Summary

Nausea and vomiting are common adverse effects of therapeutic drugs. Such symptoms are more often due to CNS effects than to direct toxic effects on the gastrointestinal tract (GIT). Drugs may cross the blood-brain barrier and activate the chemoreceptor trigger zone in the brainstem, which contains cells that are responsive to cholinergic, dopaminergic and serotonergic stimulation.

Selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) are effective and well tolerated in the treatment of major affective disorders, but their usefulness is sometimes limited by adverse effects, particularly gastrointestinal effects. SSRIs exert their beneficial effects in depressive syndromes by increasing brain serotonin levels. They also increase serotonin levels in other tissues, particularly the GIT, which contains 90% of the body’s store of serotonin and large numbers of serotonin-responsive cells. Increased serotonergic neurotransmission causes anorexia, nausea, vomiting and diarrhea in other settings, such as carcinoid syndrome, so gastrointestinal adverse effects are not unexpected with drugs that increase tissue serotonin levels. SSRI-induced nausea and vomiting are probably due to effects on the GIT as well as on the CNS.
There are complex interactions between serotonin receptor subtypes. Drugs antagonising one receptor subtype may act as agonists at another receptor. The pharmacotherapy of SSRI-induced nausea and vomiting requires an understanding of the actions and interactions of these receptors and their agonists/antagonists. The most effective drug for the treatment of SSRI-related adverse effects on the GIT is ondansetron, a serotonin 5-HT3 receptor antagonist that blocks the effects of serotonin in the brain and GIT. However, this drug has a high acquisition cost. Thus, the drug of choice may be cisapride which, although a weak 5-HT3 receptor antagonist, has the potential to reduce or abolish SSRI-induced nausea. Many patients with mild adverse effects will not require specific pharmacotherapy, as the nausea tends to abate with prolonged treatment with SSRIs because of gradual desensitisation of 5-HT3 receptors.

1. Drugs and Vomiting

Drugs are common causes of nausea and vomiting. In general, drugs cause these symptoms by stimulating receptors in the chemoreceptor trigger zone of the area postrema, which is located in the floor of the fourth ventricle of the brainstem. The chemoreceptor trigger zone is a special sensory organ that contains dopaminergic (mainly D2), serotonergic (mainly 5-HT3), histaminergic (mainly H1), muscarinic and vasopressinergic receptors. The blood-brain barrier is deficient in the area postrema, so that chemicals, toxins and neurotransmitters have free access through fenestrated capillaries to parenchymal brainstem chemoreceptor cells.

The drugs most likely to cause nausea and vomiting include dopaminergic drugs such as levodopa and bromocriptine, opioid receptor agonists, digitals preparations and antineoplastic chemotherapeutic drugs. The opioidergic and dopaminergic drugs act at opioid (especially µ) and D2 receptors. The central effects of antineoplastic chemotherapeutic drugs are mediated by 5-HT3 receptors in the area postrema, but these drugs also have effects in the gastrointestinal tract (GIT). Digitalis exerts its emetic effects by stimulation of the area postrema. Toxic actions on the gastric mucosa by these drugs and other gastrotoxic agents, such as aspirin (acetylsalicylic acid) and alcohol (ethanol), stimulate vagal afferents to the area postrema serotonin receptors.

The last 15 years have seen great strides in the pharmacological treatment of CNS disorders such as depression and epilepsy, but these advances have not been without complications. Although recently released drugs are generally better tolerated than older preparations used to treat the same conditions, adverse effects do occur and may limit the effective use of these drugs. These limitations are exemplified by the selective serotonin reuptake inhibitors (SSRIs). The development of these drugs was at least partly driven by the high incidence of adverse effects associated with the use of older antidepressants, particularly the tricyclic antidepressants. However, nausea and vomiting are common adverse effects of the SSRIs, and may limit the use or prompt the discontinuation of these drugs. The serotonin receptors in the chemoreceptor trigger zone have assumed greater importance with the advent of antidepressant drugs which affect brain serotonin levels.

In this article we review the incidence of nausea and vomiting associated with SSRIs and discuss potential mechanisms by which these adverse effects may arise. These drugs are widely prescribed and are associated with a substantial incidence of gastrointestinal adverse effects. The management of these effects may benefit from a better understanding of their causes.

2. Physiology of Drug-Induced Vomiting

Vomiting is a complex physiological act which requires coordination of the actions of multiple muscle groups, both visceral and somatic. The