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Olanzapine for the Treatment of Breakthrough Vomiting in Children Receiving Moderate and High Emetogenic Chemotherapy

The efficacy of olanzapine (mean dose 0.09 mg/kg/dose) was evaluated in 31 children 2-18 years of age, for chemotherapy induced breakthrough vomiting. Among 42 chemotherapy blocks with emesis, complete and partial responses were observed in 34 (80.9%) and 6 (14.3%) blocks, respectively, while 1/31(2.4%) patient had refractory vomiting. Mild sedation and transient transaminitis were the observed side effects.

Keywords: *Anti-emetic, Emesis, Malignancy, Vomiting.*

Chemotherapy induced vomiting (CIV) has been shown to have a detrimental influence on quality of life and treatment compliance of patients [1]. Despite the use of novel anti-emetics, breakthrough CIV can occur in 30-40% of children receiving moderate or highly emetogenic chemotherapy (MEC/HEC) [2,3]. There is paucity of data regarding choice of optimum agent and management of breakthrough CIV in children [3]. The present study was planned to demonstrate efficacy and safety of olanzapine in the treatment of breakthrough vomiting in children receiving MEC or HEC.

This observational study was conducted over a period of 6 months in children aged 2-18 years, receiving MEC or HEC who developed breakthrough emesis on protocol-defined prophylaxis, as described previously [4]. Institutional ethics committee approval and written informed consent from parents were obtained. The dose of oral olanzapine was 0.05-0.1 mg/kg/dose (maximum 5 mg/dose) once in every 24-hour period for 3 days, regardless of duration of chemotherapy block or subsequent response. The dose was rounded off to the closest half or full tablet of commercially available preparations of 2.5 mg and 5 mg strengths. Laboratory investigations included complete blood count, liver and kidney function at screening and before each cycle. Each episode of vomiting and treatment related adverse events like sedation and transaminitis were recorded as per the Common terminology criteria for adverse events ver 4.03, for atleast 5 days [5].

The primary outcome was an assessment of response for 5 days from the first dose of olanzapine. Complete response (CR) was defined as no emetic episode and use of no other rescue medications. Partial response (PR) was if patient had 1-2 emetic episodes with no use of rescue medications, and failure (refractory) if patient had more than 2 emetic episodes and/or use of rescue medications. Rescue drugs were permitted as per physician's discretion (commonly metoclopramide). Data were analyzed using IBM SPSS version 23.0, using standard physician's statistical methods.

During the study period, 108 (median age 9.2 years) pediatric cancer patients received 412 blocks of MEC and HEC. A total of 31 (31.8%) patients and 42 (10.1%) chemotherapy blocks were associated with breakthrough emesis. Eleven patients had breakthrough emesis in more than one block. Demographic data of patients is shown in ***Table* I**. The mean (range) olanzapine dose was 0.09 (0.04-0.15) mg/kg/dose.

Complete and partial responses were observed in 34 (80.9%) and 6 (14.3%) chemotherapy blocks, while 1 (2.4%) patient had refractory vomiting. One patient did not receive the

Table I Demographic Characteristics of the study Population (*N*=31)

Characteristic	(%)
Male	21 (68)
Age <10 years	18 (58)
Type of malignancy	
Hematological	17 (54)
Solid Tumor	14 (45)
Disease status	
Standard risk/Non metastatic	19 (61)
High risk/metastatic	12 (39)
Emetogenic potential	
Moderate	14 (45)
High	17 (54)
Cisplatin regimes	5 (16)
Dexamethasone	29 (93)
Intrathecal drug	14 (45)
Chemotherapy schedule	
Single day	05 (16)
Multiple day	26 (84)

drug after first dose and was not included in response assessment. The mean (SD) dose of olanzapine in patients with CR was 0.09 (0.02) mg/kg/dose and in PR was 0.08 (0.02) mg/kg/dose, *P*=0.68. There was no statistical difference in CR rates based on age (<10/>10 years, *P*=0.23), gender (*P*=0.68), emetogenic regimen (MEC/HEC, *P*=1.0) or single/multiple-day chemotherapy (*P*=0.2). The most commonly reported adverse events were grade I-II sedation in 9 patients (11 chemotherapy blocks) and increased serum transaminase levels in 3 patients (3 chemotherapy blocks). Olanzapine was discontinued in one patient due to orthostatic hypotension. The mean (SD) olanzapine dose in patients who had and did not have sedation was 0.11 (0.022) and 0.08 (0.001) mg/kg/dose, respectively; odds ratio 1.17, (95% CI: 1.08-1.27, *P*=0.0001). It is recommended to use an antiemetic with a different mechanism of action, for the treatment of breakthrough vomiting, than that used for prophylaxis [6]. A CR rate of 57% with an overall response of 86% has been reported earlier in a retrospective study on 20 subjects [7]. Our study was prospective in nature with pre-defined anti-emetic prophylactic protocols and indications for olanzapine use. We believe, this led to a more accurate and early use of olanzapine, resulting in better control of CIV and higher CR rates. Two studies in adult patients report similar results, CR, 70% and 61% respectively [8,9].

The most common side effects reported are sedation, transaminitis and weight gain [7-9]. Significant weight gain was not expected as the duration of treatment with olanzapine for refractory CIV is short. Flank, *et al*., reported sedation in 7%, and it was significantly associated with higher olanzapine dose, as also observed in our study [7].

The results of this study, despite small sample and lack of controls, suggest olanzapine as an effective anti-emetic drug for breakthrough CIV. Its low cost, oral formulation and safety profile are of added value in cost-constraint settings.

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