LEADING ARTICLE

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Anti-Emetics for Cancer Chemotherapy–Induced Emesis

Potential of Alternative Delivery Systems

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Abstract

Currently, the most commonly used routes of administration of antiemetics in chemotherapeutic regimens are oral and intravenous. Patient compliance and thus efficacy of conventional drug schedules and formulations are often impaired by difficulties associated with oral or intravenous uptake of the administered chemotherapy. Alternative or new drug delivery systems should overcome these problems by improving patient compliance.

Several new drug delivery systems are available and development of these new systems is ongoing, in particular to meet delivery requirements of modern biological therapeutics and the application of gene therapy. However, at the present time, the implementation of new techniques of alternative antiemetic drug administration for chemotherapy-induced emesis is very limited. The challenge for clinical investigations to further develop new delivery systems, in particular for antiemetic therapies, remains.

Most patients receiving chemotherapy experience numerous adverse effects. Chemotherapy-related toxicities and/or most distressing aspects are emesis and myelosuppression. Additional chemotherapy-induced adverse effects are, for example, oral mucositis, cardiotoxicity, neurotoxicity and nausea. The administration of combination chemotherapy regimens as well as the increased dose intensity of many regimens has increased the occurence of chemotherapy-induced emesis dramatically. During the last decade, knowledge in neuropharmacology of the emetic pathways has provided new insights into pathophysiological processes in patients with cancer receiving chemo- and radiotherapy.[1] Moreover, significant progress has been made in recent years in providing more effective and better tolerated drugs in order to prevent or reduce nausea and vomiting caused by cancer therapy.[2]

Antiemetics play an important role in the quality of life of a patient during and after chemotherapy, since adequate control of the debilitating adverse effects during the medical treatment of cancer patients does increase their compliance with therapy. Studies have demonstrated that the fear of nausea and vomiting is a primary concern of cancer patients.[3] The fear of chemotherapy-induced nausea and vomiting can be extreme, that is, causing patients to delay or even to refuse potentially curative or beneficial anticancer therapy.

It is crucial that physicians and nursing staff do provide patients with convenient and effective antiemetic medication in order to control one of the most debilitating adverse effects of chemotherapy. Despite the breakthroughs with new antiemetic

medication, emesis remains a major concern to patients being exposed to anticancer drugs and to repeated cycles of chemotherapy, in particular, concerning delayed and anticipatory emesis.[4,5] Apart from the development of new antiemetic agents, there is also a major focus on potential benefits from so-called alternative drug delivery systems to improve prevention and treatment of emesis and nausea, and, also, compliance with therapy. In this review, we attempt to provide a short overview of alternative drug supply techniques which may become available in daily clinical and outpatient practice.

1. Conventional Routes of Administration and Formulations

Expert panels have provided antiemetic guidelines with treatment recommendations based on literature reviews.[4,6,7] The most important factors in predicting the risks of emesis are the intrinsic emetogenicity of the chemotherapeutic agent and patient factors. Recommendations with regard to chemotherapy-induced emesis are provided for acute, delayed and anticipatory emesis.

These guidelines do not provide many details concerning the route of administration of antiemetics. Choosing biologically equivalent doses, antiemetics might be applied as oral or as intravenous medication, respectively. Several clinical trials have compared the oral route with the intravenous administration of various serotonin (5-hydroxytryptamine; 5-HT) 5-HT_3 receptor antagonists, in particular, granisetron and ondansetron. These studies have shown similar efficacy for both routes of administration.[8-11] Other studies only evaluated the efficacy and safety of either the oral or intravenous formulation, respectively, but the results are comparable to each other.[12,13]

With regard to oral syrup often administered to paediatric patients, studies comparing oral ondansetron syrup and intravenous ondansetron have also concluded that the different formulations have similar efficacy and safety.[14,15]

Normally, these conventional formulations have a good safety profile, and are effective and well tolerated; in addition, the pharmacokinetic profiles of these drugs are satisfactory. The co-medicated antiemetics used in chemotherapeutic regimens share a low adverse effect profile (most commonly reported events e.g. for 5-HT_3 receptor antagonists are headaches, transient transaminase elevation, constipation; other drugs such as metoclopramide are associated with extrapyramidal symptoms). Usually, antiemetic medication is given once daily or once prior to chemotherapy. Oral antiemetics are preferable to intravenous antiemetics because of lower costs and greater convenience for patients.[4,16,17]

1.1 Disadvantages of Current Systems

The question arises, is there a need for alternative drug delivery systems? The potential disadvantages of the oral administration of antiemetics are many and can be as general as an aversion to tablets or capsules as with other medicaments. For psychological reasons, some cancer patients do refuse oral medication. In addition, decreased bioavailability of oral formulations is a problem in patients with diarrhoea, malabsorption problems or gastrointestinal ulceration, for example. Many patients undergoing high-dose chemotherapy have severe oral mucositis which prevents the administration of oral medication because they have difficulty in swallowing and are unable to drink.

The intravenous route of administration is more time-consuming and requires additional physician or nursing time. There are disadvantages relating to this as antiemetic therapy is often used on an outpatient basis. Intravenously administered drugs are inconvenient for patients as they require additional care of catheter devices, port-a-cath etc. Moreover, costs for infusions are usually higher than those for oral formulations of the same drug.

Suppositories, which are also thought to be a conventional formulation, may overcome some of these disadvantages. However, using rectal application can be associated with differing and also with lower absorption rates.[18] In addition, it is often either impractical for or even unacceptable to patients. This antiemetic drug delivery system is

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not recommended for chemotherapeutics of high or medium emetic risk. Nevertheless, there are, for example, some studies comparing ondansetron suppositories with the intravenous and oral administration for the prevention of emesis with cyclophosphamide- or cisplatin-based chemotherapy.[19-21] The authors draw the conclusion that the different antiemetic treatments might be regarded as equivalent, that is, ondansetron suppository is a efficient, well tolerated and a suitable alternative to using the intravenous or oral formulation.

There is less concern with conventional formulations with regard to drug delivery-related problems, that is, bioavailability, absorption etc., since altering the disintegration or dissolution rates of tablets/capsules in the gastrointestinal tract by modifying the coating, the excipients, granulation procedures, and particle size is routine work for pharmacists. Pharmacokinetic profiles of antiemetics and their galenic preparations are also of minor concern with oral or intravenous administration in patients receiving cancer chemotherapy.

The major concerns of the most commonly used routes of administration and formulations of antiemetics are those associated with convenience, compliance, chemotherapy-related adverse effects (e.g. mucositis), and also costs.

2. Potential of Alternative Routes of Administration and Formulations

The major challenges for drug delivery are specifying drug dose, targeting the drug to a specific site, overcoming degradation and metabolism of the drug administered, and also of patient compliance. Alternative drug delivery systems are being developed to further improve existing systems (including, for example, oral, parenteral, topical, rectal) in order to make drugs safer, more effective, less expensive and more convenient. These technologies also aim to avoid the use of injections or oral administration. Pharmacologists are also attempting to target specific organs, sites in organs or even specific cells, for example, tumour cells. Apart from alternative routes of administration (e.g. transdermal, intranasal, oral-transmucosal, pulmonary), research is also focused on alternative formulations such as syrups, liposomes, polymer-based systems, needle-free injections by high-velocity powder injection, controlled-release systems, rapid dissolution/disintegrating systems and microencapsulation.

These techniques might be more convenient and therefore enhance compliance. Doses of drugs can be reduced with non-oral alternatives, since hepatic first-pass metabolism is avoided. When all these factors are considered, alternative drug delivery systems exhibit promising therapeutic perspectives.

2.1 Transdermal Route

The administration of therapeutic agents through the skin in order to achieve systemic effect is termed 'transdermal drug delivery'.[22,23] This method circumvents several of the disadvantages of conventional oral formulations mentioned in section 1. However, only certain drugs have appropriate physico-chemical properties to be suitable for transdermal delivery, since the skin generally represents a barrier for drug transport. In order to increase the number of agents for transdermal administration, penetration enhancement technology using chemicals, ultrasound (phonopheresis) or electric current (iontopheresis) is mandatory to enhance permeation through the skin.[24] Depending on the properties of a drug and the disease to be treated, certain plasma levels are required within or over a certain time period.

At present, only a few drugs are available as transdermal patches (e.g. nitroglycerin for angina pectoris, oestradiol for oestrogen replacement therapy, clonidine for hypertension). Scopolamine has been available as a transdermal patch for many years. However, this compound is mainly used in patients experiencing motion sickness, and not in preventing or treating chemotherapy-induced emesis. There are reports of transdermal scopolamine application for the prevention of nausea and vomiting in surgery. In a study with 40 patients undergoing minor gynaecological surgery, transdermal scopolamine as a premedication was statistically

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superior to transdermal placebo with respect to antiemetic response.[25] Transdermal scopolamine also proved to be a useful prophylaxis against nausea and vomiting in 60 patients [American Society for Anaesthesiology (ASA) class I-II] after middle ear surgery (10% of patients experienced nausea and vomiting in both classes compared with 27% and 43%, respectively, in the placebo group).[26] However, this application is also controversial since another placebo-controlled study with 263 surgical and gynaecological patients demonstrated no significant effect of transdermal scopolamine on postoperative nausea and only marginal benefit with regard to postoperative vomiting.[27]

Another compound available transdermally is fentanyl, which is primarily used as an analgesic, although its potential as an antiemetic agent has been examined. A study was performed comparing transdermal fentanyl with standard antiemetic treatment in patients with cancer receiving high-dose cisplatin.[28] Fifteen patients with advanced stage head and neck squamous cell carcinoma entered the study and were assigned to the two alternative treatment arms (group 1: intravenous ondansetron plus intravenous dexamethasone, 7 patients; group 2: transdermal fentanyl plus intravenous dexamethasone, 8 patients). In the prevention of acute nausea and vomiting, the overall efficacy of the standard antiemetic regimen (group 1) was significantly higher than that of transdermal fentanyl plus dexamethasone in achieving complete and major response, respectively. There was a trend in favour of standard antiemetic treatment, for delayed nausea and vomiting. In summary, the authors concluded that the currently available standard antiemetic regimens both for acute and delayed emesis appear to be more effective than the potential clinical alternative regimen using transdermal fentanyl.

In vitro studies have been performed to assess skin permeation profiles of various antiemetics (alizapride, bromopride, clebopride, domperidone, metoclopramide, metopimazine) in order to evaluate and predict their potential for therapeutic formulation in transdermal delivery systems.[29,30] The authors determined the permeation parameters (transdermal permeability rate constant, lag time, flux) as a measure of the intrinsic permeability of these drugs across the skin of hairless rats as a membrane. These investigations showed clebopride to be the most suitable candidate for formulation in transdermal delivery systems. In addition, there is a patent for clebopride transdermal patch which was granted in 1989/1990 in several European countries, Japan and the US (e.g. US 4,978,531). However, there are no hints in the literature of comparative clinical studies using transdermal patches with any of these antiemetics. In 1999, a patent providing a transdermal drug delivery composition with lerisetron, a new 5-HT_3 receptor antagonist under investigation as an antiemetic agent, was applied for.[31] At present, there does not seem to be any clinical use of this device in patients with cancer.

The systemic transdermal delivery of metoclopramide has been investigated using an iontophoresis technique.[32] Since this kind of metoclopramide application might lead to erythema and oedema, hydrocortisone was codelivered by the same transdermal route to avoid local irritations. Whether this more or less sophisticated drug delivery system is convenient and useful in clinical practice or in an outpatient setting is not known at present.

In this context, it needs to be considered that corticosteroids are often comedicated with antiemetics to improve the antiemetic response rates in patients undergoing chemotherapy.[4] With a non-compliant patient, it would not make sense if an antiemetic could be administered transdermally for the corticosteroid to have to be delivered orally or intravenously. For this drug class, systemic delivery could be achieved by the same alternative delivery systems as for antiemetics.[33-35]

2.2 Intranasal Route

Intransasal drug delivery is commonly used for the treatment of local diseases, for example, colds and rhinitis. Yet efforts have been made in recent years to also use this route for systemic drug supply[36] and to study nasal pathology to evaluate fac-

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tors influencing absorption and bioavailability.[37,38] Some nasal delivery systems are already marketed, in particular, for peptide hormones [for example, luteinizing hormone releasing factor (gonadorelin), oxytocin, insulin, glucagon, growth hormone releasing hormone etc.].[39]

This easy-to-use technique may also be useful for antiemetics. In the 1980s, pharmacological and pharmacokinetic studies first evaluated the intranasal application of metoclopramide.[40] Clinical trials followed suggesting that metoclopramide nasal spray is an effective, well-tolerated, easy-to-use and low-cost therapeutic alternative to parenteral injections for the prophylaxis and treatment of emesis.[41,42] In a recent review summarising several clinical trials,[43] intranasal metoclopramide showed similar efficacy to the intramuscular or intravenous formulation in patients receiving moderately emetogenic chemotherapy. However, the evaluation of intranasal metoclopramide in preventing postoperative nausea and vomiting provided less favourable results of this formulation.[44] Meanwhile, intranasal metoclopramide is commercially available in the US and several European countries for prevention and treatment of chemotherapy-induced emesis, particularly delayed emesis. This well tolerated formulation may be attributed with greater convenience and a better compliance in (out)patients.

Efforts have also been made to study intranasal delivery of the important 5-HT_3 receptor antagonists. Results of a comparative investigation of ondansetron administered intranasally and intravenously to rats showed that the drug was readily and rapidly absorbed through the nasal mucosa. The peak plasma concentration was attained within 10 minutes of delivering the dose into the nasal cavity and plasma concentrations were comparable to those achieved with the intravenous route.[45] The authors conclude that the nasal administration route for ondansetron is as effective as the intravenous one. The oral bioavailability of ondansetron ranges from 57 to 69%, whereas nasal ondansetron was completely absorbed in the animal model allowing more or less instant systemic circulation. This might be useful in clinical practice because oral formulations need to be given to patients at least 30 minutes before chemotherapy. Time saving and better compliance might be expected benefits if intranasal ondansetron should be approved by drug authorities.

2.3 Oral and Oral-Transmucosal Route

As already mentioned the oral uptake of drugs can and may cause many problems, and so many patients, particularly paediatric and geriatric patients, do not take their medication as prescribed resulting in ineffective therapy. A novel formulation has been developed for patients having difficulties swallowing or who are unable to intake fluids. This is a fast dissolving dosage form[46] and ondansetron is available in this formulation as a freeze-dried, strawberry-flavoured tablet. This formulation disintegrates instantaneously, releasing the drug which dissolves in the saliva. The clinical efficacy of the orally disintegrating formulation of ondansetron has been studied in a large multicentre trial of 427 patients with cancer receiving cyclophosphamide chemotherapy and was as equally effective as conventional ondansetron tablets.[47] The novel ondansetron formulation provides greater choice and flexibility in the management of patients with vomiting and nausea.

There are other similar applications and variations in this field of fast-dissolving oral drug delivery. For example, there are techniques for sublingual and buccal transmucosal absorption and faster onset of action.

Transmucosal antiemetic administration appears to be very advantageous for patients receiving chemotherapy. This is supported by a randomised study performed between 1987 and 1988 in patients with vestibular disorders (often accompanied with nausea and vomiting) receiving either oral or buccal prochlorperazine (an phenothiazine antiemetic agent). The buccal preparation achieved a significantly faster onset of effect than the oral formulation ($p = 0.04$), and was significantly better in reducing the frequency of nausea ($p = 0.02$) and severity of vomiting ($p = 0.05$) at 24 to 36 hours.

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Buccal prochlorperazine proved to be a well-tolerated and effective medication, and was well rated by both patients and investigators.[48] This buccal tablet is normally placed between the gingival surface of the jaw and the buccal mucosa. It swells by water absorption to produce a soft hydrated tablet which can be retained in position to provide prolonged and controlled release of the drug by diffusion for up to two hours. However, when considering highly emetogenic protocols, rapid buccal absorption of suitable antiemetics in adequate doses would be mandatory.

More alternative delivery systems are also conceivable but they lack practical application for antiemetics. Pharmaceutical companies developed platforms using polymer technologies as vehicles for local or systemic drug delivery. For example, biopolymers which adhere to a solid surface (e.g. tooth) and are dissolved in saliva. They are designed to release the active agents within minutes or up to several hours acting locally or being absorbed by the buccal mucosa. Apparently, products in preclinical development also include therapies for emesis, but further information is not yet available. In addition, permeabilisers are often required to overcome the epithelial barriers of the mucosa.[49]

2.4 Pulmonary Route

The interest in pulmonary drug delivery is steadily rising because of promising advances in aerosol techniques and delivery devices, despite shortcomings still existing.[50] Pulmonary drug administration might also be an alternative for patients who desire alternatives to conventional tablets and injections.[51] Antiemetic inhalables for systemic administration, if they become available, may well lead to better disease management.

In this context, the antiemetic properties of cannibinoids, that is, tetrahydrocannabinol (THC), should be remembered. This includes its natural and synthetic derivatives, and marijuana itself. As shown in controlled studies, cannabinoids reduce chemotherapy-induced emesis. However, the degree of efficacy is not high compared with metoclopramide, for instance. Nevertheless, cannabinoids may be useful and effective in patients responding poorly to current standard antiemetic therapy. Since the onset of drug effect is much faster with inhaled THC or marijuana than it is for oral delivery, some patients might benefit from inhalation of cannabinoids. Such patients should be evaluated on a case by case basis and treated under close medical supervision.[52-58]

2.5 Other Techniques/Formulations

An emerging area of interest is liposomal technology using lipid envelopes to encapsulate a therapeutic agent. Liposomes can be advantageous in enhancing absorption (transdermal,[59] intranasal[60]) or to target the drug to selected tissues by appropriate modifications mediated either by passive or active mechanisms. Thus, the potential toxicity from the encapsulated agent is reduced and accumulation in nondesired sites might be avoided. Current applications involve chemotherapeutics and antiinfectives, but not antiemetics as yet.

The use of a patient-controlled pump for continuous infusion of antiemetics has proven successful in facilitating outpatient administration of high-dose chemotherapy. The need for hospitalisation for treatment of nausea and vomiting was significantly reduced or even abolished in one study.[61] As technical equipment is required in this delivery system for outpatients, there may be disadvantages in terms of convenience and perhaps also costs compared with drug schedules using transdermal patches or intranasal sprays.

3. Paediatric Issues

In general, the antiemetic recommendations for adults are also reasonable for paediatric patients (with doses adjusted) with the exception of dopamine receptor antagonists, which are not considered good choices for children receiving chemotherapy.[4] Novel or alternative methods and routes of antiemetic drug administration may be a particular benefit for children.

However, it is vital that physicians understand the pharmacology of administered drugs, and the

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Table I. The advantages and disadvantages of alternative routes of antiemetic drug administration

Route	Pros	Cons
Oral	Standard; most antiemetic drugs available as oral formulations; low cost; easy-to-use; fast-dissolve techniques available; useful for outpatients	Impractical or even unfeasible in patients with mucositis, impaired GI absorption, diarrhoea, severe vomiting; psychological reasons (aversion against oral drugs)
Intravenous	Standard; precise dosage control; immediate plasma concentrations; highly effective; avoids first-pass elimination	Time-consuming; additional care and close supervision; self-administration hardly possible; sometimes painful administration; high level of compliance necessary
Rectal	Easy-to-use; useful for outpatients	Differing resorption rates, that is, irregular uptake for different reasons; impractical with some categories of patients
Transdermal	Easy-to-use; high compliance; avoids first-pass elimination; long-acting preparations and stable blood drug concentrations feasible; perhaps especially useful for delayed emesis; useful for outpatients	Limited drug uptake due to physico-chemical properties requiring additional penetration enhancement technology; for high-dose chemotherapies rapid absorption/high doses are mandatory requiring special techniques, if feasible at all; problems of skin sensitivity
Intranasal	Easy-to-use; avoids first-pass elimination; rapid absorption and instant systemic circulation possible; useful for outpatients	Special techniques necessary; risk of systemic adverse effects; not useful in patients with severe cognitive failure
Oral-transmucosal	Easy-to-use; avoids first-pass elimination; useful for outpatients	Special techniques necessary to ensure fast dissolution and absorption; not useful in patients with severe cognitive failure
Pulmonary	Avoids first-pass elimination; rapid absorption and instant systemic circulation possible	Special aerosol techniques necessary; not useful in patients with severe cognitive failure

GI = gastrointestinal.

pharmacodynamic and pharmacokinetic implications that might be unique for paediatric patients.[18] For instance, the pharmacokinetics of transdermal drug delivery systems are influenced by the blood supply and thickness of skin which is higher and thinner, respectively, in children. This is advantageous in some situations, while in others, systemic toxicity might result. There are reports, for example, on toxic effects of scopolamine patches administered to children to treat motion sickness or to prevent nausea and vomiting. Because of excessive uptake through the skin and rubbing of the patch on the eye, mydriasis occurred which was mistaken for an intracranial catastrophe in some patients.[62]

Many children object to intranasal drug application because of the discomfort of this mode and, if the drug is unpalatable, the unpleasant taste in the posterior pharynx. For significant drug absorption across the oral mucosa, the drug must normally be exposed for a prolonged time to the mucosal surface. Taste of the drug is one of the major factors to influence contact time with the mucosa. Moreover, drug absorption is generally increased when the drug is exposed to the buccal or oral mucosa compared with the tongue and gingiva. Therefore, children need to be very compliant for effective administration of this route.

In summary, the care of paediatric patients requires controlled laboratory and clinical trials to determine the safest and most effective use of medications administered by alternative routes.

4. Conclusions

Considering some of the disadvantages of conventional formulations and administration routes, novel or alternative techniques for the administration of antiemetics in clinical and outpatient practice are still limited. There is a need for better alternatives for drug delivery as this would enhance

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compliance and improve medical care. Alternative routes of administration and formulations are feasible both from a pharmacological and technical point-of-view (table I).

Novel ways of administering medication have been encouraged, in particular, by the so-called 'biotechnology explosion'. This has not only lead to new drug discovery technology and therapeutics, but also to new and better drug delivery systems, in particular, those used for peptide or macromolecule and gene therapy delivery.[63] Improvements and implementation in this area will probably also influence low-molecular drugs like antiemetics.

At present, research seems to be more focused on new antiemetic drugs, such as the neurokinin-1 receptor antagonists, rather than new delivery systems.[5,64-66] However, problems associated with conventional administration and formulations will persist.

For patients receiving chemotherapy the optimisation of antiemetic therapy in terms of safety of administration, efficacy, cost, convenience and compliance remains a subject of intense clinical research.

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