myoclonus. We further undertook an electronic patient record review of laboratory results to ascertain whether measurement of CK took place, this is recommended as it can be helpful clinically in discriminating neuroleptic malignant syndrome from serotonin syndrome.

Results

Fifteen cases of co-prescription were identified ($n = 15$) out of a total number of 70 patients prescribed linezolid. In all, 45% of cases were female. The mean age of the identified cases was 59 years. Nine cases were prescribed SSRIs, of these four were used – Sertraline ($n = 3$), Citalopram ($n = 3$), Fluoxetine ($n = 1$), Paroxetine ($n = 1$). There were three cases of use of Tricyclic ADT (Amitryptyline, $n = 3$), two cases of NaSSA (Mirtazepine, $n = 2$), and one each of co-prescription of SARI (Trazodone, $n = 1$) and SNRI (Venlafaxine, $n = 1$) with linezolid. Nine cases were recorded of administration of both linezolid and serotonergic agent concurrently, without washout period. In the remaining six cases, the antidepressant was discontinued before the commencement of linezolid, however, it remained within the 14-day risk period for serotonin syndrome. Of 15 identified cases, two were co-prescribed multiple agents, giving a total of 17 prescribed serotonergic agents. Within the positive cases identified ($n = 15$), no cases of serotonin syndrome were recorded. There was no evidence in charts of consideration of the potential risk of serotonin syndrome referencing the application of Boyer or Sternbach criteria to identify symptoms consistent with serotonin syndrome. Measurement of CK was undertaken in five cases, during the period of concurrent use of linezolid with a serotonergic agent. In three cases, results were normal, and in two cases, a low CK was noted, which is not associated with serotonin syndrome. The indication for CK testing was not documented in the clinical notes for any case.

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Discussion

Seventy patients' charts over a 3-month period were reviewed and the rate of co-prescription of linezolid and serotonergic agents was 21%. There is emerging evidence indicating serotonin syndrome is a cause for concern in this complex cohort of patients. However, in the literature thus far, the evidence is predominantly in the form of case reports, two retrospective studies and one case series. In this study, SSRIs were more commonly prescribed, which may indicate current prescribing patterns. However, several classes of agents were involved and the potential for serious interaction with agents of lesser serotonergic action is as yet unclear (Pfizer Healthcare Ireland 2012). There were no cases of serotonin syndrome identified in this study.

The clinical features of serotonin syndrome are progressive and with prompt recognition reversible by discontinuing the serotonergic agent (Taylor *et al*. 2006). While no cases of serotonin syndrome occurred in this study, the results highlight a lack of clinical awareness of the potential for serious interaction. When using the specific Boyer or Sternbach criteria, physicians can identify clinical symptoms consistent with serotonin syndrome.

A clear limitation to this study is its small size and retrospective chart review design. Therefore, we may be subject to selection bias. It was also not feasible to compare the incidence of serotonin syndrome based on specific agents as a result. Furthermore, we analysed drug prescription only and did not monitor drug administration, thus representing a further source of uncertainty.

In acutely unwell patients, clinical situations may arise that necessitate co-prescription of linezolid and serotonergic agents, without the possibility of washout or discontinuation, however, reference should be made to the potential for interaction, and vigilance employed to monitor emerging hyperserotonergic symptoms. Despite the lack of a robust evidence base on the risk of serotonin syndrome, it remains best practice to avoid co-prescription of linezolid and serotonergic agents wherever possible. Finally, we recommend regular clinical audit by hospital pharmacies owing to the seriousness of serotonin syndrome.

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