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DIPHENHYDRAMINE KINETICS FOLLOWING INTRAVENOUS, ORAL, AND SUBLINGUAL DIMENHYDRINATE ADMINISTRATION

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ABSTRACT

Eight healthy volunteers received 50 mg of dimenhydrinate, a theoclate salt of diphenhydramine, orally, sublingually, and intravenously on three separate occasions in random sequence. Plasma diphenhydramine concentrations during 12 h after each dose were measured by gas-liquid chromatography with nitrogen-phosphorous detection. Mean peak plasma concentrations after sublingual administration were slightly lower than after oral dosage (38·3 vs 47·8 ng ml^{-1}), and the time of peak concentration was similar (2·6 vs 2·3 h after dose). These differences did not reach statistical significance. The mean total area under the plasma concentration–time curve (AUC) for sublingual administration was slightly but not significantly smaller than after oral dosage (221 vs 270 h ng ml^{-1}). Systemic availability of diphenhydramine after sublingual dimenhydrinate, measured by the ratio of oral AUC to intravenous AUC, was slightly less than after oral dimenhydrinate (0·58 vs 0·69, NS), and both were significantly less than 1·0. Thus sublingual and oral administration of dimenhydrinate result in comparable, but incomplete, systemic availability of diphenhydramine.

KEY WORDS Diphenhydramine Dimenhydrinate Sublingual dosing

INTRODUCTION

Dimenhydrinate (Dramamine) is a theoclate salt of the ethanolamine derivative diphenhydramine. It is commonly used as an antiemetic in the prevention and treatment of motion sickness.[1,2] Dimenhydrinate is also used in preventing and treating vertigo, including that associated with Meniere's disease, and in the treatment of nausea and vomiting associated with the use of radiation or cytotoxic drugs.[3] Although previous studies have described the systemic

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availability of orally administered diphenhydramine,[4-7] no data exist evaluating the possible utility of the sublingual dosage route, which could be useful in various clinical situations. For some patients, oral administration may be undesirable because of nausea, vomiting or other situations when the use of the gastrointestinal tract needs to be avoided. The present study compared the pharmacokinetics and absolute systemic availability of diphenhydramine from intravenous, oral, and sublingually administered dimenhydrinate.

METHODS

Eight healthy male and female volunteers aged 18 to 45 years participated in a single-dose, three-way, crossover study after giving written informed consent. All were healthy, active, ambulatory adults, without a history of medical disease and taking no other medications.

The three trials were separated by at least 1 week, and the sequence was randomized. The modes of administration were: intravenous, oral, and sublingual. In each trial, a single 50 mg dose of dimenhydrinate (Dramamine, Searle Pharmaceuticals, Chicago, IL), the equivalent of 27·2 mg of diphenhydramine base, was administered to each subject. For the intravenous trial, 1 ml of the injectable solution (50 mg ml^{-1}) was infused into an antecubital vein over a 1-min period. For the sublingual trial, a single 50 mg oral tablet was placed under the tongue and held there for 15 min. For the oral dosage trial, subjects ingested the 50 mg oral tablet with 100–200 ml of tap water following an overnight fast. They remained fasting until 3 h after dosage, after which they resumed a normal diet.

For both the sublingual and oral trials, venous blood samples were drawn into heparinized Venoject tubes (Terumo Medical, Elkton, MD) prior to drug administration and at the following post-dosage times: 15, 30, and 45 min and 1, 1·5, 2, 2·5, 3, 4, 5, 6, 7, 8, 10, and 12 h. Following intravenous administration, an additional sample was drawn at 5 min. All samples were drawn via an indwelling butterfly cannula kept patent by a slow infusion of physiologic saline. Blood samples were centrifuged and the plasma was separated and stored at –20° until the time of assay.

Concentrations of diphenhydramine in all samples were determined by gas-liquid chromatography with nitrogen-phosphorous detection using a previously described method.[4,8] All samples from a given subject's set of three trials were extracted and analysed on the same day using the same calibration standards.

Pharmacokinetic analysis

Diphenhydramine plasma concentrations following intravenous dosage were analysed by weighted iterative nonlinear least-squares regression techniques.[9] Plasma concentrations were fitted to a linear sum of two exponential terms.

Exponents and infusion-correction coefficients from the function of best fit were used to determine diphenhydramine volume of distribution using the area method, apparent elimination half-life, total area under the plasma concentration–time curve (AUC), and total clearance. After oral and sublingual administration of dimenhydrinate, the slope (beta) of the terminal log-linear phase of the plasma concentration curve was determined by linear regression analysis. This was used to calculate the apparent elimination half-life ($t_{1/2}$). AUC up to the last detectable concentration was determined by the trapezoidal method. To this was added the residual area extrapolated to infinity, calculated as the last concentration divided by beta, yielding the total AUC. The apparent systemic availability of diphenhydramine for oral and sublingual dimenhydrinate for each subject was calculated as the ratio of the total AUC following oral or sublingual dosage divided by AUC after intravenous injection in the same subject. The effect of the route of administration on the pharmacokinetic parameters was statistically compared using a Student's *t*-test.

RESULTS

The peak plasma concentration following oral dosage was higher than after sublingual administration (47·8 vs 38·3 ng ml^{-1}) and the time of peak concentration following oral administration was reached slightly sooner after

Table 1. Kinetics of diphenhydramine after intravenous, oral and sublingual dimenhydrinate

Parameter	Mean ± SE value		
	Intravenous	Oral	Sublingual
Volume of distribution ($l\ kg^{-1}$)	3·56 ± 0·45		
Elimination half-life (h)	4·7 ± 0·5	5·3 ± 0·5	5·4 ± 0·5
Clearance ($ml\ min^{-1}\ kg^{-1}$)	8·76 ± 0·49		
Total AUC (h ng ml^{-1})	528 ± 30	270 ± 38	221 ± 41
Peak plasma concentration (ng ml^{-1})		47·8 ± 5·4	38·3 ± 4·7
Time of peak (h after dose)		2·3 ± 0·2	2·6 ± 0·3
Systemic availability (fraction of IV dose)	1·00	0·69 ± 0·09	0·58 ± 0·09

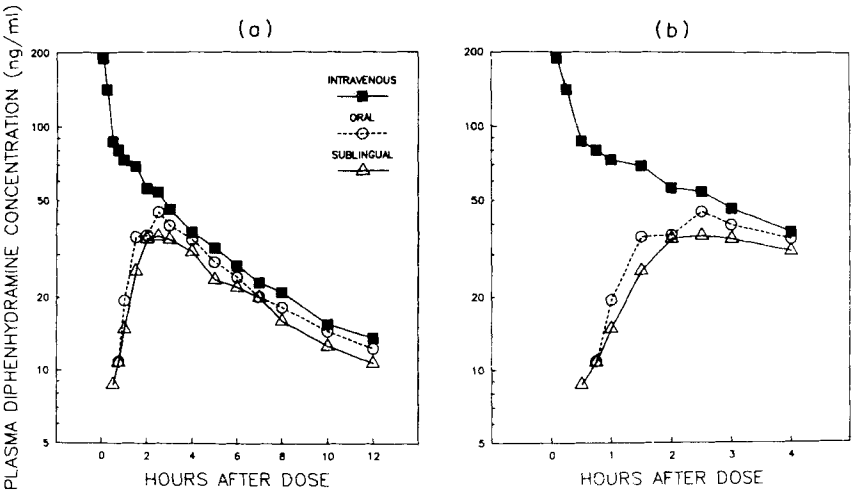

Figure 1. (a) Plasma diphenhydramine concentrations during 12 h after sublingual, oral, and intravenous administration of dimenhydrinate, 50 mg. Each point is the mean value for all subjects at the corresponding time. (b) The first 4 h after dosage shown on an expanded time scale

dosage (2·3 vs 2·6 h). However, the differences did not reach statistical significance. The mean total AUC for oral administration was larger than that following sublingual dosage (270 vs 221 h ng ml^{-1}), and systemic availability (fraction of intravenous dose) was greater following oral dosage than after sublingual administration (0·69 vs 0·58). None of these differences were statistically significant (Table 1, Figure 1). However, both values of absolute bioavailability were significantly less than 1·0.

DISCUSSION

Sublingual administration of drugs has been used in clinical practice for many years. For some drugs which undergo presystemic (first-pass) hepatic extraction, the sublingual or buccal route of administration may be desirable. In some patients, oral administration may be undesirable because of nausea, vomiting or other situations when the use of the gastrointestinal tract needs to be avoided. A number of drugs are well absorbed via the oral mucosa, and have been or still are given sublingually.[8–21]

This study describes the comparative kinetics of diphenhydramine following intravenous, oral, and sublingual administration of dimenhydrinate, the theoclate salt of diphenhydramine. Diphenhydramine availability after sublingual administration was similar to that following oral dosage on an empty stomach. Although not statically significant, peak plasma concentrations were slightly higher and reached slightly earlier after the dose following oral than after

sublingual dosage. Systemic availability of diphenhydramine by both routes was similar. Our results of the fraction of diphenhydramine available after oral administration (0·69) were similar to those reported by Blyden *et al.*[4] (0·72).

The present study demonstrates that for dimenhydrinate, both the sublingual and oral routes of administration result in comparable, although incomplete, systemic availability of diphenhydramine. Thus, when clinical circumstances warrant it, the sublingual route may be an acceptable alternative to oral or intravenous administration.

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