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Tropisetron (ICS 205-930): A Selective 5-Hydroxytryptamine Antagonist

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INTRODUCTION

OVER THE last decade, the control of vomiting caused by anticancer drugs has improved substantially. 10 years ago, no therapy was available to control the emesis caused by high-dose cisplatin (120 mg/m^2). The average patient vomited a median of 10.5 times during the first 24 h after therapy [1]. In contrast, using currently available combination antiemetic programs developed through an intensive worldwide effort of clinical research, 63% of individuals now given the same dose of cisplatin have no vomiting whatsoever [2]. Moreover, these combination programs have become easier to give and have lessened other side-effects of therapy such as diarrhoea and restlessness. Despite these developments, however, control is not complete in a significant minority of patients and some fail to benefit.

During the 1980s, the role of the neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) was extensively investigated. These studies have led to the development of several potent and highly specific compounds that interact with several different serotonin receptors [3]. Because of their specificity, these compounds have further improved our understanding of the role of serotonin in both the central and peripheral nervous system [4]. Tropisetron [1H]-Indol-3-carbonic-acid-tropine ester hydrochloride (ICS 205-930; Fig. 1) is a specific antagonist of the 5-HT$_3$ receptor (formerly called the M-receptor) developed by Richardson *et al.* through systematic methyl substitutions of the serotonin molecule [5]. This compound was found to block 5-HT$_3$ receptors on peripheral neurons [5]. Further investigation revealed the presence of 5-HT$_3$ receptors in rat brain tissue and demonstrated the ability of tropisetron to also block 5-HT$_3$ activity at that site [6]. Following the observation that tropisetron could enhance *caudad* directed gastrointestinal motility by Buchheit *et al.* [7], Costall *et al.* theorised that the compound might prevent the retroperistalsis caused by cisplatin [8]. Using the ferret model of cisplatin-induced emesis, Costall *et al.* demonstrated that tropisetron could prevent emesis in the ferret caused by 10 mg/kg of cisplatin at doses of 0.1 mg/kg and 1.0 mg/kg intravenously [8]. A dose of tropisetron of 0.01 mg/kg lessened but did not prevent vomiting. Moreover, tropisetron proved to be one of the most potent compounds tested to prevent cisplatin-induced emesis in the ferret [8]. Preliminary pharmacokinetic studies have defined a mean terminal phase half-life of 11.1 h following a single intravenous dose [9]. The unique mechanism of action, preclinical potency and effectiveness coupled with the long half-life made tropisetron a strong candidate for study as an antiemetic for the control of vomiting caused by cancer chemotherapies such as cisplatin.

DOSE-RANGING STUDIES

Only one dose-ranging trial has been reported to date among patients receiving emesis-causing chemotherapy including cisplatin [9]. Observed effects are displayed in Table 1. Overall, no dose-limiting side-effects were seen at single intravenous doses of tropisetron between 12 and 48 mg/m^2. Headaches, mild sedation and mild and transient rises of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) occurred. As predicted by the drug's mechanism of action and preclinical evaluations, no acute dystonic reactions or akathisia were observed.

EFFICACY TRIALS

Leibundgut and Lancranjan reported an initial experience using tropisetron in patients receiving anticancer chemotherapy [10]. They presented results in 11 patients (47 courses of chemotherapy) receiving cisplatin and other agents as the primary emetic stimulus. Nearly half had received chemotherapy previously. They gave tropisetron as two 15-min intravenous infusions at a dosage of 10 mg before and 10 mg after the chemotherapy administration. No vomiting or retching was noted in 31 of the 47 courses. Headache was reported in nine courses (19%) and mild sedation in seven courses (15%). The authors concluded that tropisetron was an effective antiemetic treatment and it was free from major adverse effects.

Stamatakis *et al.* conducted a double-blind, randomised study to define an optimal dose of tropisetron in 100 patients receiving cisplatin [11]. Four doses were explored: 5 mg (n = 24), 10 mg (n = 26), 20 mg (n = 27) and 40 mg (n = 23). They gave only one dose of tropisetron intravenously over 15 min prior to cisplatin. Overall, they report that 54% experienced no nausea or vomiting during the 24 h after cisplatin. These authors state that both the highest total (63%) and major (88%) control rates were among patients who received a single 5 mg dose. In the trial, 35 individuals received cisplatin at doses $\geqslant$100 mg/m^2. Among these patients, 40% had total control and 69% had major control. Headache, hypertension and somnolence occurred. No extrapyramidal effects were noted.

54 patients receiving cisplatin at doses from 50 to 100 mg/m^2 over 1 h were studied by Dogliotti *et al.* [12]. All were given 10 mg of tropisetron intravenously over 15 min both before and after cisplatin (20 mg total dose). In contrast with other investigators, Dogliotti and co-workers employed a

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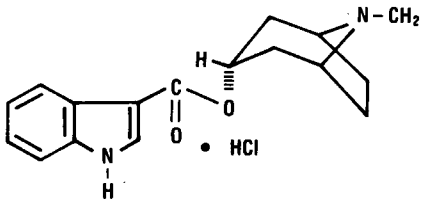

ICS 205-930

[IH]-Indol-3-carbonic-acid-tropine-ester hydrochloride

Fig. 1. Structure and chemical name of tropisetron.

Table 1. Dose-ranging trial of tropisetron among patients receiving emesis-causing chemotherapy at Memorial Sloan-Kettering Cancer Center—observed effects

Tropisetron dose (mg/m^2)	Number of patients	Headache	Mild Sedation	Mild ALT/AST rise
12	3	1	0	1
24	3	0	1	1
36	4	2	0	0
48	14	8	5	5

Tyson *et al.*, 1989 [9].

48-h rather than a 24-h observation period after cisplatin. Overall, 66% experienced no vomiting and 21% had only one or two episodes. Observed adverse effects were headache and hypotension. None were treatment-limiting.

COMPARISON TRIALS

Bregni *et al.* [13] compared the effects of tropisetron and alizapride (a newer substituted benzamide) in patients previously untreated with chemotherapy receiving either high-dose cyclophosphamide (7 g/m^2) or melphalan (200 mg/m^2). 25 patients with breast cancer or lymphoma were randomised to receive either tropisetron (10 mg intravenously day 1 then 5 mg orally every 6 h days 1–3) or alizapride (100–200 mg intravenously every 4 h day 1 then 50 mg orally every 6 h days 2–3). A mean of 5.6 vomiting episodes occurred in patients receiving tropisetron as opposed to 11.2 episodes among those given alizapride ($P=0.01$). Reported side-effects of tropisetron were headache and hypotension. 2 patients developed extrapyramidal reactions with alizapride.

In a multicentre, randomised trial, Williams *et al.* compared tropisetron (5 mg intravenously then 5 mg orally daily days 2–4) with the combination of dexamethasone (8 mg intravenously then 4 mg intravenously every 6 h for four doses) plus metoclopramide (3 mg/kg intravenously then 4 mg/kg continuous infusion over 8 h then 20 mg orally, three times a day, days 2–4) [14]. Patients were observed in the hospital for 24 h. Among the patients who received tropisetron, 20/58 (34%) experienced no emesis as opposed to 28/53 (53%) who were given the combination of metoclopramide plus dexamethasone ($P=0.04$). They state that the overall incidence of adverse effects for each regimen was similar with the exception of 8 patients (15%) receiving metoclopramide plus dexamethasone with extrapyramidal side-effects and 10 patients (17%) given tropisetron with headache.

DISCUSSION AND GOMMENT

The accumulated data demonstrates that ICS 205-930 can lessen or prevent emesis caused by anticancer chemotherapy. Side-effects are mild and transient. Because of its specificity and unique mechanism of action, tropisetron does not cause acute dystonic reactions or akathisia.

Although at least six trials have been completed to date, important information needed for the drug's development is lacking. Only doses from 3 mg/m^2 (5 mg total dose) to 48 mg/m^2 have been studied. No dose-limiting toxicities have been identified. The maximally tolerated dose (MTD) has yet to be defined. This information is critical to the development of tropisetron. In general, phase II (efficacy) trials are conducted using a dosage and schedule at or close to the maximally tolerated dose. Moreover, it would also be prudent to first explore the effects of higher doses in controlled, research settings rather than larger multicenter trials or clinical practice.

The efficacy data collected thus far suffers from the lack of a clearly defined phase II dose of tropisetron. It is vital to obtain such efficacy data so one can best judge the drug's overall usefulness compared with other safe and effective alternatives such as metoclopramide and ondansetron. Also, phase III efficacy trials can be designed properly only after accurate phase II data are analysed. Furthermore, the efficacy data currently available lacks information as to the optimal schedule of tropisetron. Its long terminal phase half-life of 11 h suggests that it may only need to be given once daily for an emetic stimulus like cisplatin. This would provide a distinct advantage over the antiemetic agents now available.

Study design and methods need to be standardised for all trials for such items as the major endpoint, emetic stimulus and measurement of nausea. Most investigators agree that the primary endpoint for efficacy trials is the percentage of patients having no vomiting or dry retches during the 24-h period following chemotherapy (complete control rate). Initial efficacy trials for new antiemetic agents are generally conducted with cisplatin given at a fixed dose or dose range [low dose (20–40 mg/m^2); moderate dose (40–90 mg/m^2) or high dose ($\leqslant 100$ mg/m^2)] and a defined duration of the cisplatin

Table 2. Complete vomiting control rates observed with tropisetron, metoclopramide and ondansetron in patients given initial cisplatin at doses $\geqslant 100$ mg/m^2

	Number of patients	Cisplatin dose (mg/m^2)	No emesis (%)	95% confidence interval (%)	Reference
Tropisetron	35	$\geqslant 100$	40	24–58	[11]
Metoclopramide	36	120	39	23–55	[15]
Ondansetron	103	$\geqslant 100$	51	42–61	[16, 17]

infusion (usually less than 3 h). Secondary endpoints include the actual number of vomiting episodes and the major control rate (generally defined as two or fewer emetic episodes), during the 24-h study period and nausea. Nausea has been most effectively measured using 100-mm visual analogue scales [2]. There are no accepted objective tests to measure nausea and no categorical scales that have been proven feasible, reliable and valid. Future trials of tropisetron should attempt to standardise dose, schedule, dose and administration of cisplatin and study methods. Appropriate phase III trials can only be planned with this information in hand.

What can be concluded about the efficacy of tropisetron based on the accumulated data? Tropisetron clearly can lessen or control chemotherapy-induced emesis. Its overall effectiveness and its ability to control vomiting caused by high-dose cisplatin make it a potentially useful antiemetic. Moreover, the 40% no-emesis rate observed with tropisetron given as a single agent in patients receiving cisplatin at dose $\geqslant 100$ mg/m^2 [11] is comparable with both metoclopramide [15] and ondansetron [16, 17], the currently available antiemetic drugs (Table 2).

The observed side-effects have been uncommon, mild and transient in all trials. Headache appears to be the most common adverse effect. It has been seen in all trials of this class of agents. In all cases it was mild and generally resolved without specific therapy. When given, acetaminophen provided relief. Mild sedation, hypotension, hypertension, sedation and transient elevations of serum ALT and AST have been seen. No patient with hepatic transaminase rises has developed a clinical illness and none have developed chronic elevations. This effect has also been observed with other serotonin analogues [18].

As predicted by the drug's mechanism of action and preclinical studies, no extrapyramidal reactions have been reported in any of the 256 patients in any trial (0% observed rate, 95% confidence limits 0–1.4%). The ability of tropisetron to control vomiting without extrapyramidal effects provides a clear advantage for this compound over the substituted benzamides such as metoclopramide, butyrophenones such as haloperidol, and phenothiazines such as prochlorperazine. This fact is especially important for patients at high risk for this complication including children, young adults and individuals of all ages receiving chemotherapy on multiple days [19].

CONCLUSIONS AND FUTURE DIRECTIONS

Tropisetron is a potent and selective 5-HT$_3$ antagonist. Trials to date show that it is safe to administer and preliminary data suggest it can effectively control chemotherapy-induced emesis (including that following high-dose cisplatin) following a single intravenous infusion. Its safety, efficacy and convenient administration schedule potentially give it distinct advantages both over metoclopramide and other serotonin antagonists.

Further trials should first focus on the identification of the optimal dosage and schedule of tropisetron in patients receiving high-dose cisplatin. Phase III trials comparing tropisetron alone with single-agent metoclopramide and ondansetron should follow. If the phase III data show an advantage for tropisetron, studies to define the lowest effective dose would then be appropriate. Additional investigations should explore the use of tropisetron in patients receiving chemotherapy (particularly cisplatin) on successive days. Tropisetron, given as a single daily dose, has the potential to allow the outpatient administration of chemotherapy programs (such as low-dose cisplatin and etoposide) that formerly required an inpatient stay. Further evaluations of an oral formulation are necessary. The development of oral tropisetron should follow the same plan of evaluation as the intravenous form as outlined above.

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