a non-specific antibody produce a similar effect, the need for specific antibody fragments would be negated.

The monitoring system we used cannot assess such an effect. More specific external monitoring of regions of interest by gamma camera could provide some evidence of the uptake of antibody. This was not possible in our study because of high background activity. Alternatively, targetted biopsy of metastases and normal liver would allow measurement of tissue radioactivity.

Further studies are therefore required to confirm these early results and also to assess any effect on tumour uptake. The need for tissue confirmation would suggest that a reproducible hepatic metastases model would be worthwhile. We are evaluating such a model together with the effect of labelled antibody on metastatic growth.

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Correlation of Anti-emetic Efficacy and Plasma Levels of Ondansetron

Steven M. Grunberg, Susan Groshen, Daniel C. Robinson, Lani L. Stevenson and Polly E. Sanderson

Intravenous ondansetron was administered at doses from 0.01 to 0.48 mg/kg every 4 h for three doses to patients receiving cisplatin 60–120 mg/m^2 for the first time. Plasma samples were collected from 28 patients at baseline and at suitable times post-dose for pharmacokinetic analysis, and were assayed for ondansetron by high-pressure liquid chromatography. Plasma trough level was defined as the level before the third dose and 4 h area-under-the-curve (AUC4) was calculated with the linear trapezoidal method. Despite wide inter-patient variation, a correlation was seen between both trough level ($r = 0.737$, $P < 0.0001$) and AUC4 ($r = 0.903$, $P < 0.001$) related to dose. Trough level was also predictive of AUC4 ($r = 0.824$, $P < 0.0001$). Frequency of complete protection (no emetic episodes) was equivalent throughout the AUC4 range, suggesting anti-emetic activity even at low AUC4. However, a trend toward better protection against failure (5 or more episodes) was seen when higher values of AUC4 were achieved, suggesting more consistent anti-emetic activity at moderate to high AUC4.
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INTRODUCTION

IDENTIFICATION OF serotonin receptors, especially 5-HT_3 receptors, in the periphery [1] and in the central nervous system [2, 3] has resulted in the introduction of a new category of selective 5-HT_3 antagonist anti-emetics. Studies in the ferret demonstrated the potency of several such anti-emetics in the control of both cyclophosphamide [4, 5] and cisplatin [4–7] induced vomiting. Clinical studies have confirmed the efficacy of 5-HT_3 antagonists in the prevention and control of chemotherapy induced vomiting in various patient populations [8–12].

We have done a dose-ranging study of ondansetron in patients receiving cisplatin for the first time [13]. Ondansetron was an effective anti-emetic over a wide range of doses with minimum toxicity and with activity similar to that of high-dose metoclopramide. Attempts to correlate anti-emetic efficacy of metoclopramide with drug levels have produced variable and contradictory results [14, 15]. To study the relation between anti-emetic efficacy and plasma concentrations of ondansetron, plasma samples were obtained during our dose-ranging study. These samples have now been analyzed.

PATIENTS AND METHODS

Eligibility

Patients for this study were taken from those participating in our dose-ranging study [13]. Adult inpatients with cancer received cisplatin in a single dose of 60 mg/m^2 or more for the first time. Patients who had vomited within 24 h before study entry, who had had severe vomiting with other chemotherapies or who had uncontrolled nausea and vomiting due to organic causes were not eligible. Serial plasma samples were obtained from all patients except those who refused frequent sampling, who had poor venous access or who had serological evidence of infections that could increase the risk to study personnel (such as hepatitis or HIV). The study was approved by the institutional review board of the Los Angeles County–University of Southern California Medical Center.

Ondansetron doses and plasma samples

Ondansetron (Glaxo Inc.) was administered intravenously over 15 min at 0.01, 0.06, 0.12, 0.18, 0.24, 0.30, 0.36 or 0.48 mg/kg for each of three doses given every 4 h beginning 30 min before cisplatin administration. Blood samples were collected at baseline and at 5, 15, 30, 60, 120 and 180 min after the end of infusion of the first dose, before and after the second and third doses, and at 12 and 24 h. Plasma was separated and frozen for later analysis by high-pressure liquid chromatography (HPLC).

Clinical observations

Patients were observed for 24 h after administration of the first dose of ondansetron. The number of emetic episodes and hours of nausea were recorded. An emetic episode was defined as a single productive vomiting episode or a series of retches lasting less than 5 min.

Drug assay

Plasma samples were analyzed for ondansetron with HPLC (Shimadzu pump LC-6A, autosampler SCL-6A and column heater CTO-6A). Reagents and conditions were proprietary (Glaxo Inc.). Ondansetron concentration was measured by monitoring ultraviolet absorption at 305 nm.

Plasma samples were analyzed in two sets, the first consisting of samples from patients who received 0.06, 0.12, or 0.18 mg/kg doses and the second consisting of samples from the remaining patients. Daily calibration curves were established from 1 to 50 ng/ml for the first set and from 1 to 250 ng/ml for the second set. Regression analysis demonstrated that the method was linear within the calibration ranges. Samples from the first set that exceeded the calibration range were diluted 3–9 fold with blank plasma and the measured value multiplied by the appropriate dilution factor. The lower limit of detection for this assay was 1 ng/ml. The coefficient of variation ranged from 3.1 to 7.8%.

Patients' plasma concentrations of ondansetron were assayed once. Calibration and quality control samples were analyzed in duplicate.

Pharmacokinetics

Variables used for analysis were: dose, plasma trough level, area under the first 4 h of the concentration-time curve (AUC4) and number of emetic episodes and hours of nausea within the first 24 h following administration of cisplatin. Trough was defined as the plasma level of ondansetron before the third dose. AUC4 was calculated for each set of plasma levels with the linear trapezoidal method [16]. AUC4 was selected for analysis since multiple plasma samples were collected during the first 4 h.

Table 1. Patient's characteristics

	Present study	Dose-ranging study [13]
Evaluable patients	28	38
M/F	23/5	30/8
Median age (range)	52 (23–73)	52 (23–73)
Median Karnofsky status (range)	80 (70–100)	80 (60–100)
Previous chemotherapy		
Yes (non-cisplatin)	3	3
No	25	35
Cisplatin dose (mg/m^2)		
60–75	6	13
100–120	22	25
Simultaneous chemotherapy		
Vinblastine	11	12
Etoposide	7	10
5-fluorouracil	4	4
Etoposide/bleomycin/vincristine	3	7
Vinblastine/doxorubicin	1	2
Mitomycin-C/vinblastine	1	1
Cyclophosphamide/doxorubicin	1	1
Cyclophosphamide/etoposide	0	1

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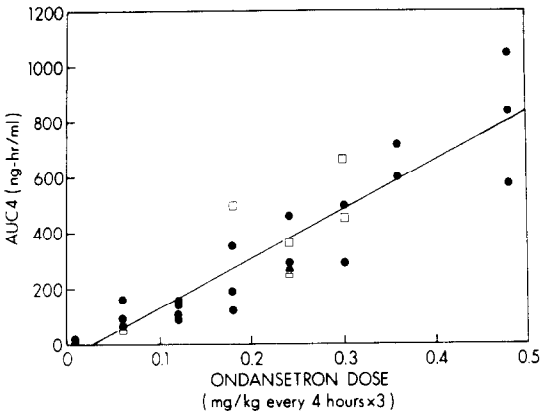

Fig. 1. Correlation of AUC4 and ondansetron dose (every 4 h for three doses) in patients receiving moderate dose 60–75 mg/m² (□) and high dose 100–120 mg/m² (●) cisplatin.

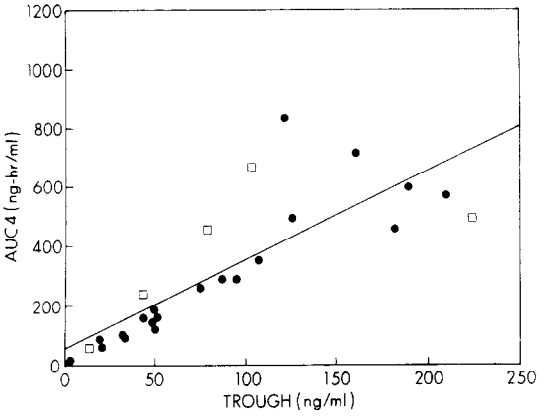

Fig. 3. Correlation of AUC4 and trough levels of ondansetron.

Scatterplots were drawn to evaluate the association between pairs of variables. For a quantitative measure of association between pairs of dose-related variables (dose, trough level, and AUC4), Pearson's correlation coefficient with two-sided P values was computed [17].

RESULTS

Anti-emetic responses

Plasma samples were obtained from 28 of the 38 clinically evaluable patients who received ondansetron (Table 1). In the clinical study 5 patients were entered at each dose level except for the 0.01 mg/kg level, which contained only 3 patients because of poor anti-emetic efficacy. Plasma samples for the present study were obtained from 2–5 patients (median 4) at each dose level. Complete protection from vomiting was achieved in 15 patients (54%) from whom plasma samples were obtained. An additional 8 patients had 1 or 2 emetic episodes. A total of 23 patients (82%) achieved major protection (0–2 emetic episodes). 5 patients had 3 or more emetic episodes. 4 of these 5 showed no anti-emetic protection (5 or more episodes). These results were similar to those observed during the dose-ranging trial in which complete protection was achieved in 44% of patients and major protection in 81% of patients [13].

Pharmacokinetics

Significant linear relations were noted between AUC4, trough level and dose of ondansetron. Correlations were seen between AUC4 and dose ($r = 0.903$, $P < 0.0001$) (Fig. 1) and between trough level and ondansetron dose ($r = 0.737$, $P < 0.0001$) (Fig. 2). Trough level and AUC4 were also well correlated ($r = 0.824$, $P < 0.0001$), especially at the lower levels (Fig. 3). However, inter-patient variability at each dose level was great enough that overlapping values of AUC4 or trough were seen for patients whose dose differed by as much as 0.12 mg/kg (Figs. 1 and 2).

Analysis of association between dose-related variables (dose, trough level or AUC4) and summaries of outcome measures (emetic episodes or hours of nausea) revealed no significant correlations. However, the strongest association was between number of emetic episodes and AUC4 (Fig. 4). All 6 patients receiving moderate doses of cisplatin had excellent anti-emetic protection, but protection of the 22 patients receiving high-dose cisplatin was more variable. Complete protection from emesis was seen with an AUC4 as low as 59 ng h/ml. A relation between complete protection and AUC4 was therefore not demonstrated. However, examination of the pattern of failure of anti-emetic protection (5 or more emetic episodes) with or without inclusion of the 6 moderate-dose cisplatin patients suggested a non-significant trend toward better protection when higher AUC4 values were achieved.

DISCUSSION

Our regimen of three doses administered every 4 h resulted in detectable ondansetron levels at all time points during the

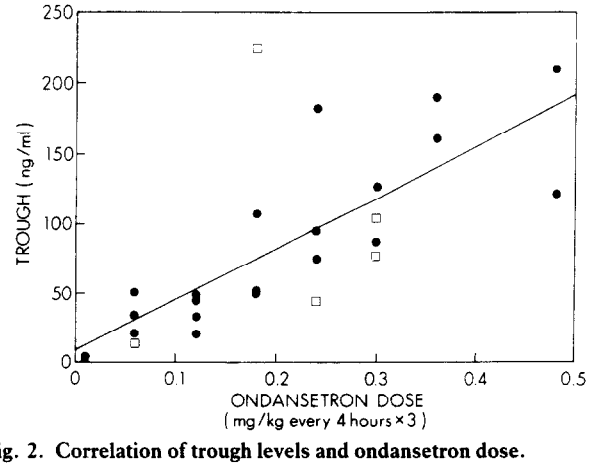

Fig. 2. Correlation of trough levels and ondansetron dose.

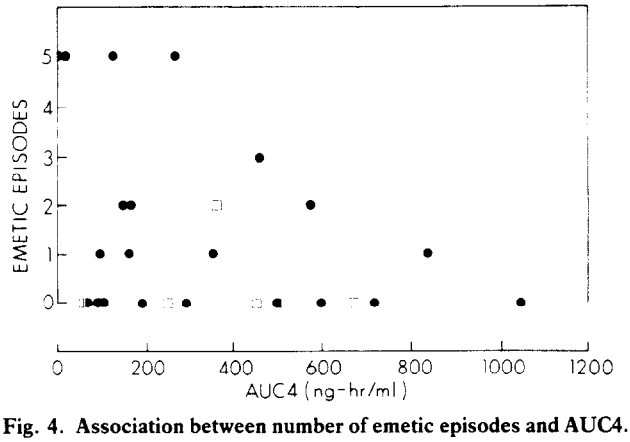

Fig. 4. Association between number of emetic episodes and AUC4.

initial 24 h observation period for doses of 0.06 mg/kg or higher (S.M. Grunberg) but revealed levels somewhat lower than expected compared with normal volunteer data [18]. Significant linear correlations between AUC4 and dose and between trough level and dose were noted in the present study. Despite this correlation of mean data, examination of inter-patient variability within the different dose levels revealed that similar AUC4 and trough levels could be obtained in selected patients who differed by as much as 0.12 mg/kg per dose. In some cases similar AUC4 and similar trough levels could therefore be demonstrated for patients receiving doses differing by as much as 100%.

Anti-emetic efficacy similar to high-dose metoclopramide can be seen with ondansetron doses as low as 0.06 mg/kg given every 4 h for 3 doses [13]. However, the wide inter-patient variability of AUC4 suggests that the AUC4 from such a dose may not always be within the effective range. Anti-emetic studies have traditionally examined complete protection (0 emetic episodes) and major protection (0–2 emetic episodes). Identification of patients who have failed to respond (5 or more emetic episodes) and prevention of this failure are important in establishing quality of life. The present study suggests that protection from failure may be associated with higher plasma levels of ondansetron.

Escalation of metoclopramide dose beyond the present high-dose metoclopramide regimens is hampered by anti-dopaminergic toxicity [19] and may be inadvisable due to the reversal of anti-emetic protection noted at high serum levels of metoclopramide [15]. The high therapeutic index of ondansetron appears to allow dose escalation sufficient to achieve the plasma levels associated with maximum anti-emetic protection without entering the range at which decreased efficacy and an increased frequency of adverse events may appear [13]. Since plasma trough level is highly predictive for AUC4 (particularly at lower levels), this single plasma value may be useful in identifying those patients in whom a sufficient AUC4 has not been achieved and in whom further dose escalation may provide increased anti-emetic protection.

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