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Review

Olanzapine for the prevention and treatment of chronic nausea and chemotherapy-induced nausea and vomiting

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ABSTRACT

Olanzapine is an atypical antipsychotic agent of the thiobenzodiazepine class. It blocks multiple neurotransmitter receptors including dopaminergic at D_1, D_2, D_3, D_4 brain receptors, serotonergic at 5-HT_{2a}, 5-HT_{2c}, 5-HT_3, 5-HT_6 receptors, catecholamines at alpha$_1$ adrenergic receptors, acetylcholine at muscarinic receptors, and histamine at H_1 receptors. Olanzapine has five times the affinity for 5-HT_2 receptors than D_2 receptors and has been used to treat schizophrenia and delirium. Olanzapine's activity at multiple receptors, particularly at the D_2, 5-HT_{2c}, and 5-HT_3 receptors which appear to be involved in nausea and emesis, has prompted its use in the treatment of nausea and vomiting refractory to standard antiemetics. Case reports and formal clinical trials have demonstrated its efficacy in the treatment of chronic nausea, the prevention of chemotherapy-induced nausea and emesis, and the treatment of breakthrough chemotherapy-induced nausea and emesis. Phase II and phase III clinical trials have demonstrated that there is a significant improvement in nausea when olanzapine is added to guideline directed prophylactic antiemetic agents 5-HT_3 receptor antagonists and tachykinin NK_1 receptor antagonists in patients receiving moderately or highly emetogenic chemotherapy Common side effects of olanzapine when used over a period of months include weight gain as well as an association with the onset of diabetes mellitus, but these effects have not been seen with short term use of daily doses of less than one week.

Contents

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1. Introduction

1.1. Chemotherapy-induced nausea and vomiting

Chemotherapy-induced nausea and vomiting (CINV) is associated with a significant deterioration in quality of life and is perceived by patients as a major adverse effect of the treatment (Bloechl-Daum et al., 2006). The use of 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists plus dexamethasone has significantly improved the control of CINV (Navari, 2013). Recent studies have demonstrated additional improvement in the control of CINV with the use of three new agents, palonosetron, a second generation 5-HT_3 receptor antagonist (Navari, 2010), aprepitant, the first agent available in the drug class of tachykinin NK_1 receptor antagonists (Curran and Robinson, 2009; Sankhala et al., 2009) and olanzapine, an antipsychotic which blocks multiple neurotransmitters in the central nervous system (Navari et al., 2007; Navari et al., 2011; Tan et al., 2009).

The primary endpoint used for studies evaluating various agents for the control of CINV has been complete response (CR) (no emesis, no use of rescue medication) over the acute (24 h post-chemotherapy), delayed (24–120 h), and overall (0–120 h) periods (Navari, 2013). Recent studies have shown that the combination of a 5-HT_3 receptor antagonist, dexamethasone, and a NK_1 receptor antagonist have been very effective in controlling emesis in patients receiving either highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC) over a 120 h period following chemotherapy administration (Curran and Robinson, 2009; Sankhala et al., 2009). Many of these same studies have measured nausea as a secondary endpoint and have demonstrated that nausea has not been well controlled (Navari, 2012).

Emesis is a well defined event which is easily measured, but nausea may be more subjective and more difficult to measure. There are, however, two well defined measures of nausea which appear to be effective measurement tools which are reproducible: the Visual Analogue Scale (VAS) and the Likert Scale (Stern et al., 2011). The VAS is a scale from 0 to 10 or 0 to 100 with zero representing no nausea and 10 or 100 representing maximal nausea. The Likert Scale asks patients to rate nausea as none, mild, moderate or severe.

1.2. Definition of nausea

Nausea is a subjective, difficult-to-describe, sick or queasy sensation, usually perceived as being in the stomach that is sometimes followed by emesis (Stern et al., 2011). The experience of nausea is difficult to describe in another person because it is a subjective sensation. Nausea and emesis are not necessarily on a continuum. One can experience nausea without emesis and one can have sudden emesis without nausea. Nausea has been assumed to be the conscious awareness of unusual sensations in the "vomiting center" of the brainstem (Fig. 1), but the existence of such a center and its relationship to nausea remain controversial (Stern et al., 2011).

Fig. 2 illustrates the various receptors that are considered to be involved in CINV. These receptors are located both in the periphery such as the gastrointestinal tract as well as in the central nervous system. Various antiemetic agents have been developed as antagonists to the serotonin and the substance-P receptors with relative success in controlling emesis. It is not clear whether the serotonin and/or the substance P receptors are important in t he control of nausea. Other receptors such as dopaminergic, histaminic and muscarinic may be the dominant receptors in the control of nausea (Navari, 2012, 2013).

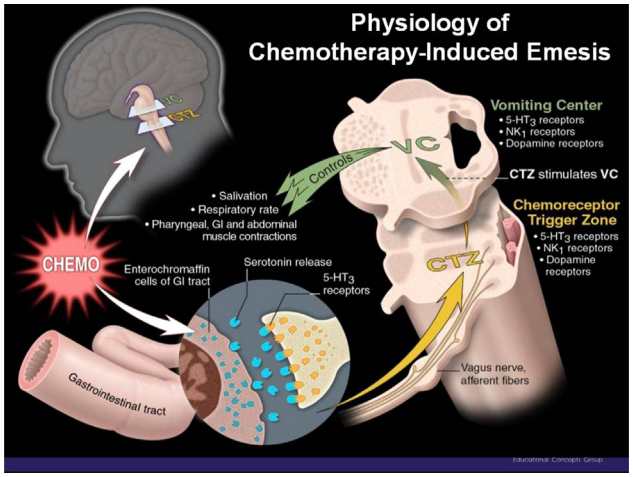

Fig. 1. Physiology of chemotherapy-induced emesis.

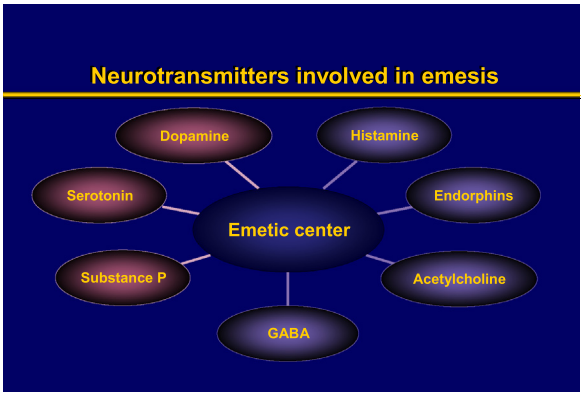

Fig. 2. Neurotransmitters involved in emesis.

2. Olanzapine

2.1. Mechanism of action

Olanzapine, an atypical antipsychotic agent of the thiobenzodiazepine class, was approved by the FDA for the treatment of the manifestations of psychotic disorders in 1996 (Fulton and Goa, 1997; Kando et al., 1997) with a generic available in 2011. Olanzapine blocks multiple neurotransmitter receptors including dopaminergic at D_1, D_2, D_3, D_4 brain receptors, serotonergic at 5-HT_{2a}, 5-HT_{2c}, 5-HT_3, 5-HT_6 receptors, catecholamines at alpha$_1$ adrenergic receptors, acetylcholine at muscarinic receptors, and histamine at H_1 receptors (Bymaster et al., 1996). Olanzapine has five times the affinity for 5-HT_2 receptors than D_2 receptors (Stephenson and Pilowsky, 1999) and is used to treat schizophrenia and delirium (Breithart et al., 2002; Kim et al., 2001). Olanzapine may reduce opioid requirements in cancer patients with uncontrolled pain, cognitive impairment, or anxiety (Khojainova et al., 2002).

The detailed mechanism of the effect of olanzapine in reducing CINV is unknown, but olanzapine does block the neurotransmitters dopamine and serotonin which are known mediators of CINV (Bymaster et al., 1996; Bymaster et al., 2001). Olanzapine blocks the serotonin mediated 5-HT_{2C} receptor, a receptor which has been shown to mediate anti-emetic activity in animal models (ferret cisplatin-induced emesis and cisplatin-induced anorexia in the hypothalmus of rats) (Rudd et al., 2006; Yakabi et al., 2010) as well as weight loss in humans (Hurren and Berlie, 2011). The effect