Guest Editorial

Postoperative nausea and vomiting: what about substance P antagonism? (or is it just another empty promise?)

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ABSTRACT
Nausea and vomiting are now considered to be ultimately mediated by a central common pathway. Neurokinin 1 (substance P) is the synaptic mediator at this level. Aprepitant is a substance P antagonist at neurokinin 1 receptors and is now available in North America for the prevention of postoperative nausea and vomiting. A basic summary is provided on the physiological and pharmacological basis of this agent.

Introduction
Postoperative nausea and vomiting (PONV) are still the most frequent side effects after general anaesthesia.\(^1\) Nearly one-third of postoperative patients will experience some degree of PONV during the first 24 hours after emergence. This incidence soars to around 70% for high-risk patients.\(^2\) It is therefore not surprising that, in a study by Macario et al., the majority of patients listed postoperative emesis as the most undesirable, and nausea as the fourth most undesirable of 10 proposed negative postoperative outcomes.\(^3\) The search for more effective agents (or techniques) to address PONV is continuing.

A promising development was the approval of aprepitant (EMEND®) by the USA Food and Drug Administration on 11 July 2006 for the prevention of PONV. Aprepitant is a substance P/neurokinin 1 (NK\(_1\)) receptor antagonist.\(^4\)

Neurokinins
A substantial multiplication in knowledge regarding the fast-acting neurokinins or tachykinins (TKs) has occurred since the discovery of substance P (SP) by Von Euler and Gaddum in 1931 as a hypotensive and spasmodogenic agent present in the equine brain and gut. In 1973, Erspamer and Melchiorri coined the term “tachykinin” to describe the fast development of contractile action in smooth muscle by SP and more recently discovered peptides, all having an identical C-terminal sequence of amino acids in common (Phe-Xaa-Gly-Leu-MetNH\(_2\)).\(^5\)

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\text{C}_{21}\text{H}_{22}\text{F},\text{N},\text{O},\text{F}_3
\]

The empirical formula of aprepitant is \(\text{C}_{25}\text{H}_{33}\text{F},\text{N},\text{O},\text{F}_5\). A much-simplified structural formula is: \[
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Chemical and physical properties
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The mechanism of action of aprepitant, although still not precisely defined, is thought to be substance P/neurokinin 1 antagonism in the central nervous system. The theory is that the final common pathway triggering PONV is mediated (or in part mediated) by NK\(_1\) receptor antagonism. Aprepitant had been used for some time in the prevention of nausea and emesis after cancer chemotherapy.\(^8\)

Operationally defined, the NK\(_1\) receptor reacts to the C-terminal sequence of TKs. This does not imply that SP is the exclusive activator of the NK\(_1\) receptor. Work by various groups (Tattersall and Gardner, Bountra) indicated that NK\(_1\) receptor antagonism produces an anti-emetic effect at a central site, suggesting the involvement of endogenous TKs in the emetic reflex pathway.\(^7\) The micturition reflex and pressor reflex to static contraction of skeletal muscle are also thought to be modulated by NK\(_1\) receptors at a spinal level. The peripheral nervous system effects of NK\(_1\) receptors are well known, namely vasodilation, augmentation of vascular permeability, stimulation of airway and salivary secretions and contraction of certain smooth muscle.\(^5\)

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The groundbreaking work by Lameck (1953) established the potential for SP to act as primary afferent neurotransmitter (involved in the signalling of painful and noxious impulses to the spinal cord). Peripherally-released SP accounts for antidromic and neurogenic vasodilation. Neurokinin A (NKA) and neurokinin B (NKB) were discovered in the mid-1980s, followed by the isolation of the genes encoding the mammalian TKs. TK receptor proteins were isolated soon after, followed by the development of a number of non-peptide TK receptor antagonists. Maggi et al. suggested in 1993 that an expectation exists for these antagonists to play a role in the treatment of human diseases in the future, owing to the putative importance of TKs in the pathophysiology of various events.\(^5\)

At a meeting in Montreal in 1986, interested parties produced an agreement on the nomenclature of TK receptors. Three distinct tachykinin receptors had already been described at that stage and named NK\(_1\), NK\(_2\), and NK\(_2\). The existence and known composition of these three distinct receptors accelerated the development of receptor-specific antagonists (peptides and non-peptides). The major effector system of all the NK receptors is considered to be stimulation of phosphoinositol (PI) breakdown.\(^6\) Tachykinin receptors can activate an array of effector systems in different tissue from the same specie.

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Clinical pharmacology

As highlighted above, aprepitant is a selective antagonist of human substance P or NK1, at the relevant receptor. No affinity (or very little) is exerted on the serotonin (5-HT3), dopamine and corticosteroid receptors. Aprepitant readily crosses the blood brain barrier to occupy the NK1 receptors to act as pure antagonist to substance P in the central nervous system.

The oral bioavailability of a 40 mg dose is not known, but at the dose range 80 to 125 mg the bioavailability is 60 to 65%. High fat-containing stomach content does not influence bioavailability. Aprepitant follows non-linear pharmacokinetics across the clinical dose range. More than 95% is bound to plasma proteins, with a mean volume of distribution at steady state (Vdss) of 70 litres. Aprepitant does cross the placenta in experimental animals.

Extensive metabolism occurs via liver microsomes, mainly CYP3A4. Oxidation at the morpholine ring and morpholine ring side-chains constitutes the main mechanism of metabolism. Seven weakly active metabolites of aprepitant have been identified in human plasma. Aprepitant is not renally excreted, although 57% of metabolites are eliminated renally. Apparent plasma clearance ranges from 62 to 90 ml/minute. Terminal half-life ranges from nine to 13 hours.

No clinically significant pharmacokinetic differences exist between males and females, different races or between 18 year olds and geriatric subjects. Sadly, no pharmacokinetic data is yet available in the paediatric population. No dose adjustments are necessary in patients with mild to moderate hepatic insufficiency. No clinical data are available in severe hepatic disease (Child-Pugh > 9). Dose adjustment is also not indicated in renal insufficiency or in patients on haemodialysis.

Clinical administration and efficacy

Two multicentre, randomised, double blind, parallel-group clinical studies compared the efficacy of aprepitant with ondansetron for the prevention of PONV (1 658 patients undergoing open abdominal surgery). The two studies were of similar design, but differed in study hypothesis, efficacy analysis and geographic location. Patients received aprepitant 40 mg, aprepitant 125 mg or ondansetron 4 mg. Aprepitant was given orally with 50 ml of water one to three hours pre-induction and ondansetron was given intravenously immediately before induction. One study concluded that aprepitant did not affect the time to first use of rescue medication when compared with ondansetron, but delayed the time to first vomiting. The second study failed to show proof that aprepitant is effective in reducing preoperative oral aprepitant 40 mg, compared with 64% of patients treated with ondansetron 4 mg intravenously at induction. The overall safety of aprepitant was evaluated in 4 400 patients. Most of the adverse effects of aprepitant reported in clinical trials evaluating the drug efficacy in the prevention of PONV were described as mild to moderate. Adverse effects were reported in 60% of patients receiving preoperative oral aprepitant 40 mg, compared with 64% of patients treated with ondansetron 4 mg intravenously at induction.

Interactions and contraindications

Aprepitant is a dose-dependent cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor and is therefore not indicated for usage with drugs utilizing this isoenzyme of cytochrome P450 for metabolism, e.g. pimozide, terfenadine, astemizole, cisapride. Concurrent usage of aprepitant with these drugs can precipitate life-threatening elevated plasma levels of these drugs.

Aprepitant significantly decreases the international normalised ratio (INR) of prothrombin in patients on chronic warfarin therapy, even after a single 40 mg dose. This effect is mediated through aprepitant induction of liver microsomal isoenzyme 2C9 (CYP2C9). The INR must be closely monitored for up to two weeks following such a single dose. Tolbutamide and phenytoin activity are also decreased due to the same effect. Oral hormonal contraception is reduced in effectiveness for at least one ovarian cycle after high doses (80 mg and more). A single contraceptive dose does not require a corticosteroid dose reduction.

PONV preventative dosage and administration

Aprepitant (EMEND®) has not been evaluated for the treatment of already established nausea and vomiting. Chronic usage is not recommended. The recommended dose for the prevention of PONV is 40 mg orally up to three hours prior to the induction of anaesthesia.

Conclusion

Aprepitant is a new agent and may find its way into the local anaesthetists’ armamentarium of already available pharmacological agents used to limit PONV. The availability of aprepitant for the anaesthetic setting in South Africa will be determined by MSD (the South African subsidiary of MERCK & Co., Inc., USA). The cost effectiveness of aprepitant will have to be evaluated locally and will determine the future of this drug in anaesthetic practice. The proof of the pudding will again be in the eating! Guest Editorial

References