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Effect of polycarbophil concentration on in vitro release and in vivo availability in beagle dogs of dihydroergotamine mesylate suppositories

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Abstract

The effect of different concentrations (5, 10 and 20% w/w) of polycarbophil on the in vitro release and in vivo availability of dihydroergotamine mesylate from polyethylene glycol suppositories was studied. In vitro release data showed that as the polycarbophil concentration in the suppositories increased, the release rate decreased. The in vivo data revealed that suppositories containing 5% polycarbophil resulted in a significant ($p < 0.05$) reduction in C_{max} and non-significant decrease in AUC and produced 62% relative bioavailability compared to that of polyethylene glycol suppositories containing 0% polycarbophil (control). The addition of 10% polycarbophil to the suppository formulation resulted in a lower reduction in C_{max} and AUC than the addition of 5% and gave 78.9% relative bioavailability. The suppositories containing 20% polycarbophil produced higher C_{max}, AUC, and relative bioavailability (127%) compared to the control. The concentration of polycarbophil in dihydroergotamine suppository formulations is critical in determining the release rate of the drug and its bioavailability.

Keywords: Polycarbophil; Dihydroergotamine; Suppository; In vitro release; In vivo bioavailability

1. Introduction

Dihydroergotamine (DHE) mesylate is the treatment of choice in relieving migraine (Goadsby and Gundlach, 1991). Its pharmacological actions are complex, acting on the cardiovascular system, both centrally and peripherally, and on the central nervous system (Reynolds et al., 1982; Gilman et al., 1985).

The oral absorption of DHE ranges from 19.5 to 53.3%, but 96% of the absorbed dose is subject to first-pass metabolism resulting in a systemic bioavailability in the range of 0.1–1.5% (Babik et al., 1981). This suggests that first-pass liver metabolism is the prime determinant of DHE oral bioavailability.

The rectal route provides an excellent alternative to the oral pathway provided that the suppository is localized in the bottom one-third of the rectal vault where the drug released in this area is carried by the inferior and/or middle hemorrhoidal veins directly into general circulation via

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the inferior vena cava, thus bypassing the liver metabolism. Polycarbophil (Markus, 1965) as a bioadhesive polymer (Gurny et al., 1984; Banker, 1980; Ch'ng et al., 1985; Longer et al., 1985; Nagai and Machida, 1985) is useful in rectal drug delivery (Hosny, 1988; Hosny and Robinson, 1991; Hosny and Al-Angary, 1995) for purposes of retaining the suppository in the lower part of the rectum, thus helping the drug avoid first-pass liver metabolism, as well as improving drug absorption by increasing the intimacy and duration of contact of the drug with the absorbing membrane.

The purpose of this study was to investigate the effects of the concentration of bioadhesive polymer, polycarbophil, on the in vitro release of DHE from polyethylene glycol (PEG) 4000 suppositories and on the bioavailability of DHE after rectal administration of these suppositories to beagle dogs.

2. Materials and methods

2.1. Materials

Dihydroergotamine mesylate was obtained from Sandoz Research Institute (East Hanover, NJ, USA). Polyethylene glycol 4000 was from E. Merck (Darmstadt, Germany). Polycarbophil was a kind gift from Lee Laboratories Inc. (Petersburg, VA, USA). All other solvents and reagents were of analytical and HPLC grade.

2.2. Methods

2.2.1. Preparation of suppositories

Suppositories containing 10 mg DHE were prepared using the fusion method by melting the PEG base at moderate temperature on a water bath, adding the drug and the polycarbophil subsequently with trituration after each addition until a homogeneous mass was produced and then pouring into a 1 g mold followed by cooling. The displacement values of DHE and polycarbophil were determined in PEG. All the suppositories contained 10 mg DHE and 0, 5, 10 and 20% (w/w) polycarbophil.

2.2.2. In vitro release of DHE

The in vitro release of DHE from PEG suppositories (control) and those containing different concentrations (5, 10 or 20%) of 30/40 mesh particles of polycarbophil was determined using an automated PU 8605/60 dissolution monitoring system consisting of USP dissolution apparatus I and a spectrophotometer (Philips PU 8620, UK) and an IBM computer (PS/2 model 30; Philips, UK). Samples were withdrawn automatically every 15 min and the absorbance of each sample was determined at 280 nm. The dissolution medium was 300 ml of distilled H_2O/ethanol (1:1) maintained at 37°C and the rate of rotation 50 rpm. Each determination was carried out in triplicate.

2.2.3. Animal studies

Six healthy male beagle dogs were used in this study. Their mean weight was 9.0 ± 1.73 kg. The dogs were maintained on a normal diet with free access to water. 1 week was permitted between successive dosing. The animals remained in good health throughout the entire period of the study. During the experimental period each dog was placed in the upright position in the restainer stand. The legs were shaven and a cephalic vein was cannulated using an 18 gauge cannula. 4-ml blood samples were withdrawn into heparinized vacutainer tubes at 0, 0.5, 1, 2, 4, 6, 8, and 12 h after rectal administration of the suppositories. The tubes were then centrifuged for 15 min and plasma was aspirated and kept frozen until analysis.

2.2.4. Assay method for DHE

Concentrations of DHE in the various samples were determined using an HPLC assay method previously developed in our laboratory (Niazy et al., 1988).

2.2.5. Pharmacokinetic analysis

The maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were obtained directly from the plasma concentration-time profiles. The area under the plasma concentration-time curve upto the last measurable concentra-

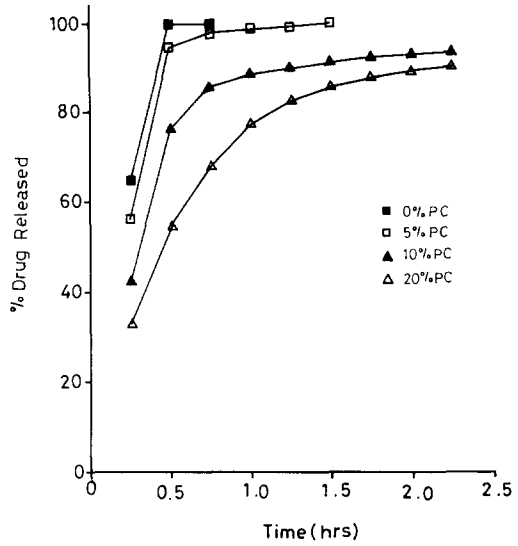

Fig. 1. Effect of different concentrations of polycarbophil (0, 5, 10 and 20% w/w) on the % release of dihydroergotamine mesylate from PEG suppositories.

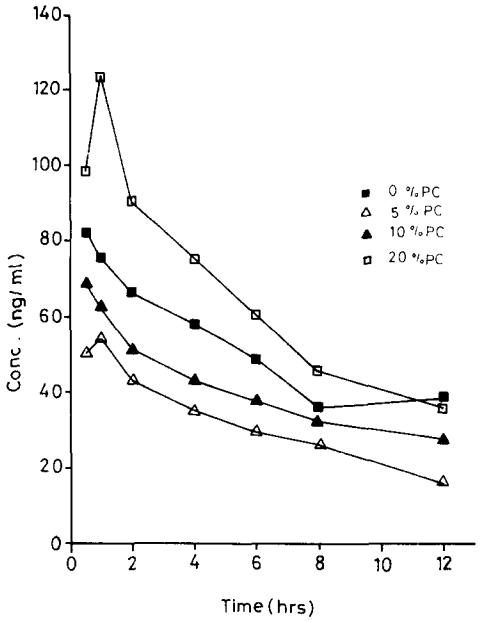

Fig. 2. Mean plasma concentration of dihydroergotamine following rectal administration of PEG suppositories containing 0, 5, 10 or 20% (w/w) polycarbophil.

tion ($AUC_{0\rightarrow t}$) was determined according to the trapezoidal rule.

2.2.6. *Statistical analysis*

All results are expressed as mean ± standard deviation ($X \pm$ S.D.). The significance of the difference between treatments was evaluated by using unpaired Student's *t*-test on a microcomputer statistical package (SAS, Statistical Analysis System). Differences were considered significant for *p* values equal to or less than 0.05.

3. Results and discussion

Fig. 1 shows the in vitro release data of DHE from PEG suppositories and from these suppositories containing polycarbophil in different concentrations (5, 10 and 20% w/w). From Fig. 1, it is evident that as the polycarbophil concentration increases in the suppository, the release rate of DHE decreases. This could be attributed to one or more of the following reasons. Polycarbophil exerts an adhesive effect between the particles, thus decreasing the surface area available for the release of DHE. Also, as the polycarbophil is added to the PEG melted suppository, there occurs a large increase in consistency. Finally, polycarbophil after swelling provides a diffusion barrier for the drug, thereby decreasing its release rate. Fig. 2 and Table 1 provide the plasma DHE

Table 1
Mean pharmacokinetic parameters of dihydroergotamine following the rectal administration of PEG suppositories containing 0, 5, 10 or 20% (w/w) polycarbophil

Parameters	Polycarbophil concentration (% w/w)			
	0	5	10	20
C_{max} (ng/ml)	82.39 ± 18.50	54.27 ± 13.10	68.31 ± 25.57	124.31 ± 20.62
T_{max} (h)	0.50 ± 0.0	0.67 ± 0.29	0.67 ± 0.29	0.83 ± 0.29
$AUC_{0\rightarrow 12\,h}$ (ng h ml^{-1})	595.05 ± 218.58	368.91 ± 73.49	469.47 ± 108.14	755.81 ± 105.82
Relative bioavailability [a]	–	62.00%	78.90%	127.02%

[a] Compared to that of PEG suppositories containing no polycarbophil.

concentrations in addition to the pharmacokinetic parameters resulted after the administration of PEG suppositories containing 0, 5, 10 and 20% (w/w) of polycarbophil. The results show that the absorption of DHE from all suppositories was rapid as indicated by the short T_{max} (0.5–0.83 h). The average peak concentrations (C_{max}) declined by 34.1 and 17.1% following rectal administration of DHE suppositories containing 5 and 10% polycarbophil, respectively, compared to the control suppositories. Moreover, the relative bioavailability from these formulations decreased by 38.0 and 21.1%, respectively.

These data show that the addition of 5% polycarbophil resulted in a greater reduction of C_{max}, AUC and relative bioavailability than that produced by addition of 10% of the polymer. This could be explained on the basis that at the 5% concentration only the effects that were mentioned before in trying to explain the decrease in the in vitro release data predominated. At the 10% concentration other effects of the bioadhesive started to take place as it has the potential to improve therapy by increasing the contact time and intimacy of contact of the drug with the absorbing membrane. These effects were very evident on using 20% polycarbophil in the formulation where C_{max} and relative bioavailability increased by 50.9 and 27.0%, respectively. At this high concentration (20%) the bioadhesive polymer effects on increasing the contact time and intimacy of contact of the suppositories with the rectal mucosa and probably retaining the dosage form in the lower part of the rectum, minimizing or avoiding upward movement which would help the drug avoid first-pass liver metabolism to a greater extent, overcome the effects of the polymer on reducing the release from the suppositories.

In conclusion, the key step in formulating such suppositories is to use the optimum concentration of the bioadhesive which achieves an improvement in blood levels and bioavailability.

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