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Extrapyramidal Reaction Associated with Ondansetron

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ONDANSETRON, a serotonin antagonist antiemetic, has not been linked to extrapyramidal side-effects in clinical trials [1]. We observed 1 case of extrapyramidal reaction in a patient following direct intravenous ondansetron administration.

A 65-year-old woman with locally advanced undifferentiated nasopharyngeal carcinoma had been treated with radical radiotherapy. 10 months later, she developed a local recurrence, with left cavernous sinus syndrome. Chemotherapy with cisplatin 100 mg/m^2 on day 1 and fluorouracil 1 g/m^2/day as a continuous infusion of 4 days was started. As an antiemetic, she received intravenous ondansetron 8 mg (0.15 mg/kg) and intravenous dexamethasone 20 mg, prior to cisplatin and ondansetron 8 mg orally at 8 h intervals afterwards for 4 days. In subsequent cycles, fluorouracil was reduced to 750 mg/m^2/day because of stomatitis. No change was made in antiemetic therapy. After the second cycle, analgesics were withdrawn and she received no subsequent concurrent medication. In the third cycle, ondansetron was given intravenously. On the third day of the cycle, the seventh dosage of ondansetron was slowly injected intravenously. Immediately after the administration, the patient experienced dystonia of the jaw, stiffness of the limbs, inability to speak, anxiety, and a burning sensation in her face and hands. The episode lasted 1–2 min and resolved spontaneously. The ampoule of the administered drug was checked and positively identified as ondansetron. The fluorouracil infusion was not stopped. The subsequent doses of ondansetron, for the rest of the third cycle and for the fourth cycle were administered diluted over a 15-min intravenous infusion, and no side-effects were noticed. A computed tomography scan showed partial tumour response.

There was a clear relation between the direct intravenous administration of ondansetron and the episode. The fact that the reaction disappeared spontaneously in a few minutes, and did not recur with the short intravenous infusion, may be due to a relation between the extrapyramidal reaction and high plasma levels. Other factors such as old age and female sex may have played a role, increasing susceptibility or modifying the drug's pharmacokinetics [2].

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Ondansetron has shown an absence of extrapyramidal side-effects, and superior activity for cisplatin-induced acute emesis compared with metroclopamide, in comparative trials [3]. Recently there have been two other reports of extrapyramidal side-effects attributed to ondansetron. In 1 case [4], the prior use of droperidol precluded a definitive association [5]. The second case occurred after ondansetron was administered by short intravenous infusion [6].

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Phase II and Pharmacokinetic Study of Fotemustine in Inoperable Colorectal Cancer

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TO FIND new active agents for colorectal adenocarcinoma, we selected fotemustine for a phase II trial because of preclinical

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and clinical activity in disseminated melanoma [1]. Between April 1988 and February 1990, 16 previously untreated patients with advanced colorectal cancer were entered (Table 1). Eligibility criteria included measurable metastatic disease with evidence of disease evolution during the two previous months, ECOG performance status 0–2 and life expectancy of at least 12 weeks. The patients were required to have normal values for haemoglobin, white cells, granulocytes, platelets, serum creatinine and liver enzymes. Response and toxicity were evaluated with WHO criteria. Fotesmustine was administered as a 1-h intravenous infusion at 100 mg/m^2 in 250 ml 5% dextrose (protected from light) on days 1, 8 and 15, followed by a 5-week rest. For responding or stabilised patients, fotemustine was administered at the same dose once every 3 weeks, depending on haematological status.

The main toxicity was a delayed and reversible grade 3–4 leucopenia (14%, nadir at week 6), neutropenia (15%), thrombocytopenia (28%, nadir at week 5) and anaemia (7%). Recovery was observed at week 8. No platelet transfusion was necessary and 3 patients received red cell transfusions. Haematological toxicity was well tolerated. The frequency of nausea and vomiting was low in the 63 courses evaluated. Including maintenance treatment, no grade 4, and only 6% of patients with grade 3 nausea and vomiting were observed. Antiemetics were often administered as preventive treatment. 1 patient had an allergic reaction during the first and the second infusion of fotemustine (with fever and erythema); drug administration was stopped and recovery occurred rapidly. No other specific toxicity was observed.

Of the 15 evaluable patients, one partial response (7%) for 14 weeks was achieved in lung and lymph node sites. Disease was unchanged in 9 patients (60%), duration 17 (range 10–22) weeks. Disease progressed in 5 patients (33%). 10 partial responders and unchanged patients received maintenance with a median of two (range one to five) courses. 11 patients with progressive disease or relapse received leucovorin (20 mg/m^2 per day) immediately followed by 5-fluorouracil (400 mg/m^2 per day), for 5 consecutive days every 4 or 5 weeks [2]. Following this, 10 patients were evaluable, 4 of whom had a partial response (40%) with a median duration of 5 months (range 3–11); 5 patients (50%) were stabilised with a median duration of 5 months (range 2–12). 1 patient was not evaluable because treatment was stopped due to an allergy.

Fotemustine pharmacokinetics was studied in 7 patients during their first course on day 1 with a HPLC assay [2]. At the end of the infusion, mean plasma concentration (C_{max}) was 1.53 (S.E. 0.31) μg/ml. Elimination was monophasic, with a half-life of 17 min [3]. Area under the curve (AUC) was 1.44 (0.23) μg.h/ml, total body clearance was 80 (12) l/h/m^2, and volume of distribution was 33 (7) l/m^2. C_{max} values were linearly correlated with total AUC ($y = 0.688x + 0.514$, $r = 0.89$, $P<0.01$), a fact which could help reduce the number of samples needed since only one sample at the end of the infusion will predict the main pharmacokinetic parameters.

Our activity and toxicity results agree with those reported by Bleiberg *et al.* [4]. Our results with salvage treatment [4] were encouraging since four partial responses of median duration of 5 months were observed after the administration of low-dose leucovorin to 10 evaluable patients. Despite the small number of patients, our results confirm that an investigational drug can be administered as first-line treatment without worsening prognosis [5]. These results also confirmed the response rate obtained with the 5-fluorouracil–leucovorin combination [3].

Table 1. Patients' characteristics

Evaluable/included patients	15/16
Male/female	7/9
Median age (range)	63 (42–76)
ECOG median performance scale (range)	0 (0–2)
Previous therapy	
Chemotherapy	0
Surgery	10
Surgery + radiotherapy	6
Metastatic sites	
Lung	8
Liver	10
Lymph nodes	1
Adrenal gland	1
Other	2

The limited fotemustine activity in colorectal carcinoma observed in this study could be partly due to low plasma concentrations at completion of the infusion. Our patients achieved a C_{max} of 1.5 μg/ml, whereas 4.4 μg/ml was achieved in melanoma patients with the same dose [6]. This difference could be due to liver metastases present in most patients sampled for pharmacokinetics. Another factor that could explain the low response rate of colorectal tumours to fotemustine could be their high DNA-repair abilities via O^6-alkylguanine-DNA transferase. Human colon and lung cell lines proficient in this enzyme are more resistant to fotemustine [7].

We have started a phase II study of fotemustine administered before 5-fluorouracil and leucovorin. This phase II scheduling is supported by recent data with colon WIDR cells demonstrating a sequence-dependent synergy of the combination fotemustine, 5-fluorouracil and leucovorin, but showing an antagonistic effect if the nitrosourea is applied after 5-fluorouracil [8].

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