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LAS 30451: A Novel 5-HT_3 Antagonist

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INTRODUCTION

WITH THE introduction of new aggressive chemotherapy regimens including cisplatin, carboplatin, dacarbazine, ifosfamide, doxorubicin and high-dose cyclophosphamide, gastrointestinal toxicity has become a major clinical problem [1]. In 1981, Gralla *et al.* [2] established high-dose metoclopramide as an efficacious treatment in preventing nausea and vomiting induced by chemotherapy. Although the antiemetic activity of metoclopramide was originally considered to be due to blockade of dopamine D-2 receptors, it now seems probable that its efficacy against chemotherapy-induced emesis is due to 5-HT_3 receptor antagonism [3]. Therefore, more potent and selective 5-HT_3 receptor antagonists have been developed in the past few years.

LAS 30451 [(±)-4-amino-5-chloro-alpha-cyclopropyl-*N*-3-quinuclidinyl-o-anisamide, Fig. 1] is a new substituted benzamide which acts as a 5-HT_3 receptor antagonist. This drug is currently under clinical evaluation in Spain and other European countries.

PHARMACOLOGICAL PROFILE

LAS 30451 inhibits serotonin-induced transient bradycardia (VonBezold-Jarisch reflex) in urethane-anaesthetised rats when administered intravenously 5 min ($ED_{50}=0.56$ μg/kg) or orally 60 min ($ED_{50}=8.7$ μg/kg) before serotonin challenge. This effect is related to 5-HT_3 antagonist properties. Using a single oral dose (10 μg/kg) LAS 30451 produces significant inhibition of the bradycardia reflex over an 8-h period. In a variety of *in vivo* and *in vitro* models, LAS 30451 has no effect on 5-HT_1, 5-HT_2, alpha-adrenergic, dopamine, histamine or muscarinic receptors [4].

LAS 30451 is approximately 50 times more potent than metoclopramide in inhibiting emesis induced by intravenous cisplatin in dogs. When administered orally or intravenously LAS 30451 inhibits dose-dependently the number of vomiting episodes induced by cisplatin (3 mg/kg intravenously) in dogs ($ED_{50}=7.1$ μg/kg orally and 3.6 μg/kg intravenously). LAS 30451 (1 mg/kg) is completely devoid of activity against the emetic effects of subcutaneous apomorphine, whereas metoclopramide at same dose inhibits vomiting.

The oral administration of LAS 30451 at the screening dose of 1 mg/kg also protects dogs (100%) against the emesis induced by dacarbazine and mechloretamine.

LAS 30451 stimulates gastric emptying in the rat. Gastrointestinal motility is also increased in dogs with implanted fistulas. LAS 30451 is virtually inactive in animal models as far as sedation and muscle relaxation are concerned. On the other hand, in models of anxiogenesis LAS 30451 exhibits anxiolytic properties at very low doses.

TOLERANCE AND PHARMACOKINETIC STUDIES

Single intravenous and oral tolerance and pharmacokinetic studies in healthy male volunteers have been carried out in the U.K. The maximum doses of LAS 30451 given by the intravenous and oral routes were 20 and 40 mg, respectively [5]. Inhibition of the skin flare following intradermal injections of serotonin solution (5×10^{-5} mol/l) was observed with all doses of LAS 30451, from 5 to 40 mg, being most marked at 10, 20 and 40 mg. The effect of the higher doses appears to be maintained for more than 24 h after dosing. The elimination half-life of LAS 30451 following intravenous administration was approximately 5–10 h. No significant alterations were observed in either haematological or biochemical laboratory screens with placebo or any dose of LAS 30451. ECG recordings, Holter monitoring and blood pressure and pulse measurements showed that administration of LAS 30451 was not associated with any cardiovascular effects. LAS 30451 was well tolerated by both intravenous and oral routes, with few adverse effects and none of a serious nature. Only diarrhoea or loose stools which occurred 1–4 h after administration of LAS 30451 at the dose level of 40 mg, was assessed as being probably drug-related.

CLINICAL EXPERIENCE

A multicentre dose-finding study has recently been carried out in Spain. 90 chemotherapy-naïve patients treated with severe emetogenic cytotoxic agents (cisplatin combinations, carboplatin, dacarbazine, cyclophosphamide–doxorubicin combinations or ifosfamide combinations) were entered in the study. Six cohorts of 15 patients each were given LAS 30451 by intravenous infusion 30 min before and 120 min after chemotherapy at doses ranging from 0.025 mg/kg × 2 to 0.4 mg/kg × 2.

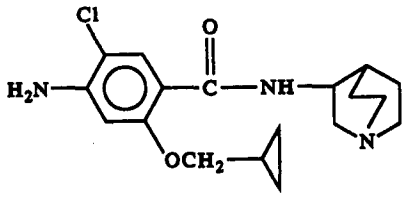

Fig. 1. LAS 30451: chemical structure.

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Table 1. *Dose-finding study of LAS* 30451: *complete protection against acute emesis*

Dose level (mg/kg × 2 intravenous)	Overall population	Cisplatin-treated patients	Non-cisplatin-treated patients
0.025	5/15 (33%)	0/2 (0%)	5/13 (38%)
0.05	5/15 (33%)	1/6 (17%)	4/9 (44%)
0.1	10/15 (67%)	4/6 (67%)	6/9 (67%)
0.2	11/15 (73%)	1/4 (25%)	10/11 (91%)
0.3	4/15 (27%)	0/5 (0%)	4/10 (40%)
0.4	5/15 (33%)	3/9 (33%)	2/6 (33%)

Overall, complete protection against acute emesis (0 vomiting episodes during the first 24 h) was obtained in 10/32 patients (31%) on cisplatin treatment and in 31/58 patients (53%) treated with other emetogenic cytotoxic drugs. The most efficacious doses in preventing acute vomiting were 0.1 mg/kg × 2 and 0.2 mg/kg × 2, with complete protection at 67 and 73%, respectively (Table 1). In this study, LAS 30451 was well tolerated. Facial flushing (2 patients), itching nose (1 patient), erythema (1 patient) and diarrhoea (1 patient) were minor complaints reported following treatment. No serious adverse events were observed at any dose levels studied. The dose of LAS 30451 for future clinical trials is likely to be 0.1 mg/kg × 2 or 0.2 mg/kg as a single intravenous administration.

Several studies comparing LAS 30451 with high-dose metoclopramide in patients under emetic chemotherapy are currently ongoing. The potential synergism between LAS 30451 and corticosteroids will also be studied.

The results of all these studies will define the practical interest of LAS 30451 and the precise role that this drug may play in the control of chemotherapy-induced nausea and vomiting.

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