Original Article

Olanzapine for cisplatin-induced hiccups: observations from a 338-patient study

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Background: Several case reports suggest that olanzapine palliates hiccups. To our knowledge, however, no larger scale studies have confirmed that olanzapine prevents or palliatives hiccups. Hence, the current study sought to substantiate the conclusions from these earlier case reports.

Methods: This multi-site single institution study focused on cisplatin-treated cancer patients because this chemotherapy agent is associated with hiccups and because olanzapine is often used as an antiemetic with this agent. Relevant data were extracted from medical records. Hiccup incidence shortly after chemotherapy was compared between olanzapine exposed and non-exposed patients. Other relevant variables were also assessed descriptively in an exploratory manner.

Results: A total of 338 patients were studied. One hundred forty-one had received olanzapine and 197 had not. Twenty-one (6%) developed hiccups. Eleven (8%) of these patients with hiccups had received olanzapine, and 10 (5%) had not [odds ratio (OR): 1.58; 95% confidence interval (CI): 0.65–3.83; P=0.31]. Of note, hiccups were more often observed in men 17 of 188 (9%) than in women 4 of 150 (3%) (OR: 3.64; 95% CI: 1.20–11.02; P=0.01).

Conclusions: Despite previous case reports and despite the relatively low incidence of hiccups in this study, it does not appear olanzapine prevents or palliates hiccups. The study of other promising agents is warranted. Furthermore, this study invites caution in relying on single case reports in making clinical decisions.

Keywords: Olanzapine; hiccups; palliation; male predominance

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Introduction

Case reports suggest olanzapine palliates hiccups (1-5). Olanzapine exerts antagonistic effects on serotonin and dopamine, both of which activate neural pathways that appear to trigger hiccups. Because of this empiric evidence and because of this mechanistic plausibility, olanzapine has been cited as an effective drug for hiccup palliation (1-5).

Although high-level evidence, such as randomized trial data, is typically sought in making therapeutic recommendations, such is not the case for hiccups. Their often-transient nature makes it difficult to discern true palliation and from spontaneous resolution of signs and

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symptoms. An absence of validated tools to assess hiccups only worsens the problematic nature of conducting clinical trials. Lastly, healthcare providers as well as patients appear to trivialize hiccups, thereby ostensibly detracting from clinical trial accrual goals.

Nonetheless, hiccups can spawn morbidity, leading to sleep deprivation, musculoskeletal pain, poor oral intake, vomiting, aspiration, and even death—a list of adverse events that behooves us to try to impose rigor when prescribing agents for their palliation (6). For this reason, we undertook the current study to assess whether olanzapine is associated with hiccup palliation. A dearth of clinical trial data on hiccups in general prompted us to undertake this exploratory observational, medical record-based study. The current study was intended to explore further whether olanzapine should be prescribed for hiccup prevention or palliation. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-159/rc).

Methods

Overview

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This multi-site single-institution study was approved by the Mayo Clinic Institutional Review Board (#21-008767). This was an observational study focused on medical records only; the Institutional Review Board waived the need for patient informed consent because of the retrospective nature of this research. This study focused on only cisplatin-treated cancer patients because this chemotherapy agent is associated with hiccups and because olanzapine is often used as an antiemetic with this chemotherapy agent (7,8).

Data acquisition

This non-interventional, observational study focused on medical records from August 2018 through August 2021 with retrospective data acquisition. This earlier date was chosen as a starting point because it coincided with the more widespread availability of olanzapine as an antiemetic and with the incorporation of olanzapine into guidelines for preventing and treating chemotherapy-induced nausea and vomiting (7,8). In this context, we assumed that, during this interval, we would readily be able to identify patients who had received olanzapine for nausea and vomiting.

This study focused only on adult, cisplatin-treated cancer patients. The medical records of these patients were categorized based on whether or not olanzapine had been prescribed for nausea and vomiting. We enriched the patient population to include an approximately equal number of patients who did and did not receive olanzapine. Medical records from each of these two categories (with and without olanzapine) were randomly selected, again, with the goal of reviewing an approximately equal number of records from each group with slight discrepancies in the number of patients per group reflective of closer medical record review (for example, cisplatin had been planned, not given, and thereby the patient did not fit into the assigned group after all). This random selection was intended to minimize confounding variables when seeking an enriched patient population. Each medical record was reviewed in detail for evidence of hiccups a few days after chemotherapy as well as for other pertinent information. Because of a previous study that suggested height is associated with hiccup development, we made a point of acquiring data on height from the medical record (9).

Of note, as per standard of care clinical practice, all patients had to have had a creatinine checked and within acceptable parameters prior to the administration of cisplatin. Therefore, creatinine was not specifically gleaned from the medical record and reported.

Statistical analysis

We intended to include at least 300 patients. As this is an exploratory medical record review study, the sample size was based on feasibility with the underlying goal of examining the association between olanzapine and hiccups. A sample size of 300 (approximately 150 per group) provided 80% power at a two-sided Type 1 error of 0.05 to detect a reduction of hiccups from 15% in the no olanzapine group, as per our preliminary data, to 5% with olanzapine (10% difference). Exploratory univariable logistic regression models were used to calculate odds ratios along with 95% confidence intervals (CIs) for variables of interest. A P value of <0.05 was deemed statistically significant in these exploratory analyses, and JMP® 16.1.0 was used.

Table 1 Demographics (N=338)

Characteristic	Olanzapine, N=141 [%]	No olanzapine, N=197 [%]
Mean age in years [standard deviation]*	57 [14]	62 [11]
Gender		
Male	77 [55]	111 [56]
Female	64 [45]	86 [44]
Cancer type		
Genitourinary	24 [17]	36 [18]
Gastrointestinal	20 [14]	38 [19]
Lung	25 [18]	31 [16]
Hematologic	17 [12]	21 [11]
Other	55 [39]	71 [36]
Height		
Above average for gender	84 [60]	117 [59]
Average or less	57 [40]	80 [41]
Cisplatin dose administered**		
≥100 mg	21 [15]	18 [9]
Less than above	120 [85]	178 [90]

*, numbers in parentheses suggest percentages unless otherwise specified; **, the dose of cisplatin was missing in one patient who received no olanzapine.

Results

Demographics

A total of 338 patients—141 of whom received olanzapine and 197 did not—are the focus of this report. Demographics appear in *Table 1*. Of note, the most prescribed dose of olanzapine was 5 mg orally (range, 2.5–10 mg), and the median cisplatin dose was 50 mg/m^2 intravenously.

Hiccups and olanzapine

Twenty-one patients (6%) developed hiccups. Eleven (8%) had received olanzapine, and 10 (5%) had not, generating an odds ratio (OR) for worse hiccups 1.58 (95% CI: 0.65–3.83; P=0.31) (*Table 2*).

Hiccups and other variables

We observed a male predisposition to hiccups. Seventeen of 188 men (9%) but only 4 of 150 women (3%) developed hiccups (OR: 3.64; 95% CI: 1.20–11.02; P=0.01) (*Table 2*). However, other variables, such as increased height and higher cisplatin dose were not associated with hiccups (*Table 2*).

In an exploratory manner, we examined whether patients had received baclofen or metoclopramide at some point during cisplatin administration, as small clinical trials have suggested these agents might palliate hiccups (10-12). We found that 11 olanzapine-treated patients were also prescribed baclofen and that 8 patients who did not receive olanzapine were prescribed baclofen. Notably, we found 11 baclofen-treated patients had developed hiccups, an observation that likely suggests healthcare providers prescribed palliative baclofen after hiccups developed. Further, we observed that 6 olanzapine-treated patients had received metoclopramide, that 4 patients who did not receive olanzapine received metoclopramide, and that that one metoclopramide-treated patient had had hiccups.

Discussion

This study suggests olanzapine does little, if anything, to prevent or palliate cisplatin-induced hiccups. Indeed, we observed that a slightly greater number and percentage of patients who had received olanzapine developed hiccups shortly after chemotherapy, although this finding did not reach statistical significance. Of note, we observed fewer patients than anticipated with hiccups with previous studies, presumably because we relied on medical record review for hiccup incidence; previous studies suggest that slightly over a third of cisplatin-treated patients develop hiccups (13). However, the fact that we observed a statistically significant male predisposition for hiccups—an observation that has been consistently reported in the hiccups literature—perhaps suggests validation of our other results (14). We conclude that when pharmacological interventions are sought to palliate hiccups, until further data become available to dictate otherwise, drugs other than olanzapine should be prescribed.

The current study raises three other points. First, case reports can be of value, but they can also prompt clinicians

Table 2 Univariable logistic regression models for hiccups

Variable	Number of patients with hiccups [%]	Odds ratio (95% confidence interval) for worse hiccups	P value
No olanzapine (referent)	10 [5]	1.58 (0.65, 3.83)	0.31
Olanzapine	11 [8]		
Female (referent)	4 [3]	3.64 (1.20, 11.02)	0.01
Male	17 [9]		
Average height or less (referent)	11 [8]	0.59 (0.24, 1.44)	0.25
Above average height for gender	10 [5]		
Lower cisplatin dose (referent)	16 [5]	2.54 (0.88, 7.39)	0.11
Cisplatin dose of ≥100 mg/m^2	5 [13]		

to prescribe ineffective agents. The often-transient nature of hiccups might mislead clinicians into thinking that a recently prescribed agent was effective when in fact the hiccups could have been self-limited, resolving on their own. Thus, basing palliative decisions on case reports alone is not prudent. Second, from a clinical standpoint, other agents have acquired stronger evidence in support of hiccup palliation. For example, two randomized controlled trials, each with small sample sizes of 4 and 30 patients, respectively, suggest baclofen might be effective for hiccups (11,12). Another randomized trial suggested that metoclopramide might be effective (10). In lieu of olanzapine, other agents, such as baclofen, might be considered (11,12). Of incidental note, we did observe that several patients in this study were ultimately prescribed baclofen, but, ostensibly, baclofen was prescribed after hiccups developed and thus did not confound conclusions related to olanzapine, as reported here.

Third, a medical record review, as described here, offers more rigor than single case reports but poses other challenges. To our knowledge, few studies have relied on patient-reported outcomes to assess hiccup incidence, but the use of such methodology, as opposed to medical record review, would be important for future studies. Medical record review also runs the risk of interjecting bias even with attempts to focus on a homogenous group of cisplatin-treated patients. For example, although unlikely because of olanzapine's sedative effects and because of the results we report here, it is possible that patients with hiccups might have taken extra olanzapine at home, derived hiccup relief from olanzapine, and therefore did not report hiccups during a follow up clinic appointment (7,8). Thus, we view the results reported here as important but by no means definitive.

In summary, despite limitations that include risk of confounding variables, a small incidence of hiccups in the patient sample, and a reliance of medical record review (as opposed to patient-reported outcomes), this study suggests olanzapine should not be prescribed for hiccup palliation. More importantly, this study underscores the need to implement other study designs—beyond single patient case reports—to explore other pharmacologic agents that might be helpful for hiccup palliation.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-159/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-159/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This multi-site single-institution study was approved by the Mayo Clinic Institutional Review Board (#21-008767). This was an observational study focused on medical records only; the Institutional Review Board waived the need for patient informed consent because of the retrospective nature of this research.

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