



# Antiemetic Regimen with Olanzapine in Pediatric Patients Receiving Highly Emetogenic Chemotherapy

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Chemotherapy-induced nausea and vomiting (CINV) are so significant and prevalent that the discovery of antiemetics was recently voted, by both physicians and patients alike, as one of the “Top 5 Advances in 50 Years of Modern Oncology.”<sup>1</sup> We recently published the results of a phase-III study which explored whether the addition of olanzapine to standard pediatric antiemetic regimens would improve their efficacy.<sup>2</sup>

## How This Trial on the Use of Olanzapine as an Antiemetic in Children Came About

At the time the study was conceptualized in 2017, the standard of care for antiemesis in children receiving highly emetogenic chemotherapy (HEC) was the three-drug combination of an neurokinin 1 (NK1) receptor antagonist (NK1RA), a 5-HT<sub>3</sub> receptor antagonist (5HT<sub>3</sub>RA), and dexamethasone. In 2016, Navari et al had published the results of their randomized control trial (RCT) comparing a combination of an NK1RA, dexamethasone, a 5HT<sub>3</sub>RA, and either 10-mg olanzapine or placebo in either arm. Their results significantly favored the olanzapine arm (►Table 1).<sup>3</sup> Consequently, since 2017, the American Society of Clinical Oncology (ASCO) guidelines have included a four-drug regimen including olanzapine, for adults receiving HEC or experiencing breakthrough nausea and vomiting.<sup>4</sup>

Meanwhile, the pediatric guidelines for antiemesis in HEC recommended the use of aprepitant, a 5HT<sub>3</sub>RA, and a corticosteroid. Nevertheless, the safety of olanzapine in the pediatric population had already been established by then, and the Pediatric Oncology Group of Ontario (POGO) had recommended the use of olanzapine for the management of breakthrough CINV after HEC in children, although based on limited evidence.<sup>5</sup> There was no data from prospective trials on the use of olanzapine for preventing pediatric CINV.

It was against this backdrop that we decided to conduct our trial. We had earlier conducted an RCT in children aged 5 to 18 years receiving HEC, comparing the combination of ondansetron, dexamethasone, and either aprepitant or placebo in each arm, that is, a three-drug regimen versus a two-drug regimen.<sup>6</sup> In that study, the complete response (CR) rate was significantly better in the aprepitant arm during the acute phase (►Table 1). It was hoped that the addition of olanzapine as a fourth agent would improve CR rates in both acute and delayed phases by at least a further 20%.

## Study Design–Related Challenges and Results

The study was designed as an investigator-initiated, open-label RCT.<sup>2</sup> Patients in the study arm received olanzapine at a dose of 0.14 mg/kg/dose once daily (rounded to the nearest 2.5 mg; up to a maximum of 10 mg) on each day of chemotherapy and for 3 days afterward. One of the primary challenges in designing the study was the unavailability of the syrup formulation of aprepitant which hindered precise weight-based dosing. This was overcome by using weight-based dose-bands, with those weighing 15 to 40 kg receiving 80 mg on days 1 to 3, while those weighing 40 kg or more received 125 mg on day 1 and 80 mg on days 2 and 3. Such dosing was possible due to the high therapeutic index of aprepitant and convincing safety data from previous pediatric trials.<sup>6–8</sup> Another way of overcoming this would be by using the intravenous (IV) preparation.<sup>9</sup> We also have an ongoing RCT examining the efficacy of single-dose IV fosaprepitant versus 3-day oral aprepitant in children receiving single or multiday HEC (no.: CTRI/2019/05/019082). However, fosaprepitant may not be as cost effective as oral aprepitant.

The second major design challenge was the assessment of nausea, as the assessment of the severity of nausea in the

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**Table 1** Summarized results from selected studies on antiemetic prophylaxis in patients receiving highly emetogenic chemotherapy

Sl. no.	Study (year)	Study population and Regimen studied	CR rate in the acute phase	CR rate in the delayed phase	CR rate in the overall phase	Significant toxicities
1.	Bakhshi et al (2015) <sup>6</sup>	Chemotherapy-naïve children aged 5–18 years, scheduled to receive highly emetogenic chemotherapy Aprepitant versus placebo, in addition to dexamethasone, and ondansetron	48 vs. 12% ( $p < 0.001$ ), favoring the aprepitant arm	34 vs. 30% ( $p = 0.7$ ), favoring the aprepitant arm	22 vs. 9% ( $p = 0.1$ ), favoring the aprepitant arm	No grade 3 or 4 toxicities in either arm
2.	Navari et al (2011) <sup>14</sup>	Chemotherapy-naïve adults aged 18 years or older, scheduled to receive highly emetogenic chemotherapy Olanzapine versus aprepitant, in addition to palonosetron and dexamethasone	97 vs. 87% ( $p > 0.05$ ), in the olanzapine and aprepitant arms, respectively	77 vs. 73% ( $p > 0.05$ ), in the olanzapine and aprepitant arms, respectively	77 vs. 73% ( $p > 0.05$ ), in the olanzapine and aprepitant arms, respectively Nausea was better controlled in the olanzapine arm	No grade 3 or 4 toxicities in either arm
3.	Babu et al (2016) <sup>15</sup>	Chemotherapy-naïve adults aged >18 years and <60 years, scheduled to receive highly emetogenic chemotherapy Olanzapine vs. aprepitant, in addition to palonosetron and dexamethasone	84 vs. 86% ( $p > 0.05$ ), in the olanzapine and aprepitant arms, respectively	88 vs. 86% ( $p > 0.05$ ), in the olanzapine and aprepitant arms, respectively	78 vs. 80% ( $p > 0.05$ ), in the olanzapine and aprepitant arms, respectively	No grade 3 or 4 toxicities in either arm
4.	Navari et al (2016) <sup>3</sup>	Chemotherapy-naïve adults aged 18 years or older, scheduled to receive highly emetogenic chemotherapy Olanzapine vs. placebo, in addition to dexamethasone, a NK1RA, and a 5-HT3RA	86 vs. 65% ( $p < 0.001$ ), favoring the olanzapine arm	67 vs. 52% ( $p = 0.007$ ), favoring the olanzapine arm	64 vs. 41% ( $p < 0.001$ ), favoring the olanzapine arm	No grade 3 or 4 toxicities attributed to olanzapine 5% experienced severe drowsiness on day 2
5.	Radhakrishnan et al (2019) <sup>9</sup>	Children aged 1–12 years scheduled to receive moderately or highly emetogenic chemotherapy Fosaprepitant vs. placebo, in addition to ondansetron and dexamethasone	86 vs. 60% ( $p < 0.001$ ), favoring the fosaprepitant arm	79 vs. 51% ( $p < 0.001$ ), favoring the fosaprepitant arm	70 vs. 41% ( $p < 0.001$ ), favoring the fosaprepitant arm	Approximately 10% of patients in either arm had grade III/IV leucopenia, and ~7% in each arm had grade III/IV febrile neutropenia
6.	Naik et al. (2020) <sup>2</sup>	Chemotherapy-naïve children aged 5–18 years, scheduled to receive highly emetogenic chemotherapy Olanzapine vs. placebo, in addition to dexamethasone, a NK1RA, and a 5-HT3RA	78 vs. 59% ( $p = 0.001$ ), favoring the olanzapine arm	74 vs. 47% ( $p < 0.001$ ), favoring the olanzapine arm	64 vs. 38% ( $p < 0.001$ ), favoring the olanzapine arm	Somnolence was experienced more frequently in the olanzapine arm (35 vs. 11%; $p < 0.001$ ), but there were no grade 3 or 4 toxicities attributable to olanzapine. One patient died at home in the olanzapine arm, but the cause could not be ascertained

(continued)

**Table 1** (continued)

Sl. no.	Study (year)	Study population and Regimen studied	CR rate in the acute phase	CR rate in the delayed phase	CR rate in the overall phase	Significant toxicities
7.	Radhakrishnan et al (2020) <sup>13</sup>	Children aged 5–18 years scheduled to receive moderately or highly emetogenic chemotherapy. Olanzapine or Metoclopramide were given in either arm as rescue therapy for breakthrough nausea and vomiting	–	–	72 vs. 39% ( $p = 0.003$ ), in the 72 hours after administration of the rescue drug, favoring the olanzapine arm	One patient (2.5%) in the olanzapine arm had grade-3 drowsiness and none had grade 4. Hyperglycemia was more common in the olanzapine arm

Abbreviations: CR rate, complete response rate for vomiting; acute phase within 24 hours of chemotherapy; delayed phase, beyond 24 hours and within 120 hours of chemotherapy; overall phase, within 120 hours of chemotherapy; NK1RA, neurokinin-1 receptor antagonist; 5-HT3RA, 5-HT3 receptor antagonist.

pediatric age group is notoriously difficult. In our trial, the Edmonton Symptom Assessment Scale (ESAS) was used to grade nausea.<sup>10</sup> Although the ESAS has not been validated for use in children, since no pediatric nausea-assessment tools had been validated in Hindi or in the Indian population in general, it was decided to use the ESAS due to its simplicity and the lack of a better alternative.

The results of our phase-III RCT conclusively showed that the CR rates for vomiting in both acute and delayed phases were significantly improved with the addition of olanzapine in children exposed to HEC (► **Table 1**). The incidence of somnolence was higher in the olanzapine arm (35 vs. 11%), but there were no cases of grade 3 or higher somnolence.

### Study Limitations

The principal limitations of our study were the use of the ESAS scale as mentioned above and the modified dosing of aprepitant that had to be used because its syrup formulation is not available in India. Since 15 kg was the minimum weight, children below 5 years of age could not be included. CINV in this segment of the pediatric population has been difficult to study in the Indian context. A double-blind RCT would have been a more robust design but could not be done due to logistic constraints. The incidence of somnolence in the olanzapine arm might have been lower with a lower dose of 0.1 mg/kg, but we did not test this lower dose as part of our study.

### Conclusion and Future Perspectives

The last update of the antiemetic guidelines by POGO in 2017 did not mention olanzapine in their recommendations.<sup>11</sup> However, recent research in India has already established olanzapine to be a useful agent for both prophylaxis and rescue therapy in pediatric CINV.<sup>2,12,13</sup> Notably, even with olanzapine, the CR rate achieved was only 70%. Nearly two-thirds of the patients also experienced significant nausea, and more research is required toward improving nausea control. Further research could also explore lower doses of olanzapine, and whether a three-drug regimen composed

of olanzapine, a 5HT3A, and a steroid could be noninferior to the aprepitant-based regimens in children, as has been proven in the adult population.<sup>14–16</sup> The cost effectiveness of such regimens also needs to be established, as this one is of the principal attractions of olanzapine.<sup>17,18</sup> The role of olanzapine in moderately emetogenic chemotherapy and in steroid-sparing antiemetic regimens requires more attention. On the NK1RA front, the dosing of fosaprepitant in the pediatric population and the ideal schedule of administration of NK1RAs in children receiving multiday chemotherapies need evaluation.<sup>11</sup>

Ginger has already been shown to be a cost-effective, widely available alternative add-on antiemetic.<sup>19</sup> More research exploring the role of various traditional, indigenous, or alternative therapies should be considered.<sup>20</sup> Additionally, quality of life also needs to be studied in children undergoing trials which are examining the efficacy of antiemetic regimens, as this is now recognized as an equally important aspect of efficacy.<sup>21,22</sup>

### Conflict of Interest

None declared.

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