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# A phase I study of a new $5HT_3$-receptor antagonist, BRL43694A, an agent for the prevention of chemotherapy-induced nausea and vomiting*

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**Summary.** In a phase I study of BRL43694A, a $5HT_3$-receptor antagonist, a single dose of 40 μg/kg was given to 24 patients. All patients received cytostatic treatment expected to cause nausea and vomiting. During the first 24 h, 12 patients were completely protected from nausea and vomiting, 4 experienced nausea and 8 had moderate vomiting; mild headache occurred in 10 patients. No cardiovascular (including ECG) changes took place. Apart from headache, no neurological side effects occurred.

## Introduction

It has recently been demonstrated that compounds that selectively antagonise the effects of 5-hydroxy-tryptamine (5HT) at $5HT_3$-receptors can inhibit vomiting caused by the cytostatic treatment in experimental animals [2, 10, 14]. BRL43694A (endo-*N*-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1-methyl-1H-indazole-3-carboxamide hydrochloride), developed by Beecham Pharmaceuticals, is a potent and selective antagonist of $5HT_3$-receptors. It is approximately 260–500 times more potent than metoclopramide as a $5HT_3$-receptor antagonist and is better tolerated [2]. In a 28-day repeat intravenous (i.v.) study in rats, the non-toxic effect level was 3 mg/kg per day, with signs of acute CNS stimulation being dose-limiting at 9 mg/kg per day. In dogs, the maximum tolerated, single i.v. dose was 3 mg/kg.

In male volunteers, no drug-related changes in hematology, clinical chemistry (blood and urine), pulse, blood pressure or ECG were observed following a single dose of 2.5–40 μg/kg, given by slow i.v. infusion. At single doses of up to 40 μg/kg q 4 h ×3, BRL43694A was well tolerated; at doses of 80 μg/kg and above, constipation was reported. BRL43694A appeared to have no CNS effects. The terminal half-life in plasma ranged from 4–6 h in individual subjects; the mean at each dose level was approximately 4–6 h. The disappearance was multiphasic and only became log linear after several hours. Most of the drug is eliminated by metabolism. This study was undertaken to investigate the tolerance to 40 μg/kg BRL43694A given as a single dose.

## Materials and methods

A total of 24 patients who were given cytostatics expected to cause marked nausea and vomiting were entered in this phase I study of BRL43694A; 21 of these patients were cytostatic-naive. The study involved 16 women and 8 men; the median age was 46.5 years (range, 20–66). The performance status (PS) according to Eastern Cooperative Oncology Group (ECOG) [11] rating was 0 in 10 patients, 1 in 8, and 2 in 6.

All patients had normal serum electrolyte, serum urea and creatinine levels. Bilirubin, transaminase, serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT) and serum gamma glutamyltransferase gamma (GT) values were never more than twice the upper normal limit, and serum alkaline phosphatase levels were only allowed up to twice normal in the presence of bone metastases. All patients had a normal haemogram, including haemoglobin, haematocrit, red blood cells, total white blood cells, differential count and platelet count, at the start of treatment. All patients gave written informed consent.

The patients had the following advanced malignant neoplasms: ovarian cancer, 7; Hodgkin's disease, 4; colon cancer, 3; rectal cancer, 2; breast cancer, 2; malignant mesothelioma, 2; malignant cylindroma, 1; leiomyosarcoma, 1; embryonal carcinoma of the testis, 1; and malig-

**Table 1.** Headache and thirst experienced per time period

| Time (h) | Number of patients | | |
|---|---|---|---|
| | Headache | | Dry mouth |
| | Grade 1 | Grade 2–3 | |
| Pre-treatment | 2 | 0 | 1 |
| 0–6 | 7 | 0 | 2 |
| 6–12 | 8 | 0 | 2 |
| 12–18 | 5 | 0 | 2 |
| 18–24 | 5 | 0 | 2 |
| 0–24 | 10 | 0 | 2[a] |

[a] One patient was receiving oral morphine for pain

Grade 1, mild headache; grade 2, moderate headache; grade 3, severe headache

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nant fibrous histiocytoma, 1. An additional patient with colorectal cancer was registered in the study but did not receive BRL43694A, as he developed ECG changes following the administration of cytostatics. His initial (PR) time was 0.16 s, which became 0.22 s. This patient's data is therefore not included in this report. The cytostatic treatments given were: (a) platinum-containing[1–4] regimens, nine patients; (b) 4'-epi-Adriamycin (150 mg/m$^2$), five patients; (c) MOPP, three patients; (d) FIVB[5], two patients; (e) BCVPP[6], one patient; (f) CAF, two patients; (g) ifosfamide and mesna, two patients.

A 12-lead ECG was carried out and pulse and blood pressure were measured prior to and immediately following the administration of cytostatic treatment. BRL43694A (40 μg/kg) was infused over 30 min, beginning 15–20 min after the administration of cytostatics. After BRL43694A administration, a 10-s 12-lead ECG was carried out. Pulse and blood pressure were recorded at 1, 2, 3, 4, 6, 12 and 24 h after BRL43694A administration. A follow-up haemogram and biochemistry were done 1 week later, as was a further follow-up ECG.

A linear analogue scale and record of nausea and emesis were done before the administration of cytostatics as well as prior to and 6, 12, 18, 24, 48 and 72 h following the administration of BRL43694A. These recordings were done by the patients, and objective monitoring was also carried out. All patients were admitted to hospital for at least the first 24 h.

## Results

All 24 patients given BRL43694A were evaluable for toxicity and response. As all patients were admitted to hospital for at least 24 h, objective evaluation could be carried out and correlated with the linear analogue scale.

### *Toxicity*

The only documented side effects ascribed to BRL43694A were headache and thirst (Table 1). Mild headache (grade 1 ECOG) [11] was experienced by ten patients; no grade 2 or grade 3 headache occurred. Two patients had had grade 1 headache prior to the administration of BRL43694A. During the first 6 h (post-BRL43694A administration), four patients experienced grade 1 headache that started 2–4.5 h after BRL43694A administration and lasted 1, 2, 6 and 24 h. During the next 6-h period, two additional patients experienced grade 1 headache that lasted between 2 and 5 h. One patient had a grade 1 headache that lasted 3.5 h. Two patients complained of dry mouth, one of whom had this symptom prior to BRL43694A administration (this patient was receiving oral morphine for pain); the second patient complained of dry mouth that started 4 h after BRL43694A administration and lasted 24 h. None of the 24 patients showed changes in pulse rate, blood pressure or ECG readings or developed neurological symptoms.

**Table 2.** Nausea and vomiting experienced per time period

| Time (h) after BRL43694A | Number of patients with nausea and/or vomiting | | |
|---|---|---|---|
| | Grade 0 | Grade 1 | Grade 2 |
| 0–6 | 18 | 2 | 4 |
| 6–12 | 17 | 2 | 5 |
| 12–18 | 15 | 6 | 3 |
| 18–24 | 15 | 5 | 4 |
| 0–24 | 12 | 4 | 8 |

Grade 0, none; Grade 1, nausea; grade 2, nausea and vomiting controllable; grade 3, nausea and vomiting intractable

### *Therapeutic effect*

Among the 24 evaluable patients, no grade 3 nausea and vomiting occurred. The worst degree of nausea and vomiting for the 24-h period following BRL43694A administration was assessed: 12 of the 24 patients had neither nausea nor vomiting, based on direct questioning and completion of visual analogue scales by the patients themselves, whereas 4 patients only became nauseous and 8 vomited. The number of patients with nausea (grade 1) or nausea and vomiting (grade 2) per 6-h period for the first 24 h are shown in Table 2.

During the first 6 h, no nausea or vomiting occurred in three-quarters of the patients, and even at 24 h, nearly two-thirds of the patients were experiencing neither nausea nor vomiting. During the 12 h following BRL43694A administration, grade 2 nausea and vomiting occurred in three of the nine patients receiving cisplatin combination chemotherapy, and by 24 h, four of the nine patients vomited. None of the patients given MOPP, ifosfamide and mesna or FIVB developed nausea or vomiting during the first 24-h period.

Of the 24 patients, 6 required additional anti-emetic therapy during the first 24-h period. Two patients were given 25 mg chloropromazine HCl by mouth: one, 4 h after BRL43694A was given, and one, 8 h after treatment. Four patients were given prochlorperazine mesylate (25 mg via the rectum after 9 h, 17 h and 21 h, and 12.5 mg i.m. 19 h after the initial dose of BRL43694A). Two of these six patients experienced no vomiting during the first 24-h period, one had one to two episodes and three had three to five episodes of vomiting.

## Discussion

Nausea and vomiting constitute the most commonly encountered subjective side effect experienced by patients receiving cytostatic treatment. Currently available anti-nausea regimens only give protection against nausea and vomiting at doses where significant side effect occur. Nausea and vomiting were expected for all treatments given in the present study. Only a single dose of BRL43694A was given following the administration of the cytostatic treatment.

[1] DDP, 50 mg/m$^2$ i.v., day 1 + CTX, 600 mg/m$^2$ i.v., day 1 (four patients)

[2] DDP, 50 mg/m$^2$ i.v., day 1 + ADM, 50 mg/m$^2$ i.v., day 1 (two patients)

[3] DDP, 50 mg/m$^2$ i.v., day 1 + CBDCA, 280 mg/m$^2$ i.v., day 1 + CTX, 600 mg/m$^2$ i.v., day 1 (two patients)

[4] DDP, 20 mg/m$^2$ i.v., days 1–5 + bleomycin, 30 IU i.v., days 1, 8, 15 + VP-16, 100 mg/m$^2$ i.v., days 1–5 (one patient)

[5] FIVB: 5-FU, 500 mg/m$^2$ i.v., days 1–4 + DTIC, 260 mg/m$^2$ i.v., days 1 and 2 + VCR, 1 mg/m$^2$ i.v., days 1 and 4 + BCNU, 90 mg/m$^2$ i.v., day 1

[6] BCVPP: BCNU, 100 mg/m$^2$ i.v., day 1 + VLB, 5 mg/m$^2$ i.v., day 1 + CTX, 600 mg/m$^2$ i.v., day 1 + procarbazine, 100 mg/m$^2$ p.o., days 1–10 + prednisone, 60 mg/m$^2$ p.o., days 1–10

Of the 24 evaluable patients, 14 experienced no nausea or vomiting during the first 12-h period and only 7 patients vomited. None of the patients developed grade 3 nausea and vomiting. The terminal half-life of BRL43694A in the plasma of volunteers was between 4 and 6 h. If the nausea and vomiting occurring only in the first 6 h is analysed, 18 of the 24 evaluable patients were completely free of nausea and vomiting and only 4 of 24 vomited. No cardiovascular or neurological side effects were documented. No changes in haemogram or biochemistry were attributed to BRL43694A, and no ECG changes occurred due to BRL43694A. Two patients complained of dry mouth; in one of these it was attributed to BRL43694A. The most important side effect was headache, which occurred in ten patients; this was never more than ECOG grade 1 and responded to treatment with paracetamol.

Preliminary results have been reported in phase I trials of BRL43694A involving 108 patients [1, 3–6]. The dose given varied from 10 to 100 μg/kg. Anti-emetic effects were noted at doses >20 μg/kg [3], with good therapeutic effect at doses of 40 μg/kg. Headache was reported in 2 of 14 [6] patients in one series and 5 in 14 [5] in another.

Other $5HT_3$-receptor-antagonists are currently undergoing clinical trials for their anti-emetic effects. BMY-25801 (a non-dopaminergic anti-emetic with prolonged action) has been reported to protect completely 50% of patients from cisplatin-induced emesis [13]. All of the patients showed transient, non-symptomatic increases in QRS, PR and QTC intervals. Other side effects have included headache, loose stools and dry mouth [12]. A study investigating GR 38032F [15] has shown that this compound appears to be effective in preventing the emesis induced by high-dose melphalan in most patients; the side effects observed included light-headedness. In a further study with the same compound [8], control of emesis was found to occur in 36% of patients given cisplatin; toxicities documented were headache, sedation and an increase in transaminase levels (SGOT/ALT). Other side effects that have occasionally been ascribed to GR 38032F include dizziness, tingling, tinnitus, bitter taste, flushed face and transient bronchospasm at a single-dose level exceeding 0.15 mg/kg [7]. ICS 205–930, another effective anti-emetic $5HT_3$ antagonist, has been given in doses of 10–20 mg to 25 patients. The documented side effects included mild to moderate headache, mild sedation and diarrhoea [9].

Of particular significance is that BRL43694A has not caused cardiovascular or neurological changes. Unlike some of the other $5HT_3$-receptor-antagonists under investigation, with BRL43694A, ECG changes in the present as well as other studies have not been encountered. In this phase I study, a single dose of 40 μg/kg was well tolerated and showed therapeutic activity.

At a time when many patients' apprehension about receiving cytotoxic treatment is caused by expected nausea and vomiting, the development of effective anti-emetic treatment has become considerably important for the medical oncologist and his patient. The $5HT_3$-receptor-antagonists therefore open a potential window of opportunity for the more acceptable management of patients receiving cytostatics. Among the $5HT_3$-receptor-antagonists currently in clinical trial, BRL43694A appears to be promising, and fewer side effects are ascribed to this anti-emetic.

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