PHARMACOKINETICS AND DISPOSITION

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Changes in gastrointestinal motility influence the absorption of desmopressin

Abstract Objective: The antidiuretic effect of desmopressin is widely utilized in the treatment of neurogenic diabetes insipidus and nocturnal enuresis in children. The objective of the present study was to assess how changes in gastrointestinal motility, induced by erythromycin and loperamide, influence the pharmacokinetics of orally administered desmopressin.

Methods: This study was conducted using an open randomized, three-period, three-treatment design in 18 healthy subjects. On each study day a single oral dose of 400 µg desmopressin was administered in the morning. The desmopressin dose was either given alone (reference) or after pretreatment with either loperamide tablets (4 mg at −24, −12 h and −1 h) or erythromycin capsules (250 mg q.i.d, with the first dose in the morning 3 days before the study day and the last dose at −1 h). On each study day, blood was sampled up to 8 h after dosing for assessment of desmopressin concentration.

Results: Compared with administration of 400 µg of desmopressin alone, pretreatment with loperamide produced significantly (P < 0.05) altered pharmacokinetics of desmopressin as the endpoints; area under the curve up to infinity (AUC), area up to the last determinable plasma concentration (AUCt) and maximum plasma concentration (Cmax) increased 3.1-fold (95% CI 2.3–4.2), 3.2 (2.3–4.4) and 2.3 (1.6–3.2), respectively. Although the estimates were lower, pretreatment with erythromycin did not result in any significant changes in these endpoints. There were no significant changes observed between the three treatments regarding the terminal elimination half-life (t1/2). However, significant

(P < 0.05) changes in the time to reach Cmax (tmax) values (median and range) were observed as, compared with administration of desmopressin alone (1.3 h and 0.5–4.0), it was longer after pretreatment with loperamide (2.0 h and 0.5–3.0) and shorter following pretreatment with erythromycin (0.9 h and 0.5–1.3).

Conclusion: Presumably due to slower gastrointestinal motility, pretreatment with loperamide significantly increases the gastrointestinal absorption of desmopressin. Except for a shortening of tmax, pretreatment with erythromycin did not significantly influence absorption of the drug.

Key words Gastrointestinal motility · Absorption · Desmopressin

Introduction

Desmopressin (dDAVP) is a synthetic analogue of the neurohypophysial hormone vasopressin (antidiuretic hormone). In contrast to its endogenous prototype, desmopressin has essentially no pressor effect [1]. The antidiuretic effect of desmopressin is utilized in the treatment of neurogenic diabetes insipidus [2, 3] and nocturnal enuresis in children [4, 5]. Since desmopressin releases blood coagulation factors such as factor VIII and von Willebrandt factor, it is also used in high doses in some bleeding disorders [6]. Desmopressin is usually administered intranasally. However, as some gastrointestinal absorption exists, the oral route can be an alternative to most patients [5, 7]. The oral bioavailability of desmopressin has been estimated to be approximately 0.1% after administration in healthy volunteers [8]. This low oral bioavailability of desmopressin increases the risk of a highly variable absorption, in some instances precipitated by interactions with drugs or food. A variable absorption may cause difficulties in predicting the magnitude and duration of the antidiuretic effect achieved after a certain oral dose. A recent study
investigated the effect of food ingestion on the gastrointestinal absorption of orally administered desmopressin [9]. The results indicate a reduced and delayed absorption when desmopressin is administered with or 1.5 h after a meal. However, the influence of changes in gastrointestinal motility on the absorption of desmopressin has not been investigated previously. Gastrointestinal motility can be affected by some drugs. Erythromycin is a widely used macrolide antibiotic that increases gastrointestinal motility, it has been suggested that erythromycin stimulates the receptor for the gastrointestinal peptide motilin [10]. Slowing of gastrointestinal motility and reduced gastrointestinal secretion can be elicited by loperamide, a synthetic opioid that probably acts predominantly on μ-receptors in the gastrointestinal tract [11]. The objective of the present study was to assess how changes in gastrointestinal motility influence the pharmacokinetics of orally administered desmopressin, using erythromycin and loperamide as pharmacological tools.

Materials and methods

Subjects

A sample size of 18 subjects was estimated to be sufficient for attaining the objectives of this study. Two subjects were withdrawn after their first study periods: one subject suffered a femur shaft fracture after a fall and another subject was withdrawn due to non-compliance with the protocol (resumed smoking). As the withdrawn subjects were replaced, a total of 20 healthy subjects were recruited and began their participation in the study. The data from the 18 subjects who completed the trial are reported here. Thus, the study population comprised nine males and nine females, (age 23–45 years, weight 54–89 kg) who were non-smokers and free of medication (except for six of the females who used hormonal contraceptives). The subjects had no clinically relevant deviations from normal in the pre-study physical examination or laboratory check. None of the subjects had a history of hepatic or gastrointestinal disease. The study was approved by the University Ethics Committee and the Swedish Medical Products Agency. Written informed consent was given by each subject prior to their entry into the study. All experiments were conducted in accordance with current Swedish law.

Trial protocol

The study was conducted using an open randomized, three-way, Latin-square design. On each study day a single oral dose of 400 μg desmopressin as immediate release tablets (2 × 200 μg Minirin, Ferring, Malmö, Sweden) was administered. The desmopressin dose was either given alone (reference) or after pretreatment with either loperamide (Imodium, Janssen-Cilag, Beerse, Belgium) tablets (4 mg at −24, −12 h and −1 h) or erythromycin (Ery-Max, Astra, Södertälje, Sweden) capsules (250 mg q.i.d, with the first dose in the morning 3 days before the study day and the last dose at −1 h). Each subject kept a medication diary in order to document compliance with the protocol. At each study day the subjects arrived at the Department of Clinical Pharmacology after a fasting period of at least 10 h; intake of water and pretreatment medications was allowed but intake of food was prohibited. Each study day included blood sampling for assessment of desmopressin up to 8 h after dose. Blood samples (5 ml) were taken from an antecubital vein before and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5 h and 8 h after desmopressin intake. Each of the 3 study days were separated by a wash-out period of at least 12 days. Adverse events were recorded after open questioning and spontaneous reports on the study days. In addition, the subjects were contacted by telephone approximately 14 days after the last study day for the recording of adverse events.

Analysis of desmopressin concentrations

Blood samples (5 ml) were collected in vacuum tubes containing 0.05 ml K₂EDTA; 0.47 mol−1; 21% (Venoject, Terumo Europe, Leuven, Belgium) for analysis of desmopressin. The samples were centrifuged as soon as possible, but always within 45 min. Plasma was stored at −70 °C until assay. Before analysis all samples were extracted with acetone and petroleum ether. Dry extracts were stored at −20 °C. Plasma desmopressin levels were measured with a radioimmunoassay technique, using a specific antiserum raised in rabbits as described by Lundin et al. [12]. The lower limit of detection in the assay was 5.0 pg desmopressin·ml−1 plasma; however, by doubling the amount of plasma extracted, the limit of quantification was determined to be 2.5 pg desmopressin·ml−1 plasma. The intra- and interassay coefficients of variation of spiked K₂EDTA plasma were with SD 10.1 ± (3.9)% and 13.2% at 5.0 pg desmopressin·ml−1; 3.6 (3.9)% and 7.7% at 10.0 pg desmopressin·ml−1 and 5.0 (2.2)% and 6.9% at 100 pg desmopressin·ml−1, respectively. The recovery of desmopressin from spiked K₂EDTA plasma was 105% at 5.0 pg desmopressin·ml−1, 103% at 10.0 pg desmopressin·ml−1 and 98.9% at 100 pg desmopressin·ml−1.

Pharmacokinetic calculations and statistical procedure

The results presented in this report are based on a per protocol analysis of the 18 subjects who completed the trial. Estimates of the area under the curve up to infinity (AUC), the area up to the last determinable plasma concentration (AUC₀) and maximum plasma concentration (Cmax) were selected as primary endpoints in the protocol. The time to reach Cmax (tmax) and the terminal elimination half-life (t1/2) constituted the secondary endpoints in this study. The pharmacokinetic calculations, based on plasma concentrations of desmopressin, were performed by means of a non-compartmental analysis using model 200 of WinNonlin version 1.1 (Scientific Consulting, Apex, N.C., USA). Plasma concentrations below the level of quantification (LLQ) at early time points were set to zero. Plasma levels below the LLQ appearing in the terminal phase were set to missing in the kinetic calculations, but set to zero for calculation of median plasma concentrations. If two Cmax values occurred, the first of these was used in the description of tmax.

Application of regression analysis to the last time points was used for assessment of the elimination rate constant (k) and half-life (t1/2). The median with (range) number of points in regression for analysis of tmax alone, pretreatment with erythromycin and pretreatment with loperamide were 10.5 (4–11), 9 (5–11) and 11 (9–11), respectively. Extrapolation using k was employed to calculate AUC.

The analysis of logarithmically transformed primary pharmacokinetic parameters (AUC, AUC₀ and Cmax) was planned to be based on an ANOVA model with treatment, periods and subjects effects. As it turned out that the period effect was not statistically significant for any parameter, the period effect was excluded from the model, which now only contains treatment and subject. For these parameters geometric means (95% confidence limits) are presented. Non-parametric analysis of variance (Kruskal-Wallis and Wilcoxon as follow-up test) was used for the analysis of tmax and t1/2. For these parameters median (min-max) values are reported. All tests were performed using a 5% level of significance.