Mini Review

Clinical Potential of a New Class of Antiemetic for the Prevention of Chemotherapy-Evoked Acute- and Delayed Vomiting: Supportive Evidence from the Least Shrew (*Cryptotis Parva*) Model of Emesis

Darmani NA*, Chebolu S and Zhong W

Department of Basic Medical Sciences, Western University of Health Sciences, USA

*Corresponding author: Darmani NA, Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, USA

Abstract

This mini-review summarizes our recent published findings on the: i) emetic potential of cysteinyl leukotrienes LTC_4, LTD_4 and LTE_4 in the least shrew (*Cryptotis parva*) model of emesis, ii) mechanism of action of their corresponding cysteinyl leukotrienes receptor 1 ($CysLT_1R$) antagonist, pranlukast, against LTC_4-induced vomiting, and iii) potential of pranlukast as a new class of antiemetic for the suppression of the acute- and delayed phases of vomiting caused by the cytotoxic cancer chemotherapeutic agent, cisplatin. Pranlukastis currently used in patients for the treatment of various respiratory disorders including asthma. Our findings demonstrate that unlike other leukotrienes (e.g. LTA_4, LTB_4 and LTF_4), the above discussed leukotrienes are effective emetogens with the following potency order: $LTC_4=LTD_4>LTE_4$. Prior treatment with pranlukast was shown to completely suppress LTC_4-evoked emesis suggesting that $CysLT_1Rs$ are involved in vomiting. These and other findings indicate an important role for the emetic leukotrienes in the mediation of chemotherapy-induced nausea and vomiting (CINV). In fact we have demonstrated that blockade of the $CysLT_1R$ by pranlukast, not only can reduce cisplatin-evoked vomiting, but also intracellular markers of cisplatin-induced emetic signals. Moreover, pranlukast potentiated the antiemetic efficacy of serotonin $5-HT_3$ receptor antagonists, tropisetron and palonosetron, against CINV. If analogs of pranlukast such as montelukast and zafirlukast can also provide similar antiemetic potential, then clinical trials should be initiated since this class of drugs are relatively inexpensive than available effective antiemetic regimens against CINV.

Keywords: Cisplatin; Pranlukast; Least shrew; Palonosetron; Tropisetron; Emesis

Abbreviations

CINV: Chemotherapy-Induced Nausea and Vomiting; GIT: Gastrointestinal Tract; $5-HT_3R$: Serotonergic $5-HT_3$ Receptors; DVC: Dorsal Vagal Complex; NK_1R: Neurokinin NK_1 Receptors; SP: Substance P; NTS: Nucleus of the Solitary Tract; CysLT1: Cysteinyl Leukotriene 1; IP: Intraperitoneal; ERK1/2: Extracellular Signal-Regulated Protein Kinases 1 and 2; PKA: Protein Kinase A; PKCα/β II: Protein Kinase C Alpha/Beta II

Introduction

In this short review we briefly discuss: i) the progression of neurotransmitter hypothesis of chemotherapy-induced nausea and vomiting (CINV) and the current Status of clinically-relevant antiemetics for the prevention of CINV, ii) cost-effectiveness of antiemetics, and iii) introduction of pranlukast as an inexpensive new class of antiemetic for the prevention of CINV.

The neurotransmitter basis for chemotherapy-induced nausea and vomiting (CINV) and the current status of clinically-relevant antiemetics for the prevention of CINV

It is well recognized that cisplatin-like cytotoxic cancer chemotherapeutics evoke nausea and vomiting in cancer patients. The initial bout of vomiting occurs within a few hours of completion of intravenous administration of such chemotherapeutics to cancer patients and is referred to as the early- or acute-phase CINV [1]. This phase often subsides one day after the start of chemotherapy. Thereafter, a quiescent phase is observed where there can be little or no emesis as exemplified in the case of the least shrew animal model of emesis in the middle of Figure 1A and Figure 1B. Cancer patients will then experience additional bouts emesis, called the delayed-phase vomiting, which frequently starts from day three and can persist up to seven days post-treatment. Depending on the dose and route of administration, vomit-competent animals also exhibit both phases of CINV which can last from 2 (least shrews, see Figure 1) to 3 days (ferrets) post-cisplatin treatment [2-3]. Based upon the information obtained from animal models, the neurotransmitter basis of acute- and delayed-phases of CINV began in the late 1970s. Thus, initially it was proposed that the acute emesis is due to serotonin release from the enterochromaffin cells in the gastrointestinal tract (GIT), which will then stimulate the serotonergic $5-HT_3$ receptors ($5-HT_3R$) located on the GIT vagal afferent neurons leading to afferent signaling to the brainstem [4]. Subsequently, the brainstem emetic nuclei in the
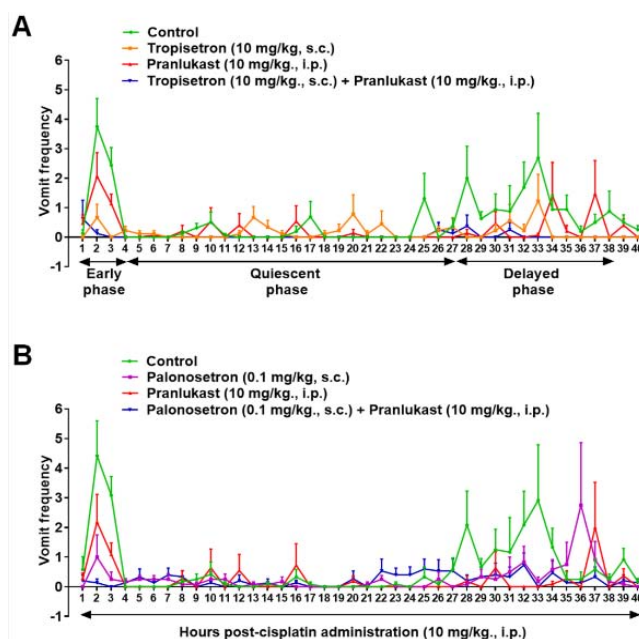
Figure 1: Antiemetic effects of the CysLT$_1$R antagonist, pranlukast, either alone or in combination with a first generation 5-HT$_3$R antagonist tropisetron, or a second generation 5-HT$_3$R antagonist palonosetron, on the mean frequency of vomiting per hour evoked by cisplatin. Different groups of least shrews were injected either with their corresponding vehicles (control groups), pranlukast (10mg/kg, i.p.), tropisetron (10mg/kg, s.c.) or palonosetron (0.1mg/kg, s.c.), or a combination of the said doses of pranlukast with tropisetron (Figure 1A), and pranlukast with palonosetron (Figure 1B) 30 min prior to cisplatin administration (10mg/kg, i.p.). Graphs A and B show the mean frequency of vomits (means ± S.E.M.) per hour over the 40-hour observation period.

dorsal vagal complex (DVC) are activated which evoke vomiting via vagal efferents. The delayed phase was thought to be due to activation of central neurokinin NK$_1$ receptors (NK$_1$R) subsequent to release of substance P (SP) in the medial nucleus of the solitary tract (NTS) in the DVC [4].

Nearly all cancer patients receiving large doses of cisplatin vomit. The above discussed emetic neurotransmitter dogma led to a renaissance in the development of new classes of prophylactic antiemetics (e.g. "the setrons") which replaced the various classes of dopamine D$_2$ receptor antagonists which were partially helpful in less than 30% of patients receiving chemotherapy [5]. Thus, introduction of the first generation 5-HT$_3$R antagonists (e.g. ondansetron, granisetron and dolasetron) in the clinic began in early 1990s for the treatment of early-phase CINV. The setrons are often combined with a glucocorticoid such as dexamethasone for their anti-inflammatory/antiemetic properties and the combination has been effective in 47–61% of patients receiving moderately or highly emetogenic chemotherapeutics (MEC and HEC, respectively) [6-8]. A decade later, the NK$_1$R antagonist aprepitant was introduced for reduction of delayed-phase vomiting [9]. The combination of the three discussed classes of antiemetics is often referred to as the "triple antiemetic regimen" and has revolutionized prophylactic antiemetic treatment in the clinic approaching 73-89% complete response rates [7,9]. Moreover, use of dexamethasone with longer-acting NK$_1$R antagonists such as netupitant or rolapitant combined with a first or second generation 5-HT$_3$R antagonist (e.g. palonosetron) can achieve a similar or greater clinical success against both phases of CINV [10-11]. Latest antiemetic data obtained from the least shrew [12] and ferret [3] animal models of CINV support the efficacy of these new antiemetics in the above discussed clinical settings.

Furthermore, recent basic and clinical findings argue against the aforementioned well-established neurotransmitter CINV dogma in that serotonin released from the GIT evokes the acute phase CINV, while release of SP in the brainstem accounts for the delayed phase. Based up on our findings from the least shrew [2] and latest published clinical data [13] encompassing the full cycle of CINV, we proposed a revision of this elegant yet simple CINV neurotransmitter hypothesis to include other emetic mediators and concomitant involvement of both central and peripheral anatomical loci for the mediation of both early and delayed emesis. Indeed, early- and delayed-phases of CINV require not only serotonin, but also SP to be concomitantly released in the GIT and brainstem, as well as simultaneous release of other emetic neurotransmitters (such as dopamine) and mediators including prostaglandins and leukotrienes [5]. In fact as discussed earlier, palonosetron, netupitant and rolapitant do attenuate both phases of CINV in patients [14-15] and animal models of CINV, but not completely [3,12].

Cost-effectiveness

Even though improved efficacy by newer antiemetics can reduce healthcare resource utilization, it comes at a high cost [16-17]. In addition, with all of the recent advances in prophylactic antiemetic therapy, a significant number of cancer patients as well as animals still experience CINV following treatment with large doses of cisplatin-like drugs [3,7,12]. The latter findings suggest involvement of additional emetic mediator's for induction of CINV. Thus, physicians should not only consider the choice of antiemetic regimen for cancer patients, but also the overall cost which can confound prophylactic antiemetic therapy since the price of newer drugs such as the palonosetron/netupitant oral preparation (Akynzeo), or rolapitant (Varubi), can approach $600 per capsule/tablet in the USA.

Thus, many patients in the USA and most people in the developing countries may not afford such prices. In fact a recent meta-analysis [18] considers the high cost of antiemetic regimen a factor in clinical decision making. Although the exact mechanism of antiemetic action of the discussed glucocorticoid dexamethasone (a very affordable drug) still remains unknown, this class of drugs is inexpensive and helps to attenuate CINV especially when combined with older setrons and NK_1R antagonists. It has been suggested that glucocorticoids' antiemetic efficacy could be due to their anti-inflammatory effects [19] probably via a reduction in the synthesis of prostaglandins and leukotrienes [20]. Although not all, but several prostaglandins (e.g. PGE2 and PGF2a) and cysteinyl leukotrienes (e.g. LTC_4 and LTD_4), appear to be potent emetogens [21-24]. Regarding LTC_4, the evoked vomiting was shown to be suppressed in a dose-dependent manner in the least shrew by the anti-asthmatic drug pranlukast [21]. Although not available in the USA, the cost of other members of this class of drugs (montelukast and Zafirlukast) that are sold in the USA is less than one dollar per pill. Based on pranlukast's efficacy against LTC_4-induced vomiting [21], we envisaged it may have potential utility against cisplatin-evoked emesis.

Antiemetic potential of pranlukast against cisplatin-evoked acute and delayed vomiting

We recently introduced a new class of antiemetic, the anti-asthmatic drug pranlukast, against cisplatin-evoked vomiting in the least shrew model of CINV [25]. Pranlukast along with montelukast and zafirlukast are cysteinyl leukotriene 1 (CysLT1) receptor antagonists, which are well-tolerated drugs and are used clinically for the treatment of respiratory diseases including chronic sinusitis, asthma and allergic rhinitis [26-27]. An intraperitoneal (i.p.) dose of 10mg/kg pranlukast by itself significantly reduced the mean frequency of vomits by 70% and fully protected 46% of least shrews during the delayed-phase of cisplatin (10mg/kg, i.p.) - evoked vomiting (Figure 1). Although pranlukast tended to substantially reduce both the mean frequency of vomits and the number of shrews vomiting during the early-phase, these reductions failed to attain significance. When pranlukast was combined with a first (tropisetron) - or a second (palonosetron)-generation 5-HT_3R antagonist, it potentiated their antiemetic efficacy during both acute- and delayed-phases of cisplatin-evoked vomiting (Figure 1A and Figure 1B). In fact per hour efficacy antiemetic profile of pranlukast combined with palonosetron or tropisetron during both phases of CINV in the least shrew resembles those of: i) the NK_1 receptor antagonist netupitant (5mg/kg) plus palonosetron (0.1mg/kg) in the same species [12]; ii) netupitant plus ondansetron in ferrets [3]; and iii) ondansetron plus aprepitant in combination with dexamethasone in ferrets [3]; and iv) palonosetron plus netupitant in combination with dexamethasone in ferrets [3].

For validation of intracellular emetic markers for CINV in the least shrew, we recently examined time-dependent activation/phosphorylation of extracellular signal-regulated protein kinases 1 and 2 (ERK1/2), protein kinase A (PKA) and protein kinase C alpha/beta II (PKCα/β II) in their brainstem at many time-points following cisplatin (10 mg/kg, i.p.) injection [12]. Cisplatin significantly elevated brainstem phospho-ERK1/2 levels at all time-points following cisplatin administration except at 40h post-cisplatin injection. PKA phosphorylation tended to be elevated throughout the delayed-phase, but a significant increase only occurred at the 33 h peak delayed-phase. Brainstem phospho-PKCα/β II levels were enhanced during acute-phase with a significant elevation occurring at the 2h peak immediate-phase. In corresponding behavioral studies, a combination of palonosetron (0.1mg/kg) and the NK_1 receptor antagonist netupitant (5mg/kg) suppressed cisplatin-evoked vomiting nearly completely during both acute- and delayed phases [12]. In the latter study, neither palonosetron, netupitant nor their combination had any significant effect on elevated phospho-ERK1/2 levels during peak acute emetic phase (i.e. 2h post-cisplatin treatment). This suggests additional mechanism is probably responsible for the evoked acute emesis. In our latest published study [25], administration of either palonosetron, tropisetron or pranlukast alone also failed to prevent cisplatin-evoked enhancement of ERK1/2 phosphorylation levels at the 2h peak acute-phase, but unlike the discussed case for netupitant/palonosetron combination [12], a regimen of pranlukast with either palonosetron or tropisetron did reverse ERK1/2 activation at the peak acute-phase [25]. Furthermore, neither palonosetron nor netupitant alone [12], nor tropisetron or palonosetron by themselves [25], could prevent cisplatin-evoked ERK1/2 activation during the 33h peak delayed-phase. Surprisingly, pranlukast pretreatment alone did prevent the evoked ERK1/2 activation during the 33h peak delayed-phase [25], and this suppression persisted even when pranlukast was combined with either palonosetron or tropisetron. On the other hand, netupitant could only prevent the latter effect when combined with palonosetron [12]. Thus, although both netupitant and pranlukast generally produce similar antiemetic profile against cisplatin-induced vomiting, their intracellular mechanism of action at the level of ERK1/2 phosphorylation differs.

Regarding cisplatin-evoked PKCα/β II phosphorylation observed at the 2h peak acute-phase, single pretreatment with either netupitant [12], palonosetron, tropisetron or pranlukast [25] failed to prevent the evoked activation. However, as was observed with netupitant plus palonosetron combination [12], pranlukast prevented the evoked increase in PKCα/β II phosphorylation when it was combined with either palonosetron or tropisetron [25]. Thus, in the latter phosphorylation event, both netupitant and pranlukast behave in a similar manner. In the case of cisplatin-induced PKA phosphorylation at the peak delayed emetic-phase, individual pretreatment with either netupitant [12], palonosetron or pranlukast [25] did prevent the evoked increase. Furthermore, a combination of netupitant plus palonosetron [12], or pranlukast combined with either tropisetron or palonosetron [25], did produce a similar inhibitory effect on the evoked PKA phosphorylation. Thus, the overall behavioral and intracellular signaling effects of pranlukast via blockade of CysLT1 receptors generally appear to be similar to the NK_1R antagonist netupitant with some differences.

Conclusion

We have introduced a new class of antiemetic pranlukast [25] for the suppression of delayed-phase of cisplatin evoked vomiting. When it is combined with a first or second generation 5-HT_3 receptor antagonist, it potentiates their antiemetic efficacy during both phases of CINV. Clinical potential of pranlukast and its analogs (montelukast, zafirlukast, etc) as a new class of antiemetic against CINV and other causes of vomiting requires initiation of clinical trials.

Acknowledgement

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