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Potential of Substance P Antagonists as Antiemetics

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Abstract

The introduction of serotonin 5-HT_3 receptor antagonists into clinical practice allowed for a dramatic improvement in the management of nausea and vomiting. Despite this, postoperative and chemotherapy-induced emesis remains a significant, unresolved issue in many patients even when a combination of antiemetic drugs is used. Numerous neurotransmitters have been implicated in triggering emesis; however, the tachykinin substance P, by virtue of its localisation within both the gastrointestinal vagal afferent nerve fibres and brainstem emetic circuitry, and its ability to induce vomiting when administered intravenously, is thought to play a key role in emetic responses. Because substance P is the most likely endogenous ligand for the neurokinin-1 (NK_1) receptor, the development of nonpeptide NK_1 receptor antagonists led scientists to evaluate these compounds as antiemetics. The five NK_1 receptor inhibitors that have been studied initially in humans are: vofopitant (GR-205171), CP-122721, ezlopitant (CJ-11974), MK-869 (L-754030) and its prodrug L-758298. Except for monotherapy in acute cisplatin-induced emesis, this new class of drugs has proven to be highly effective in the control of both chemotherapy-induced nausea and vomiting, and postoperative nausea and vomiting. No major adverse event was reported in the preliminary trials. Further investigation is mandatory in order to assess the optimal treatment regimen and to make sure the wide spectrum activity of the NK_1 receptor inhibitors does not cause significant adverse effects in the context of the treatment of nausea and vomiting.

1. An Overview of the Critical Concepts in Antiemetic Research

From time immemorial, vomiting (or emesis) has been a major concern in the practice of human medicine. In various ancient civilisations, the induction of vomiting with emetics was even used as a therapeutic tool.[1] At the present time, vomiting is viewed not as a therapy but more usually as a distressing adverse effect associated with various medical practices. Vomiting, the culminating sign of nausea, is primarily a protective reflex occurring in a wide variety of vertebrates in response to the ingestion of a hazardous compound. However, in addition to this physiological response to the assimilation of toxins, vomiting can also occur in an extreme variety of circumstances which defy a simple description. In brief, emesis remains a critical problem during recovery from surgical procedures carried out under general anaesthesia, in anticipation of anticancer cytotoxic therapy (i.e. psychological vomiting), and in other circumstances involving motion and vestibular disturbances (e.g.

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Ménière disease). Lastly, vomiting can occur in natural circumstances where its benefits remain obscure (e.g. pregnancy sickness).

The essential co-ordinating circuitry for producing the complex act of vomiting (i.e. the ill-localised 'vomiting centre') is thought to be located within the medulla oblongata of the brainstem (fig. 1).[2] The numerous neurochemicals involved in that circuitry are not fully identified. The afferent systems triggering emesis release various neurotransmitters so that pharmacological agents exhibiting an effective antiemetic profile against one kind of vomiting can be ineffective against emesis induced by other stimuli. This is obvious in animal models of emesis, for which compounds acting as serotonin 5-HT_3 receptor antagonists exhibit potent antiemetic activity against acute chemotherapy-induced emesis but fail to block the emetic re-

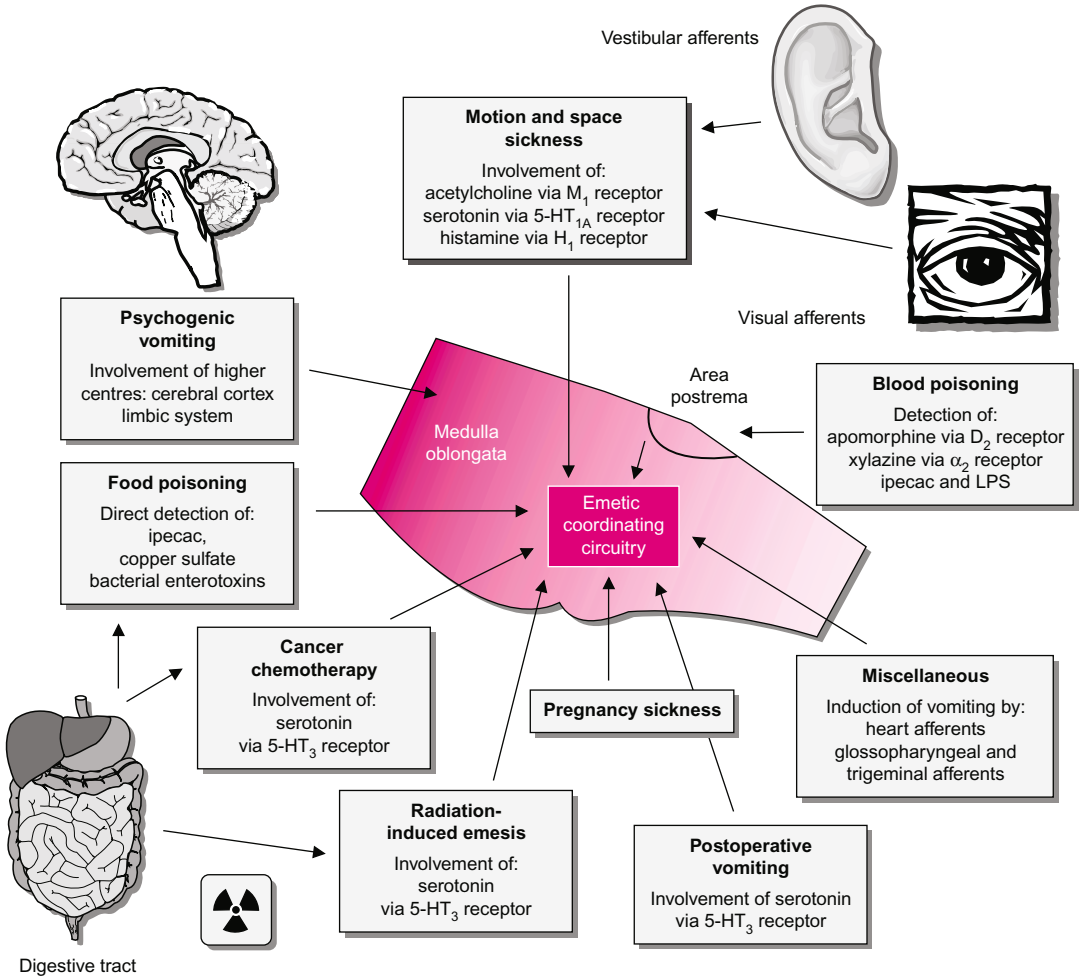

Fig. 1. Diagrammatic summary of different trigger inputs for vomiting. The emetic coordinating circuitry is located within the medulla oblongata of the brain stem. The area postrema is thought to contain a chemoreceptor trigger zone for vomiting. Neurotransmitters and receptor subtypes of major importance for eliciting vomiting are indicated for various inputs. **D_2** = dopamine type 2 receptor; **H_1** = histamine type 1 receptor; **LPS** = lipopolysaccharide; **M** = muscarinic cholinergic; **α2** = α adrenergic type 2 receptor; **5-HT** = 5-hydroxytryptamine (serotonin). Adapted from Grélot & Miller.[2]

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sponses to other emetogens such as opioid and dopaminergic agonists, copper sulfate or motion. In humans, the introduction of selective serotonin 5-HT_3 receptor antagonists has incontestably represented a major advance in the control of acute emesis associated with antineoplastic cytotoxic therapy. However, there are still areas in emesis control where further improvement would be desirable, e.g. motion sickness and delayed cisplatin-induced emesis.

An attractive strategy to block emesis irrespective of its eliciting stimulus would be to treat patients (or animals) with a pharmacological agent able to depress the activity of neurones within the medullary emetic circuitry. Recently, chemicals acting as partial (buspirone and ipsapirone) or full (8-OH-DPAT and SUN-8399) agonists of the 5-HT_{1A} receptor, have shown broad-spectrum antiemetic activities in several species without marked adverse effects.[3] Since tolerance to the antiemetic effects of 5-HT_{1A} receptor agonists did not develop rapidly, these compounds were expected to be clinically relevant. Unfortunately, most investigations in various animal models have shown that 5-HT_{1A} receptor agonists have comparatively weak antiemetic properties, particularly against cisplatin-induced emesis, so that their clinical development rapidly appeared to be jeopardised.

The pharmacological quest to develop a highly effective broad-spectrum antiemetic has led neuroscientists to investigate the role of neurotransmitter systems other than the serotonergic one and, in particular, the opioid system. Indeed, the neurotransmitter systems that opioid drugs modulate have been clearly implicated in emesis. In humans, morphine and related analgesic drugs, both of which are poorly selective opioid receptor agonists, have the potential to increase the incidence of postoperative nausea and vomiting. However, compounds such as fentanyl or sufentanil activating mainly the μ subtype of opioid receptors have demonstrated a potent and broad-spectrum antiemetic activity in various animal species.[4] Unfortunately, fentanyl enhances postoperative nausea and vomiting (PONV) in human patients suggesting that species-related differences exist in the way opioid receptors modulate the emetic reflex. Since it is currently still difficult to separate pharmacologically the antiemetic properties of opioid receptor agonists from other unwanted adverse effects (e.g. respiratory depression), clinically accessible opioid drugs (agonists and antagonists) cannot be considered as promising antiemetics.

Recently, special attention has been focused on the role of neuropeptides, such as tachykinins, since they have been immunohistologically identified in the dorsal vagal complex of the ferret, an area regarded as essential in eliciting vomiting. The emetic action of the tachykinin substance P (SP) was described by Carpenter et al.[5] Its putative role within the medullary emetic circuitry was first clearly pointed out by Andrews and Bhandari.[6] They demonstrated that resinferatoxin, an ultrapotent capsaicin analogue, exhibits antiemetic properties in the ferret against both a centrally acting emetic chemical (i.e. loperamide) and 2 peripherally acting agents (i.e. radiation and copper sulfate). Andrews and Bhandari[6] suggested that resinferatoxin exerts its potent antiemetic activity by depleting SP at a central site in the emetic pathway. In this context, the development of potent and highly selective non-peptide neurokinin-1 (NK_1) receptor antagonists, able to cross the blood-brain barrier to antagonise the central effects of SP, became crucial for providing powerful tools for investigating the physiological role of SP in emesis. More generally, there was also strong demand for the development of these compounds in several fields other than emesis, and the main indications foreseen for such drugs also include pain, migraine, rheumatoid arthritis, inflammatory bowel disease, asthma and chronic bronchitis.

2. The Tachykinins: Receptor Subtypes and Antagonists Relevant to Antiemetic Research

Tachykinins are members of a family of neuropeptides sharing the common C terminal sequence Phe-Xaa-Gly-Leu-MetNH_2. In the early 1970s, the term 'tachykinin' was invented by

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Ersparmer and Melchiorri,[7] to describe the rapid development of the contractile action produced by these peptides in smooth muscles. In mammals, the tachykinin family includes at least 6 chemicals, with the physiological effects of SP, neurokinin A (NK_A) and neurokinin B (NK_B) the most precisely characterised. These peptides exert a plethora of biological effects through 3 G-protein-coupled receptor subtypes, identified as NK_1, NK_2 and NK_3 receptors.[7] According to the 'Montreal nomenclature',[8] the NK_1 receptor is defined as the mediator of the biological activities encoded by the C terminal sequence of tachykinins, for which SP is a more potent agonist than NK_A or NK_B. Since SP is believed to play a key role within the central emetic circuitry, selective NK_1 receptor antagonists are expected to express potent antiemetic activity. A number of peptide-based NK_1 receptor antagonists with linear or cyclic sequences have been reported (e.g. spantide, L-668169; GR-82334; FR-113680; FK-224, etc.) but their inability to gain access to the CNS through the blood-brain barrier was thought to represent a limitation to a putative clinical use for the control of emesis. In 1991, following a thorough screening strategy, the first non-peptide NK_1 receptor antagonist was produced: CP-96345 ([(2S,3S)-cis-2-(diphenylmethyl)-N-[(2-methoxyphenyl)-methyl]-1-azabicyclo[2.2.2]-octan-3-amine]), and subsequently reported the series of piperidines exemplified by CP-99,994 [((2S,3S)-cis-3-(2-methoxybenzylamino)-2-phenylpiperidine)dihydrochloride].[9] Succeeding intensive chemical and pharmacological research conducted by all the major pharmaceutical companies led to the disclosure of a wide variety of non-peptide NK_1 receptor antagonists belonging to different chemical classes, i.e. piperidines, perhydroisoindolones, quinuclidines, tryptophane derivatives and steroids.[10] The most recently synthesised compounds are highly selective, exhibiting nanomolar or subnanomolar affinities for human NK_1 receptors expressed in various cells.

When comparing the pharmacological effects of various NK_1 receptor antagonists, it is essential to keep in mind that species-related differences exist in the primary sequence of the NK_1 receptor protein.[11] These variations, which do not affect the agonist efficacy, determine dramatic species-related variations in the potency of non-peptide antagonists. For instance, the prototypical NK_1 receptor antagonist CP-96345 binds with subnanomolar affinity to bovine brain, but it is 35-fold less active in displacing [^{3}H]SP binding to rat brain. Therefore, the antiemetic efficiency of a given compound in an animal model is not conclusively predictive of its potential in humans.

In addition, several factors can preclude a number of highly selective, potent NK_1 receptor antagonists from being of clinical utility. More precisely, some of these pharmacological agents have been reported to bind without any enantio selectivity with L-type Ca^{2+} channels irrespective of the species. For instance, CP-96345 has an equal affinity for Ca^{2+} channels and NK_1 receptors in the rat, so that many of the behavioural effects in that species might be due to the blockade of ion channels. Consequently, it is essential to be cautious in interpreting results with NK_1 receptor antagonists.[12] In addition, this implies that NK_1 compounds selected for clinical trials must exhibit the lowest 'non-specific' binding to Ca^{2+} channels to avoid severe cardiovascular adverse effects. Obviously, this point has been taken into account for chemicals administered during preliminary clinical trials, since CP-122721 ([(+)-(2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine]), a potent and noncompetitive antagonist, exhibits a high affinity for human NK_1 receptors but a moderate one for Ca^{2+} channels.[13] Similarly, vofopitant [GR-205171] ([2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]-(2S-phenyl-piperidin-3S-yl)amine), another compound tested in human patients, has a subnanomolar affinity to human NK_1 receptors [expressed in Chinese hamster ovary (CHO) cells], and it is at least 1000-fold selective with respect to non-tachykinin receptors and ion channels.[14] Finally, the affinity for the human NK_1 receptor of a third compound tested clinically: MK-869 [L-754030] ([2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)-phenylethoxy)-3(S)-(4fluoro)phenyl-4-(3-oxo-1,2,4-

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triazol-5-yl)methylmorpholine]), is similar to that of CP-122721 and that of vofopitant, whereas its affinity for the Ca^{2+} channel is negligible (i.e. IC_{50} >1 µmol/L).[15]

The final two requirements for the clinical development of a NK_1 receptor antagonist are the long-lasting efficacy and the oral biodisponibility of the compound. Thus, the poorly orally active phenylpiperidine CP-99994 was further chemically optimised but superseded in development by both CP-122721 and vofopitant.

3. Antiemetic Activity of NK_1 Receptor Antagonists in Animal Models

During the last 6 years, the antiemetic profiles of 16 compounds have been evaluated and fully described to our knowledge in 24 publications. The emetic challenges were conducted in the ferret, the house musk shrew (*Suncus murinus*), the cat, the dog, and more recently, the piglet, using 13 different emetogens (table I). The experimental procedures in these numerous studies presented such marked differences concerning the choice of the animal species, the way to elicit vomiting (i.e. with chemicals, motion, X-irradiation, electrical stimulation of afferent pathways), and the nature, the dose, the route and timing of administration of the different NK_1 receptor antagonists, that a detailed description of the results would be tedious. However, the common conclusion brought forward in these studies was that NK_1 receptor antagonists displayed an unprecedentedly potent, and usually

Table I. Neurokinin-1 (NK_1) receptor antagonists with proved potent anti-emetic activities in animals against various emetogens

NK_1 receptor antagonists (route of administration)	Animal species	Emetogens	Reference
CP-99994 (SC,IP,IV)	Ferret, shrew[a], dog, cat	a+d-CDDP, $CuSO_4$, cyclophosphamide, ipecac, morphine, apomorphine, irradiation, nicotine, loperamide, ethanol, motion, vagal stimulation[b]	16-25
CP-122721	Ferret	a-CDDP, $CuSO_4$, ipecac, loperamide	26
GR-203040 (SC,IV)	Ferret, shrew[a], dog	a-CDDP, $CuSO_4$, cyclophosphamide, ipecac, morphine, irradiation	20,27
Vofopitant [GR-205171] (SC,IV)	Ferret, shrew[a], dog, piglet	a+d-CDDP, irradiation, vagal stimulation[b]	14, 28-31
L-741671 (IV,ICV)	Ferret	a-CDDP	32
L-742694 (IV)	Ferret	a-CDDP	20
L-743310 (ICV)	Ferret	a-CDDP	32
MK-869 [L-754030] (IV,po)	Ferret	a-CDDP, morphine, apomorphine	15
RP-67580 (IP)	Shrew	Nicotine	23
CI-1021 [PD-154075] (IP)	Ferret	a+d-CDDP	33
Dapitant [RPR-100893] (IV)	Ferret	a-CDDP	20
HSP-117 (ICV)	Ferret	CuSO4, morphine	34
Nolpitantium [SR-140333] (ICV)	Piglet	a-CDDP	Grélot et al., unpublished observations
Sendide (SC)	Ferret	a-CDDP	35

a House musk shrew (*Suncus murinus*).

b Electrical stimulation of the abdominal vagus nerves.

a+d-CDDP = acute and delayed cisplatin-induced vomiting; **$CuSO_4$** = copper sulfate; **ICV** = intracerebroventricular; **IP** = intraperitoneal; **IV** = intravenous; **po** = by mouth; **SC** = subcutaneous.

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long-lasting, high antiemetic activity. This high level of efficacy was observed irrespective of the route of administration (i.e. oral, subcutaneous, intraperitoneal, intravenous, intracerebroventricular), with drugs able to penetrate the CNS.

A concise history of the major results leading to the clinical development of the NK_1 receptor antagonists as antiemetics is summarised in this section.

The idea that these compounds could represent a new class of therapeutic agents for the treatment of emesis was first published by Bountra and coworkers in 1993.[16] In this study, CP-99994 was used against 5 different emetogens [cisplatin (CDDP), copper sulfate, cyclophosphamide, morphine and radiation] and showed exceptional antiemetic properties. Using the ferret model, they showed that intraperitoneal administration of CP-99994 (racemic) 3 mg/kg reduced the total number of retches induced by morphine (0.5 mg/kg, subcutaneously, 3-hour trial) and cyclophosphamide (200 mg/kg, intraperitoneally, 7-hour trial) by 84 and 96%, respectively. The effectiveness of CP-99994 against the other emetogens ranged between these 2 observations. Tattersall et al.,[21] confirmed these results soon after, and demonstrated that the nearly complete control of the acute emetic response to cisplatin (10 mg/kg, intraperitoneally) achieved in the ferret with (+)CP-99994 (3 mg/kg intravenously) was most likely the result of a stereospecific blockade of NK_1 receptors, since CP-100263 (i.e. the inactive enantiomer) was totally ineffective at the same dose. Subsequently, the optimised chemicals GR-203040,[27] CP-122721,[26] and then vofopitant,[36] have proven to have more potent antiemetic potential than CP-99994. In the ferret, CP-122721 (0.3 or 1 mg/kg, subcutaneously) abolished the emetic response to copper sulfate, loperamide, ipecac syrup and cisplatin. In fact, this chemical antagonised the acute emetic response to cisplatin during a 2-hour trial with an inhibitory dose (ID_{50}) of 0.03 mg/kg.

The long-lasting antiemetic effects of NK_1 receptor antagonists were first reported by Gardner et al.[36] Indeed, vofopitant (0.3 mg/kg, subcutaneously) promptly abolished cisplatin-induced emesis for a 4-hour period, and then, minimal emesis occurred during the subsequent 20-hour period. A similar observation was made in the piglet, in which a single administration of vofopitant (1 mg/kg, intravenously) reduced by 91 and 86%, respectively, the number of emetic events produced during the acute and delayed phases of cisplatin-induced emesis.[29] Moreover, a 1 mg/kg dose administered at the transition between the acute and delayed phases abolished the delayed emetic response to cisplatin for at least 44 hours.[29] In that species, the long-lasting antiemetic effect of vofopitant was surprising, since a pharmacokinetic study revealed that vofopitant (1 mg/kg, intravenously) has a fairly short plasma half-life (3.4 ± 0.8 hours).[29] The ability to achieve a sustained blockade of central tachykinin NK_1 receptors in the absence of high plasma drug concentrations *in vivo* was also reported in a pain model (i.e. in the formalin paw test) in the gerbil with L-733060.[37] This might suggest that these two NK_1 receptor antagonists are rapidly distributed to their sites of action from where there are slowly eliminated. This property is advantageous since it strongly limits the occurrence of unwanted nonspecific effects in peripheral tissues (e.g. blockade of Ca^{2+} channels) associated with high plasma concentrations of the drugs.

In animal models, several NK_1 receptor antagonists displayed a potent activity against vomiting elicited by some emetogens which are still difficult to control in human patients. Thus, CP-99994, CI-1021 (PD-154075) and vofopitant, provided a satisfactory control of the delayed emetic response to cisplatin in both the piglet and ferret.[19,24,25,29,33] The ultra-potent efficacy against both acute and delayed cisplatin-induced emesis has been clearly evidenced in the laboratory of one of the authors (Dr Grélot). Comparison with results from our previously published and unpublished studies performed on more than 600 piglets demonstrated that vofopitant has the highest ratio of antiemetic activity/dose of any compound ever tested in our experimental model (i.e. cisplatin-induced emesis).[38]

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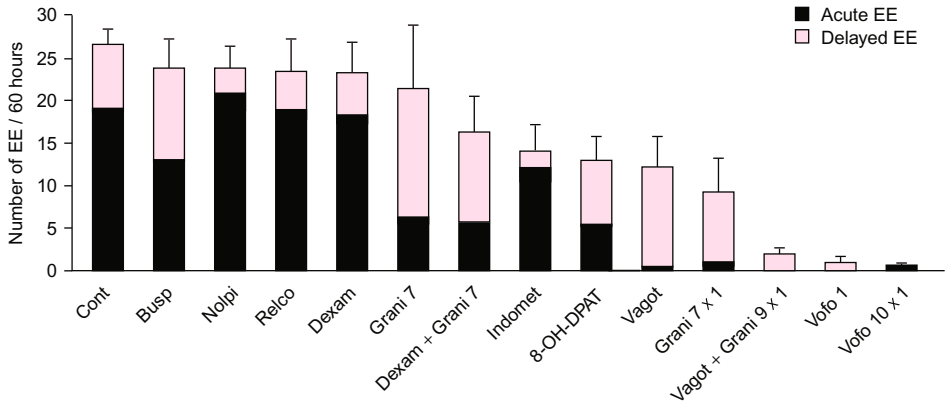

Fig. 2. Antiemetic properties of various pharmacological treatments and surgical procedures in piglets receiving a single high dose of cisplatin [CDDP, intravenously (IV), 5.5 mg/kg ≈125 mg/m^2], and then observed continuously for 60 hours (details in Milano et al.[38]). From left to right: control (**Cont**) animals (n = 35); buspirone (**Busp**), a 5-HT$_{1A}$ receptor agonist, 15 mg/kg 15 minutes before CDDP (n = 7); nolpitantium (**Nolpi**) [SR-140333], a selective tachykinin NK$_1$ receptor antagonist, 3 mg/kg 15 minutes before CDDP (n = 8); relcovaptan (**Relco**) [SR-49059], a selective vasopressin V$_{1a}$ receptor antagonist, 3 mg/kg 15 minutes before CDDP (n = 7); dexamethasone (**Dexam**), a corticosteroid, 20mg 15 minutes before CDDP, and 10mg 12 and 36 hours after CDDP (n = 7); granisetron 7 mg/kg (**Grani 7**), a selective 5-HT$_3$ receptor antagonist, 15 minutes before CDDP (n = 7); dexamethasone 20mg 15 minutes before CDDP, and 10mg 12 and 36 hours after CDDP plus granisetron 7 mg/kg 15 minutes before CDDP (**Dexam + Grani 7**) [n = 7]; indomethacin (**Indomet**), a cyclo-oxygenase inhibitor, 10 mg/kg 1 hour before CDDP, and then 15 and 39 hours after CDDP (n = 7); **8-OH-DPAT**, a selective 5-HT$_{1A}$ receptor agonist, 1 mg/kg 15 minutes before CDDP (n = 7); bilateral cervical vagotomy (**Vagot**) performed 3 to 4 days before CDDP (n = 6); granisetron 1 mg/kg given every 5 hours during the first 30 hours post-CDDP (**Grani 7 × 1**) [n = 7]; cervical bivagotomy plus granisetron 1 mg/kg given every 5 hours from the 15th to the 60th hour post-CDDP (**Vagot + Granis 9 × 1**) [n = 6]; vofopitant (**Vofo 1**) [GR-205171], a selective tachykinin NK$_1$ receptor antagonist, 1 mg/kg 15 minutes before CDDP (n = 13); vofopitant 1 mg/kg given every 6 hours throughout the 60 hours observation period (**Vofo 10 × 1**) [n = 5]. The line above each bar indicates the standard error of the mean (SEM) of the cumulative (acute + delayed) severity of the emetic crisis. The highest control of emesis was achieved by using the NK$_1$ receptor antagonist vofopitant. Note that nolpitantium was totally ineffective, probably because of poor penetration in the CNS. Results from Milano et al.[38] Grélot et al.,[29,39] and personal unpublished observations. **EE** = emetic events.

This is demonstrated clearly in figure 2. The clinical potential of NK$_1$ receptor antagonists can also be extended to provocative motion (CP-99994),[18,24,25] GR-203040,[27] postanaesthesia-induced emesis (vofopitant),[40] and ethanol-induced vomiting (CP-99994).[17] Finally, in addition to the antiemetic effect, tachykinin NK$_1$ receptor antagonists may have potential in the treatment of drug-induced conditioned aversive behaviour and nausea.[29,41]

4. Putative Site of Action of NK$_1$ Receptor Antagonists

As mentioned in section 1, the putative involvement of SP within the central emetic circuitry was proposed by Andrews and Bhandari,[6] on the basis of the emetic action of resinferatoxin in ferrets. This was confirmed by Matsuki et al.,[42] and Shiroshita et al.,[43] who demonstrated that the capsaicin analogue (subcutaneous in *S. murinus* and intracerebroventricular in the dog) first induced transient emesis or retching, and then blocked these emetic responses to radiation and copper sulfate, and afferent vagal electrical stimulation, respectively. In a converging point of view, the broad-spectrum antiemetic profile of the NK$_1$ receptor antagonists suggests that they might act principally at central sites. This assertion has been conclusively supported by studies demonstrating that peptide-based potent NK$_1$ receptor antagonists (i.e. GR-82334, sendide, spantide, and FK-888), unable to block vomiting when administered intravenously, appear much more effective when injected by an intracerebrovascular route.[20,36,44] Similarly, nolpitant-

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ium (SR-140333), a highly selective nonpeptide compound, inactive at the dose of 3 mg/kg (intravenously) against the acute emetic response to cisplatin in both ferrets[20] and piglets, reduced this response by 90% in the latter species when applied centrally (1.5mg, intracerebrovascularly) [Grélot et al., unpublished observation].

It is very strongly suspected that the nucleus tractus solitarius (NTS) neurons lying ventrally to the area postrema in the so-called subnucleus gelatinosus trigger the emetic act.[2] This medullary area is a converging site for projections arising from the area postrema, and the vestibular and vagal afferents.[45] NTS is a good candidate for the site of action of NK_1 receptor antagonists. Extensive SP-like immunoreactivity has been identified in this region and the tachykinins have been proposed as transmitters in vagal afferents.[46-48] Using *in vitro* autoradiography, Watson et al.[25] showed that the high density [^{3}H]-SP binding in the NTS was displaced by CP-99994. Similarly, recent positron emission tomography (PET) studies in rhesus monkeys have demonstrated that peripherally administered ^{11}C-labelled vofopitant has a distribution into brain regions consistent with specific binding to NK_1 receptors.[49] Injection of CP-99994, L-741671 or MK-869 (30µg) into the vicinity of the NTS inhibited cisplatin-induced emesis in the ferret.[32] Moreover, the SP-induced discharge of action potentials of single NTS neurons recorded in slices of ferret brain stem is inhibited by HSP-117, an NK_1 receptor antagonist with potent antiemetic activity.[34] Altogether, these results suggest, but do not demonstrate, that NK_1 receptor antagonists exert their main antiemetic action by depressing the neural activity of NTS neurons, i.e. within the central emetic circuitry.

However, a possible contribution from peripheral sites to this potent antiemetic effect should not be ignored. Indeed, sendide (3 mg/kg, intravenously), a peptide-based drug, is active against cisplatin-induced emesis in the ferret probably via a gastrointestinal tract site of action.[35] The proposed mechanism underlying this effect might involve a blockade of the NK_1 receptors located on vagal terminals in the gut. This would decrease the intensity of the emetic afferent message to the medullary emetic circuitry.[35] In that view, the peripheral effect of NK_1 receptor antagonists might resemble that of the 5-HT_3 receptor antagonists on the serotonergic activation of vagal terminals. However, this hypothesis remains to be demonstrated since the possibility of a nonspecific interaction of sendide on 5-HT_3 receptors or Ca^{2+} channels located on vagal terminals was not investigated.

5. Antiemetic Activity of NK_1 Receptor Antagonists: Clinical Studies

In humans as well as in animals, the number of transmitters involved in the emetic process accounts for the incomplete efficacy of single drug therapies for nausea and vomiting of various aetiologies.

Maybe because of their central role on a potential, final common pathway, NK_1 receptor antagonists have offered a broader spectrum antiemetic activity than 5-HT_3 receptor antagonists, dopamine receptor antagonists, anticholinergic agents or corticosteroids. It seems likely that, as was observed for pain management,[50] combining medications from different classes may optimise the efficacy of NK_1 receptor antagonists for the treatment of nausea and vomiting.

Data from the first published clinical studies seem to confirm the usefulness of this new class of drugs in humans. Investigations have been carried out in two types of indications: cancer chemotherapy-induced nausea and vomiting (CINV) and PONV.

The 5 investigational drugs studied so far are: vofopitant, CP-122721, ezlopitant (CJ-11974), MK-869 and its prodrug L-758298.

Vofopitant is a potent and selective NK_1 receptor antagonist with high affinity for the human NK_1 receptor and potent antiemetic activity in various animal models of emesis. It is a high clearance compound (979 to 1821 $ml \cdot min^{-1}$) with a large volume of distribution (412 to 888L) and a moderately long elimination half-life of 5 to 8 hours in patients.[51] Ezlopitant is a selective NK_1 receptor

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antagonist with a Ki of 0.4 nmol/L, which proved highly active in the ferret model of emesis. MK-869 a trisubstituted morpholin acetal, is a selective NK_1 receptor antagonist also very active in animal models. MK-869, has been studied in humans directly and after administration of its prodrug L-758298.[52,53]

5.1 Chemotherapy-Induced Nausea and Vomiting

Five preliminary studies have dealt with the prevention of acute and/or delayed CINV after high dose cisplatin in patients with cancer. Four of these studies were double-blind, randomised studies and one was open labelled. Three were dose-ranging studies (table II).

Despite the small numbers of patients included in the trials, the design allowed comparison between arms consisting, respectively, of either a placebo, a NK_1 receptor antagonist, a 5-HT_3 antagonist, the combination of a 5-HT_3 antagonist plus dexamethasone, or a NK_1 receptor antagonist with a 5-HT_3 antagonist plus dexamethasone.

One study compared a NK_1 receptor antagonist alone (L-758298) with ondansetron alone, and another compared a NK_1 receptor antagonist alone (vofopitant) with its combination with ondansetron. In another report, the NK_1 receptor antagonist alone (CP-122721) was compared with its combination with ondansetron plus dexamethasone. The two remaining protocols were placebo-controlled comparisons of a usual regimen of granisetron plus dexamethasone with this regimen combined with a NK_1 receptor antagonist (ezlopitant or MK-869) administered according to various regimens.

In the study arms where a NK_1 receptor antagonist was administered alone, it proved either ineffective or not superior to ondansetron for the control of acute CINV after high doses of cisplatin. Fumoleau et al.[54] reported on the lack of efficacy of intravenous vofopitant 5 or 25mg when given as a single antiemetic to prevent acute (24 hours) CINV after cisplatin treatment (≥80 mg/m^2). However, this study group consisted of only 4 patients. Conversely, Van Belle et al.,[58] found that L-758298, 60 or 100mg intravenously, was almost as effective as ondansetron 32mg for the prevention of first day CINV. The percentages of complete responders (no emetic episode and no escape medication) and major responders (1 or 2 emetic episodes and no escape medication) were 37 and 17%, respectively, with L-758298 (failure rate: 47%), and 48 and 9%, respectively, in the ondansetron group (failure rate: 44%). Although not favourable to L-758298, these figures look more encouraging than those observed during the first 24 hours in the short series of Fumoleau et al.[54] with vofopitant. One possible explanation for this discrepancy may be the lower dose of cisplatin in the Van Belle et al.[58] series (≥50 mg/m^2). In one early study by Kris et al.,[56] CP-122721 alone (50 to 200mg single oral dose) allowed 15% of the patients to be free from acute emesis.

Except for these results in acute CINV, the NK_1 receptor antagonists have shown dramatic antiemetic activity in cisplatin-treated patients with cancer. This is true for the prevention of acute CINV in association with a 5-HT_3 receptor antagonist or with a 5-HT_3 receptor antagonist plus dexamethasone, and also for the prevention of delayed CINV (days 2 to 5 or 7) either when used as monotherapy prophylaxis or in combination regimens.

In a study by Fumoleau et al.,[54] intravenous vofopitant 25mg plus ondansetron 8mg provided complete control of acute emesis in all patients and absence of nausea in 4 out of 5. Acute emesis was also absent in 100% of patients receiving CP-122721 with ondansetron plus dexamethasone.[56] In the work by Hesketh et al.,[52] the rate of no acute emesis was increased from 66.8 to 85.7% when oral ezlopitant 100mg twice daily was administered in combination with granisetron and dexamethasone. However, this difference did not reach statistical significance. The well-designed 3-arm study published by Navari et al.[53] showed that the combination of MK-869 with a preventive regimen of granisetron plus dexamethasone provided a 93% no acute emesis rate which was statistically different from the 67% observed in the group receiving placebo plus the 2 conventional drugs.

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Table II. Summary of the preliminary clinical studies of NK_1 receptor antagonists as antiemetics in humans

Type of study	Type of emesis	NK_1 receptor antagonist	No. of participants	Additional agents	Outcomes	Reference
MC, DB, R, P	Prevention of acute CINV after cisplatin ≥80 mg/m^2	Vofopitant 5mg or 25mg IV	4/16	None	Ineffective at 24h	54
		Vofopitant 5mg IV	7/16	Ondansetron 8mg IV	No emesis: 5/7 at 24h and no nausea: 2/7 at 24h	
		Vofopitant 25mg IV	5/16	Ondansetron 8mg IV	No emesis: 5/5 at 24h and no nausea: 4/5 at 24h	
MC, DB, R, PC	Treatment of established PONV after gynaecological surgery	Vofopitant 25mg IV	36	None	Vofopitant ≥ to PC for complete control of emesis and nausea	55
Open label, P	Prevention of acute and delayed CINV after cisplatin ≥80 mg/m^2	CP-122721 200mg po	17	None (7/17)	15% no acute emesis and 86% no delayed emesis	56
				Ondansetron + dexamethasone (10/17)	100% no acute emesis and 80% no delayed emesis	
DB, R	Prevention of PONV after gynaecological surgery	None	22/68	Ondansetron 4mg IV	No differences for nausea scores but less emetic episodes in groups treated with CP-122,721	57
		CP-122721 200mg po	22/68	None		
		CP-122721 200mg po	24/68	Ondansetron 4mg IV		
MC, DB, R, P, PC	Prevention of acute and delayed CINV after cisplatin ≥100 mg/m^2	Ezlopitant 100mg po twice a day, 5 days or PC	61	Granisetron 10 µg/kg IV + dexamethasone 20mg IV	No emesis on day 1: 85.7% (p = 0.090 *vs* PC) No emesis days 2 to 5: 67.8% (p = 0.042 *vs* PC)	52
MC, DB, R, PC	Prevention of acute and delayed CINV after cisplatin ≥70 mg/m^2	MK-869 400mg po before cisplatin and 300mg on days 2 to 5	54	Granisetron 10 µg/kg IV + dexamethasone 20mg orally before cisplatin	No emesis on day 1: 93% (p < 0.001 *vs* PC) No emesis days 2 to 5: 82% (p < 0.001 *vs* PC)	53
		MK-869 400mg po before cisplatin and PC on days 2 to 5	54		No emesis on day 1: 93% (p < 0.001 *vs* PC) No emesis days 2 to 5: 78% (p < 0.001 *vs* PC)	
		None	51		No emesis on day 1: 67% No emesis days 2 to 5: 33%	
MC, DB, R	Prevention of acute and delayed CINV after cisplatin ≥50 mg/m^2	L-758298 60mg or 100mg IV before cisplatin	30	None	L-758 298 is almost as effective as ondansetron in acute emesis (day 1), and superior to ondansetron against delayed emesis (days 2 to 7)	
		None	23	Ondansetron 32mg IV before cisplatin		58

CINV = chemotherapy-induced nausea and vomiting; **DB** = double-blind; **IV** = intravenous; **MC** = multicentre; **P** = preliminary; **PC** = placebo controlled; **po** = by mouth; **PONV** = postoperative nausea and vomiting; **R** = randomised.

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As far as delayed emesis is concerned, a favourable profile of the NK_1, receptor antagonists has been shown for CP-122721 and for L-758298 when used alone; and for CP-122721, ezlopitant and MK-869 when used in combination regimens.

In the short series by Kris et al.,[56] a single prophylactic dose of CP-122721 allowed prevention of delayed vomiting in 6 of 7 patients (86%), while the combination with a $5\text{-}HT_3$ receptor antagonist and dexamethasone produced this result in 8 of 10 patients (80%).

L-758298 alone proved significantly superior to ondansetron alone in the prevention of vomiting and nausea on days 2 to 7 after cisplatin administration.[58]

When administered in combination with granisetron and dexamethasone over 5 days, oral ezlopitant 100mg twice daily allowed 67.8% of the patients to remain with no emesis during days 2 to 5 ($p = 0.042$ compared with 36.6% observed with placebo).[52]

The study by Navari et al.[53] confirmed the results with MK-869 seen in acute CINV for delayed emesis. Prevention of delayed emesis (days 2 to 5) was best achieved when MK-869 was administered either on day 1 or on days 1 to 5 in combination with granisetron and dexamethasone ($p < 0.001$ versus placebo). This regimen also brought significantly higher satisfaction scores when compared with placebo ($p = 0.001$) and this result on a non-surrogate end-point certainly deserves to be emphasised. The study suggests a benefit with continuation of MK-869 treatment beyond the first day and through the entire chemotherapy cycle, but this needs to be investigated further.

5.2 Postoperative Nausea and Vomiting

So far, 2 studies of NK_1 receptor antagonists in the prevention or treatment of established PONV have been published (table II).

Comparing oral CP-122721 200mg with intravenous ondansetron 4mg and with the combination of the 2 agents in the prevention of PONV, Gesztesi et al.[57] found no differences for postoperative nausea scores among the 3 groups but a significantly lower incidence of emetic episodes when CP-122721 was part of the prophylactic regimen. The combination of CP-122721 and ondansetron provided no additional benefit.

In a placebo-controlled study in the setting of established PONV, Diemunsch et al.[55] showed intravenous vofopitant 25mg as a single agent to be superior to placebo for complete control of emesis and nausea. This benefit was maintained throughout the entire 24-hour study period. The percentage of patients requiring rescue medication during the 24 hours after drug administration was also less after treatment with vofopitant (61 *vs* 83% after placebo).

5.3 Safety

The safety and tolerability of the NK_1 receptor antagonists in humans has never been a concern in the clinical studies discussed in this section, and all the investigational drugs were well tolerated in all patients, with no drug-related toxicity. This was true for the clinically observed effects and for the measured laboratory parameters. No adverse events were reported that would preclude further clinical studies of NK_1 receptor antagonists.

Despite the implication of SP in pain mechanisms, no obvious effects on pain threshold or on analgesia were observed in the human PONV studies. This is in contrast to the results of the study by Dionne et al.,[59] showing that the NK_1 receptor antagonist CP-99994 was effective in pain reduction after third molar extraction.

Other potential indications of the NK_1 receptor antagonists include asthma, anxiety, arthritis, migraine, schizophrenia, glaucoma as well as ocular hypotension, neural injury and stroke. It is so far unknown whether the doses required to treat CINV and PONV may provoke adverse effects related to this wide spectrum activity.

6. Conclusion

Major improvement in the treatment of nausea and vomiting has been achieved with the advent of $5\text{-}HT_3$ receptor antagonists. This class of drugs has become the gold standard in the management of

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both CINV and PONV,[60] whereas motion sickness is still resistant to the setrons. Despite these advances, and although combination therapy with other classes of antiemetics have further improved results, nausea and vomiting still remain a significant problem, notably in cancer chemotherapy and after surgery, where these symptoms can prove most distressing. The recent introduction of the NK_1 receptor antagonists seems promising firstly on a theoretical basis, since these drugs act on a target in the emesis mechanism which has not yet been exploited; secondly, on a preclinical basis, since NK_1 receptor antagonists showed excellent results in various animal models of emesis; and finally if one considers the preliminary human data published so far. Interestingly, as in the case of the $5\text{-}HT_3$ receptor antagonists, no major concern about safety has been raised after the initial human trials. Much work is still needed in order to consolidate these results and to answer questions concerning the optimal dose, the optimal schedule and duration of treatment, and the optimal antiemetic drug combinations with the NK_1 receptor antagonists. Occurrence of other foreseeable effects of this class of drugs should also be controlled for in large scale trials.

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