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Short Communication

Oral Levonantradol in the Control of Cancer Chemotherapy-Induced Emesis

John Welsh[1], Fraser Stuart[1,2], Graeme Sangster[1], Robert Milstead[1], Stanley Kaye[1], Hayden Cash[3], David Charlton[3], and Kenneth Calman[1]

[1] Department of Oncology, Glasgow University, 1 Horselethill Road, Glasgow G12 9LY, Scotland
[2] Department of Pharmaceutics, University of Strathclyde
[3] Pfizer Ltd, Sandwich, Kent, England

Summary. *A dose-ranging study with oral levonantradol was performed in 20 cancer patients. The optimum oral dose which attenuated vomiting accompanying chemotherapy was 1 mg 4-hourly. Side-effects comprised dizziness, confusion, euphoria, drowsiness, and difficulty in concentrating. There was no cardiovascular toxicity. Overall toxicity appeared to be dose-related and was mild and acceptable.*

Introduction

Newer and often more aggressive chemotherapeutic regimens have produced an increase in response rates and even cures in certain tumour types. In many cases this improvement has been associated with pronounced toxicity, of which nausea and vomiting may be the most distressing symptom to the patient. In a recent study [12] up to 6% of patients refused further chemotherapy because of intractable vomiting. Conventional anti-emetics have been of limited value in the control of nausea and vomiting [4–6]. Several studies of the anti-emetic potential of steroids have been conducted, with inconclusive findings [9]. Sallan has shown anti-emetic properties to be associated with delta-9-tetrahydrocannabinol (THC) [10]. Increasing knowledge of the mechanisms involved in emesis [3, 9] has led logically to the investigation of the anti-emetic potential of combinations of anti-emetic drugs known to work by different mechanisms and known to have non-additive side-effects. A second approach to this problem is to develop new compounds or analogues of existing drugs. One such compound, developed but structurally distinct from 9-8-hydroxy-hexahydrocannabinol, is levonantradol. This drug has been shown in both animal (H. Cash 1981, personal communication) and limited human (H. Cash 1982, personal communication) studies to be an active anti-emetic. Present data concerning this drug are limited largely to IM administration.

The purpose of this study was to perform a dose-ranging study and to assess the anti-emetic potential and side-effects of an oral formulation of levonantradol in single doses up to 1 mg 4-hourly.

Patients and Methods

Twenty patients with histologically proven malignancy, 16 of whom were receiving combination chemotherapy including cis-platin (dose 40–60 mg/m^2), were included in this study. During the previous course of chemotherapy these patients had experienced intractable nausea and vomiting and failed to respond to conventional anti-emetics, which included prochlorperazine, chlorpromazine, metoclopramide, cyclizine, and droperidol. Chemotherapeutic regimens were unchanged during the levonantradol assessment.

The number of vomiting episodes was recorded by the nursing and medical staff.

The starting dose was 0.25 mg levonantradol 4-hourly. Patients 1–6 received 0.25 mg, patients 7–10 received 0.5 mg, patients 11–15 received 0.75 mg, and patients 16–20 received 1 mg, all 4-h. Anti-emetic therapy was commenced 30 min prior to the chemotherapy. Levonantradol was continued for up to 24 h. Patients entering the study gave informed consent.

Results

The number of vomiting episodes decreased with increasing dose of levonantradol. The incidence of side-effects was 16% at 0.25 mg and 80% at 1 mg. Table 1 summarises these results. The 0.25 mg and 0.5 mg doses were associated with little relief

Table 1. Physician's overall evaluation

		Dose of levonantradol			
		0.25 mg	0.5 mg	0.75 mg	1.0 mg
Nausea	None	0	0	1	3
	Mild	2	0	3	1
	Moderate	2	3	1	0
	Severe	2	1	0	1
Vomiting (0–24)	0	0	0	1	2
	1– 4	3	2	2	1
	5–10	2	2	2	2
	10	1	0	0	0
Appetite	Good	1	0	0	0
	Normal	0	0	1	3
	Fair	2	1	1	0
	Poor	3	3	3	2
Side-effects	None	5	4	2	2
	Mild	1	0	2	3
	Moderate	0	0	1	0
	Severe	0	0	0	0

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Table 2. Details of reported side-effects

Description	Dose level of levonantradol			
	0.25 mg	0.5 mg	0.75 mg	1.0 mg
Drowsiness, sedation	1		1	
Concentration difficulty	1			
Dizziness			1	4
Confusion				2
Euphoria			1	1
No. of patients with side-effects	1	0	3	4
No. of patients without side-effects	5	4	2	1
Total number of patients	6	4	5	5

of nausea and vomiting. Alleviation of the degree of nausea or vomiting was recorded in the majority of the patients receiving 0.75 mg and 1 mg.

Table 2 summarises the side-effects associated with levonantradol in this study. Dizziness was the commonest side-effect and was not associated with changes in the cardiovascular system.

Despite side-effects, 80% of patients who received 0.75 mg or 1 mg were prepared to take levonantradol during their next course of chemotherapy.

Discussion

There is an urgent need for efficient control of nausea and vomiting iatrogenically induced by the majority of therapeutic regimens used in the treatment of malignant disease [13]. Studies have shown high-dose IV metoclopramide to be effective against cis-platin induced vomiting [2]. In this initial study the anti-emetic activity of levonantradol becomes apparent at 0.75 mg and 1 mg. Side-effects were well tolerated in doses up to 1 mg. A recent study using doses of oral levonantradol of 1.5 mg and above was associated with side-effects which outweighed any anti-emetic efficacy [11]. A low incidence of side-effects was obtained using THC in young cancer patients [10], but the same dose of THC in an older patient population produced unpleasant toxicity [1]. The median age in our study was 37 years, and this may explain, in part, the absence of severe toxicity. A recent pharmacokinetic study has demonstrated that the half-life of levonantradol is 30 min [8]. The short half-life indicates the need for a more frequent dosage regimen. The exact mode of action of levonantradol is unknown, but unlike most other anti-emetics it is devoid of activity upon the dopaminergic system.

It is concluded that the drug has considerable anti-emetic properties, the results being more impressive in view of the fact that 80% of the anti-neoplastic combinations contained cis-platin. The side-effects were tolerable in this small group of relatively young patients.

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