Pharmacokinetics of Droperidol in Healthy Volunteers Following Intravenous Infusion and Rectal Administration from an Osmotic Drug Delivery Module

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INTRODUCTION

Droperidol, a butyrophenone derivative, has been used for the prevention and treatment of nausea and vomiting in postoperative patients and in patients undergoing chemotherapy. Efficacious parenteral doses have been reported to be in the range of 0.25 to 5 mg (1). The main side effects of droperidol, somnolence and extrapyramidal reactions, have been observed at the higher doses used.

Droperidol is currently administered via intravenous and intramuscular routes. One problem with oral administration is that droperidol is a moderate- to high-clearance (CL) drug and is extensively metabolized in the liver (2–4). Another problem is the difficulty in using the oral route in patients who are nauseated and/or vomiting. The rectal route obviates the problems of the oral route while avoiding the invasive procedures associated with iv or im administration.

The conventional rectal dosage form is a suppository. Theeuwes (5), however, has suggested that drugs could be administered rectally via an osmotic delivery module (ODM; Osmet, ALZA Corp., Palo Alto, CA) to achieve continuous drug delivery over a prolonged time period. Because the rectally administered ODM retains its integrity, easy removal of the device is possible by pulling an attached string should adverse effects require the termination of treatment.

The objective of this pilot study was to evaluate the feasibility of rectal administration and to determine the bioavailability of droperidol delivered continuously from an ODM compared to an intravenous infusion of a commercially available product (Droleptan).

MATERIALS AND METHODS

The controlled-release system, ODM, which was used to deliver the drug to the rectal mucosa, is comprised of an outer semipermeable membrane and a single-compartment reservoir (5,6). A string is attached to each unit for easy removal. All units were presoaked in water for 3 hr before insertion to reduce the time to onset of delivery. Following administration, the ODM imbibes water from the alimentary tract at a rate controlled by the semipermeable membrane and the osmotic pressure. The imbibed water generates hydrostatic pressure on the flexible lining of the drug reservoir, gradually compressing it and producing a flow of the drug through the delivery orifice. Each ODM module contained 3 mg equiv droperidol in aqueous solution and was designed to deliver at a constant rate for 15 hr. The *in vitro* release profile of droperidol from six ODMs was studied by a method described by Theeuwes (6), using 150 ml of receptor fluid and sampling every 3 hr.

Clinical Protocol. Eight healthy male subjects between 19 and 29 years of age and with body weights between 64 and 76 kg completed the open-label, randomized, crossover study. Each subject received 3 mg droperidol rectally via an ODM inserted for 24 hr or intravenously as a 24-hr constant-rate (125-μg/hr) infusion. Each treatment was followed by a washout period of 7 days. Subjects arrived at the inpatient center on the night preceding each treatment and remained for 36 hr after dosing. All subjects received their treatments within 30 min of each other after their morning bowel movement and breakfast. This study was conducted at the Charterhouse Clinical Research Unit Ltd., U.K. and was approved by the ethics committee of that institute.

Blood Sampling and Analytical Determinations. Blood samples (10 ml each) were drawn at 0, 0.5, 2, 4, 6, 8, 10, 14, 18, 24, 26, 28, 30, 33, and 36 hr after the start of each treatment into a heparinized tube. Plasma samples were analyzed for droperidol concentrations using radioimmunoassay with a minimum detection limit of 0.20 ng/ml (2).

Pharmacokinetic Methods. The observed maximum plasma droperidol concentration (C_{max}) and its corresponding sampling time (t_{max}) were determined for both ODM and intravenous administrations. The elimination rate constant (k_{el}) was obtained by linear regression of the log plasma droperidol concentration–time data obtained after stopping the intravenous infusion.

The elimination rate constant (k_{el}) following intravenous administration was used for extrapolation of areas to infinity of both the intravenous infusion ($AUC_{infusion}$) and the ODM (AUC_{rectal}). The apparent elimination half-life (HL) was calculated as $0.693/k_{el}$, and CL as the intravenous dose/$AUC_{infusion}$. Absolute bioavailability (F) was calculated as the ratio of the dose normalized AUC for the ODM treatment to that for intravenous infusion.

The following noncompartmental parameters for both ODM and intravenous administrations were calculated using equations developed by Watari and Benet (7). Mean residence time (MRT) corrected for the duration of infusion was calculated as

$$MRT = AUMC_{infusion}/AUC_{infusion} - \text{Infusion Duration}/2$$

Mean input time (MIT) for ODM was calculated using the *in vitro* release rate data as follows:

$$MIT_{osmet} = \sum_{i=1}^{n} R_i * [(t_i^2 - t_{i-1}^2)/2]/\text{Dose}$$

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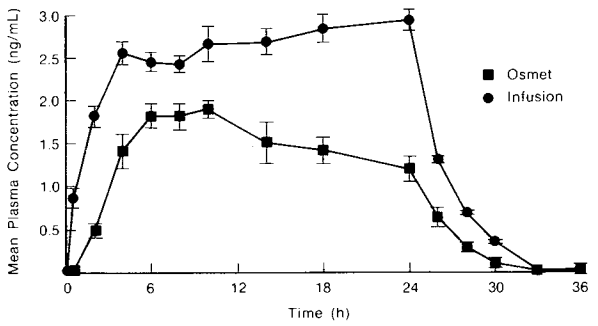

Fig. 1. Mean (±SE) plasma droperidol concentration during and following 24-hr intravenous infusion or rectal administration of droperidol via ODMs, to eight healthy volunteers.

where R_i is the *in vitro* rate of droperidol release between time t_i and t_{i-1} and Dose is the total amount released. Mean absorption time (MAT) was calculated as

$$MAT_{rectal} = AUMC_{rectal}/AUC_{rectal} - MRT - MIT_{osmet}$$

Assuming absorption to be a first-order process, the apparent absorption rate constant (k_a) for droperidol was calculated as

$$k_a = 1/MAT_{rectal}$$

Absorption half-life was calculated by

$$t_{1/2,abs} = 0.693 * MAT_{rectal}$$

RESULTS

Following rectal administration of droperidol, the mean plasma droperidol concentration increased during the first 10 hr and then declined slightly up to 24 hr. Following the removal of ODM (24 hr), the droperidol plasma concentrations declined rapidly and were detectable in only three subjects by 30 hr after administration. Following intravenous administration, the plasma droperidol concentrations increased rapidly within the first 4 hr and then remained relatively steady through the end of the infusion (24 hr), when they declined rapidly (Fig. 1). The mean maximum concentration achieved following ODM administration was lower than that obtained following intravenous administration (2.1 vs 3.2 ng/ml; Table I, Fig. 1).

Plasma droperidol concentrations obtained following intravenous infusion were fitted to a one-compartment infusion model. Using noncompartmental methods, mean CL and MRT values of 39.4 L/hr and 2.7 hr were obtained (Table I). Using noncompartmental techniques and assuming a first-order process, MAT for droperidol administered from an ODM module was 3.9 hr (Table I), suggesting that absorption of droperidol from the rectum is slow, with a mean absorption half-life of 2.7 hr. No detectable amounts of droperidol were found in any of the recovered ODMs, suggesting that all the droperidol in each ODM was delivered.

DISCUSSION

The mean maximum droperidol concentration achieved following ODM administration was 66% of that obtained following intravenous administration. The elimination half-life following intravenous administration was estimated to be 1.9 hr (in Table I, mean k_{el} = 0.362, $0.693/k_{el}$ = 1.9), a value similar to the 2.2 hr reported by Cressman *et al.* (8).

The mean total CL value obtained in this study was 39.4 L/hr (9.3 ml/min/kg; Table I). A slightly higher CL value of 14.1 ml/min/kg was observed in anaesthetized patients (2). The difference in CL values may be due to difference in the subject population. A CL value of 9.3 ml/min/kg in healthy volunteers and 14.1 ml/min/kg in anaesthetized patients categorizes droperidol as a moderate- to high-CL drug. Because the blood-to-plasma ratio of droperidol is unity (9), and if one assumes that systemic CL is equal to hepatic CL and that hepatic blood flow is 21.4 ml/min/kg (10), then the extraction ratio (ER) of droperidol, in the present study, should be about 0.43. This suggests a maximum possible oral bioavailability ($F = 1 - ER$) of 0.57. The mean droperidol bioavailability when administered rectally by ODM was estimated to be 50% (range, 39 to 65), suggesting that all the delivered droperidol was absorbed from the upper end of the rectum.

Using the Wagner–Nelson method (11), both the amount absorbed and the rate of absorption (appearance) during various sampling times were calculated following both intravenous and rectal administrations. Figure 2 depicts

Table I. Noncompartmental Pharmacokinetic Parameters Obtained Following Both Intravenous and Rectal Administrations of Droperiodal to Healthy Volunteers

		Intravenous							Rectal					
Subject	Weight (kg)	AUC_{inf} (ng-hr/ml)	C_{max} (ng/ml)	T_{max} (hr)	MRT (hr)	K_{el} (hr^{-1})	CL (L/hr)	CL (ml/min/kg)	C_{max} (ng/ml)	T_{max} (hr)	MAT (hr)	F (%)	K_a (hr^{-1})	AUC_{inf} (ng-hr/ml)
1	76.0	55	2.4	10.0	2.58	0.323	46.8	10.26	2.1	6.0	4.61	65	0.217	42
2	75.0	70	3.3	18.0	3.23	0.348	37.0	8.22	2.0	8.0	3.94	51	0.254	40
3	69.0	64	3.0	24.0	2.84	0.381	44.7	10.80	1.8	10.0	5.84	55	0.171	38
4	64.0	76	4.0	10.0	2.51	0.377	37.6	9.79	2.3	6.0	1.39	38	0.719	31
5	67.0	74	3.3	18.0	3.05	0.340	35.0	8.71	2.3	4.0	2.23	49	0.448	42
6	71.0	68	3.1	24.0	2.54	0.384	37.8	8.87	2.2	10.0	4.53	41	0.221	33
7	70.0	79	3.3	14.2	2.52	0.354	36.2	8.62	1.8	6.0	3.64	38	0.275	32
8	74.0	65	3.0	23.8	2.55	0.392	39.6	8.92	2.7	8.8	4.77	65	0.210	49
Mean	70.8	69	3.2	17.8	2.73	0.362	39.4	9.27	2.1	7.3	3.87	50	0.314	38
SD	4.2	9	0.6	5.9	0.28	0.025	4.2	0.84	0.3	2.3	1.44	11	0.184	6

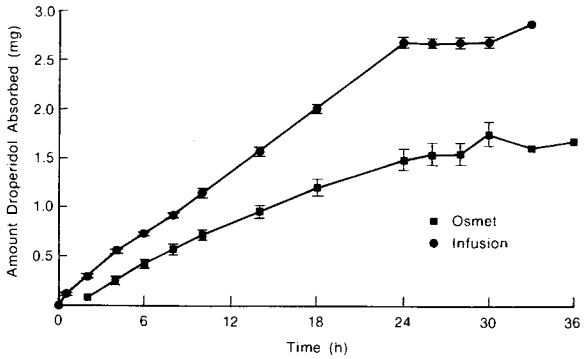

Fig. 2. Mean (±SE) cumulative amount of intact droperidol absorbed following rectal and intravenous administration to eight healthy volunteers.

the mean *in vivo* cumulative absorption (appearance) profiles for intact droperidol when administered rectally and intravenously. The amount of droperidol absorbed following rectal administration is less, as reflected by its 50% bioavailability. As expected, there is continuous absorption of droperidol up to 24 hr. Observation of this absorption up to 24 hr is in agreement with the duration of release from the ODM (15 hr) plus the time for 90% absorption to occur (8.8 hr, i.e., 3.3 half-lives of absorption; Table I) after the release from the ODM is complete.

In conclusion, the antiemetic drug, droperidol, can be administered rectally to achieve therapeutically relevant concentrations. Dose-ranging studies need to be conducted to define the optimal dose for maximum efficacy and minimum side effects. Compared to the conventional suppositories, rectal ODM offers several advantages for drugs with a narrow therapeutic index, a relatively short half-life, and/or wide variations in dose requirement, including the following: (i) rapid absorption of drug results in quick onset of effect; (ii) sustained drug delivery up to 24 hr avoids the toxic effects associated with the peak blood or plasma concentrations and permits low-dose delivery; and (iii) therapy can be discontinued when desired simply by removing the system.

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