ONDANSETRON

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Nausea and vomiting associated with chemotherapy can be severe and may persist for several days after treat ment(1). Chemotherapy induced emesis adversely affects patients quality of life. Patients rate nausea and vomiting as the most distressing side effects of cancer treatment(2). It is estimated that these symptoms can result in 25-50% of patients delaying one or more scheduled courses of therapy or even refusing further treatment(3).

Advances were made in understanding of the emetic reflex. It was reported that the efficacy of metoclopramide used as an anti-emetic could be improved by increasing the dose(4). Metoclopramide is a dopamine (D2) receptor antagonist(5) and it was seen that metoclopramide also antagonized 5 HT3 receptor with a much lower affinity(6). These observations, and others from clinical studies with ondansetron in migraine patients, prompted investigation of ondansetron as a selective 5-HT3 receptor antagonist as an anti-emetic.

Physical Characteristics

It is a white crystalline powder and the chemical name is 1,2,3,9 - tetra hydro-9 methyl 3-(E 2 methylimidazole-1 methyl) carbazol-4-one, hydrochloride dihydrate. The molecular formula is C18 H_{19}NOHCL, $2H_2O$ and the molecular weight is 365.8 Daltons. The laboratory code is GR 38032 F (hydrochloride dihydrate).

Mechanism of Action

Action of Ondensetron on 5 HT Receptors

Ondansetron is a potent, highly selective 5 HT3, receptor-antagonist. It's precise mode of action in the control of vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5 HT in small intestine initiating a vomiting reflex by retarding vagal afferents via 5 HT3 receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause release of 5HT in the area postrema, located on the floor of the IV ventricle and this may also promote emesis through a central mechanism(7). Thus the effect of ondansetron in the management of nausea and vomiting induced by cyotoxic chemotherapy and radiotherapy is probably due to antagonism of 5 HT3 receptors on neurons located both in the peripheral and central nervous system. The mechanism of action in post operative nausea and vomiting are not known. However, there may

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be a common pathway with cyotoxic induced nausea and vomiting. In psycho-motor testing, ondansetron does not alter plasma prolacin correlation.

Pharmacokinetics and Metabolism(8)

In normal human volunteers it was shown that following a oral dosing the peak plasma value was at around 1.5 hours with a maximum plasma concentration of about 30 ng/ml, and thereafter plasma concentration falls in a parallel fashion to intravenous dose. It has a terminal eliminitation half-life of about 3 hours and a steady state volume of distribution of about 140 cc. The plasma protein binding is 70-76%. Ondansetron is cleared from the systemic circulation predominantly by metabolism. The absolute oral bioavailability of ondansetron to man is 59%. Less than 10% of parent drug is recovered unchanged in the urine; the major metabolites are glucuronide conjugates (45%) and sulphate conjugates (20%). Hydrox-ylation products N-demethylation products. (10%) while unidentified products account for 15%. Clearance of ondansetron is significantly reduced and half-life is significantly prolonged in patients with moderate or severe impairment of hepatic failure(9). In such patients, a total daily dose of 8 mg should not be exceeded.

Formulations

Ondansetron is available in India as 4 mg and 8 mg film coated tablets under the brand name zofer (Natcopharm. Ltd) and as injectable ampoules containing 2 mg of ondansetron/ml. Each 4ml (8mg) ampoule costs Rs. 40.00 and a 5 day course of ondansetron tablets (10 tablets) costs Rs. 40.00. The other brand available in India is Emeset (Cipla Ltd). Each 4 ml ampoule contains 8 mg of ondansetron. The cost is Rs. 40 per ampoule.

Storage and Precautions

Ondansetron injection warrants storage below 30°C and protection from light. No other special storage conditions are necessary. Ondansetron injection should not be administered in the same syringe or infusion as any other medication. Ondansetron injection ampoules are not to be autoclaved. Ondansetron tablets should be stored below 30°C.

Therapeutic Uses

(a) *Radiotherapy Induced Emesis:* Radiotheapy produces emesis when the epigastric region or upper abdomen are treated or when these areas are irradiated during total body irradiation. Irradiation of the limbs, head does not seen to stimulate emesis. The amount of emesis is related to the amount of radiation being greater when large volumes of tissues are irradiated or when high doses are given. Adult patients are more susceptible than children(10).

(b) Chemotherapy Induced Emesis: Although not all patients receiving chemo therapy will experience nausea and vomiting, it has been estimated that it occurs in upto 70% of patients(ll). There are several predictive factors that have to be taken into account when assessing the likelihood of occurrence of nausea and vomiting; some are related to patient characteristics, but by far the important factor is the chemotherapy they will be receiving. There is a wide range in the emetic potential of chemotherapeutic drugs(12). The range varies from

high dose cisplatin which causes emesis in almost all patients to weak emetogens, such as the vinca alkaloids (vincristine and vinblastine). The dose, schedule and route of administration of these drugs also influences their potential to cause emesis. Cytotoxic agents are usually given in combination, which may result in increased emesis. The potentials of commonly used chemotherapeutic agents to induce emesis is summarized in *Table I.*

Dosage in Children

Ondansetron is administered as a single IV dose of 6 mg/m^2 immediately before chemotherapy followed by 4 mg orally after 12 hours. Subsequently, 4 mg orally, is given twice daily for 5 days to prevent delayed emesis.

Side Effects

The following side—effects can occur: headache, a sensation of flushing or warmth in the head and epigastrium, and occasional transient, asymptomatic increases in aminotrahsferases. Ondansetron is known to increase large bowel transit time and may cause constipation in some patients. There have been rare reports of immediate hypersensitivity reactions sometimes severe. Rare cases of transient visual disturbances (e.g., blurred vision) and dizziness have been reported during rapid intravenous administration of ondansetron. There has been rare reports suggestive of involuntary movement disorders without definitive evidence of persistent clinical sequelae.

Use in Pregnant and Nursing Mothers

Ondansetron is not teratogenic in animals. There is no experience in humans. As with other medicine, ondansetron should not be used during pregnancy,

TABLE I—*Potential of Commonly Used Chemotherapy Agents to Induce Emesis*

High potential	Moderate potential	Low potential
Cisplatin	Cytarabine	Etoposide
Decarbazine	Procarbazine	Mitomycin C
Dactinomycin	Cyclophosphamide	Methotrexate
Mechlorethamine	Carboplatin	5-Fluorouracil
	Anthracyclines	Hydroxyurea
	Nitrosoureas	Bleomycin
		Vinblastine
		Vincristine
		Chlorambucil
		Melphalan
		Busulphan
		Teniposide

Adapted from Howden *et al.*(9).

especially during the first trimester, unless the expected benefit to the patient is thought to outweigh any possible risk to the fetus.

Lactation

Ondansetron is excreted in the breast milk of rats, mothers receiving ondansetron should not breastfeed their babies.

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