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Multiple dose pharmacokinetics of fiduxosin under fasting conditions in healthy elderly male subjects

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Abstract

Selective α_{1a}-adrenoceptor antagonists are effective agents for treatment of benign prostatic hyperplasia, a disorder occurring in middle-aged and elderly males. The objective of this study was to determine the pharmacokinetics of fiduxosin, a novel α_{1a}-adrenoceptor antagonist, following multiple dose administration. This was carried out in a Phase I, randomized, double-blind, placebo-controlled, parallel group, multiple oral dose study of fiduxosin. Single once-daily oral doses of 30, 60, 90 or 120 mg of fiduxosin or placebo were administered to healthy elderly male subjects (n = 48; 8 active and 4 placebo per dosing group) for 14 consecutive days. Fiduxosin plasma concentration-versus-time profiles for days 1, 7 and 14 were used to assess fiduxosin pharmacokinetics. Steady state was achieved by day 7. At steady-state mean T_{max} (time to maximum plasma concentration), CL/F (apparent oral clearance) and V_β/F (apparent volume of distribution) ranges were 1.8–7.8 h, 27.3–47.2 L h^{-1} and 846–1399 L, respectively. T_{max} and V_β/F were independent of dose. C_{max} (maximum plasma concentration), C_{min} (minimum plasma concentration) and AUC_{24} (area under plasma concentration vs time curve from 0 to 24 h) for days 7 and 14 were linearly proportional with dose over the 30–120 mg/day dose range and were unchanged from day 7 to day 14. It was concluded that fiduxosin multiple-dose pharmacokinetics were dose-independent and time-invariant over the 30–120 mg/day dose range under fasting conditions.

Introduction

Benign prostatic hyperplasia (BPH) is the most common cause of voiding dysfunction in men. The prevalence of BPH increases with age. Approximately 50% of all males older than 65 years have some degree of prostatic enlargement and one-third of these men have clinical symptoms consistent with bladder outlet obstruction (Jonler et al 1994b). There are two components of BPH-related bladder outlet obstruction: a dynamic and a static component (Jonler et al 1994a). The dynamic component is determined primarily by smooth muscle tone in prostate, prostatic urethra and bladder base, while the static component is related to the mechanical obstruction caused by the bulk of the enlarged prostate (Jonler et al 1994a). The smooth muscle cells in the prostate are innervated and regulated by the adrenergic portion of the autonomous nervous system. The dynamic component of BPH may be treated by α_1-adrenoceptor antagonists like terazosin, doxazosin and alfuzosin (Jonler et al 1994a, b; Chapple 1996). However, as these compounds were initially developed as antihypertensive agents, their use is associated with hypotensive effects, in some cases a liability in BPH patients, as well as dizziness and

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asthenia (Jonler et al 1994a). Pharmacological and molecular studies have revealed a number of different α_1-adrenoceptor subtypes (Price et al 1993, 1994; Wilde & McTavish 1996). The α_{1a}-adrenoceptor subtype has been identified as the most abundant α_1-receptor in the prostate and it mediates smooth muscle contraction (Price et al 1994; Chapple 1996).

Accumulating pre-clinical (Price et al 1993, 1994; Testa et al 1993; Yamada et al 1994) and clinical (Schulman et al 1996; Wilde & McTavish 1996) data support the concept that agents targeted towards the α_{1a}-adrenoceptor may represent an effective treatment for the relief of the symptoms of BPH with a reduced propensity to elicit the side effects seen with nonselective compounds. Clinical data from studies on the use of tamsulosin, a selective α_{1a}-antagonist, indicate that even a modest degree of α_{1a}:α_{1b}-adrenoceptor selectivity (7- to 38-fold) results in clinical benefit with an incidence of hypotension or orthostatic hypotension no greater than placebo (Kawabe 1995; Wilde & McTavish 1996). Fiduxosin is a novel selective α_{1a}/α_{1d}-adrenoceptor antagonist. A uroselective α_1-adrenoceptor antagonist targeted at prostatic α_{1a}-adrenoceptors which is more selective than existing agents, such as tamsulosin, with reduced hypotensive liability and incidence of dizziness would be a major advance in pharmacotherapy for BPH.

The single-dose pharmacokinetics of fiduxosin have been previously evaluated (Dutta et al 2001a). This is the first study exploring the pharmacokinetics of fiduxosin following multiple-dose administration under fasting conditions. Since the intended use of fiduxosin is in the middle-aged or elderly male population, pharmacokinetics were evaluated in healthy elderly ($\geqslant$ 60 years) male subjects.

Materials and Methods

Subjects

Subjects were healthy non-smoking males, at least 60 years of age, within 20% of the upper and lower boundaries of weight set forth in the Metropolitan Life Insurance Table. In the screening period before dosing, candidates received a full explanation of the study and underwent pre-study procedures. All enrollees gave written, informed consent, as approved by the ethics committee at U-Gene Research B. V., Utrecht, The Netherlands, before study participation. Subjects were judged to be in good health based on the results of medical history, physical examination, vital signs, electrocardiogram and routine clinical laboratory evaluations. Subjects had not taken any prescription or over-the-counter medication in the two weeks leading up to study drug administration, and were excluded if they required any medication on a regular basis, had a history of drug sensitivity or a significant allergic reaction to any drug, history of drug or alcohol abuse, history of fainting spells or black outs, history or current evidence of cardiovascular disorder or history of clinically significant dizziness. Subjects were excluded from the study if they had received any injectable drug within 30 days, or any investigational drug within the six weeks preceding study drug administration. Subjects were also excluded from the study if they had donated or lost 450 mL or more blood volume or had received a transfusion of any blood product during this period.

Study design

This was a Phase I, randomized, double-blind, placebo-controlled, parallel group, multiple oral dose study of fiduxosin. Forty-eight elderly male subjects were equally divided into four dosing groups. A randomization schedule was computer-generated for each dosing group before the start of the study. Within each dosing group eight subjects were randomized to receive fiduxosin and the remaining four were randomized to receive matching placebo. The drug administration schedules were designed such that successively higher doses were administered after safety had been determined for the previous group. Dosing for each group was separated by at least seven days to allow evaluation of the safety data from the preceding group. Single daily oral doses of 30, 60, 90 or 120 mg fiduxosin (Abbott Laboratories, Abbott Park, IL) or placebo were administered for 14 consecutive days (days 1–14). Subjects from each dose group were confined to the research unit for approximately 18 days. Standardized research unit meals were served during confinement and subjects were not permitted to engage in any strenuous activity or exercise during the study. All doses were administered orally with 180 mL of water after an 8-h fast and the first post-dose meal was consumed approximately 2 h after dosing.

Blood samples (7 mL) were collected for determination of fiduxosin plasma concentrations. The blood samples were collected into heparinized tubes before dosing at 0 h and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16 and 24 h after dosing on study days 1, 7 and 14. After the last dose on day 14, blood samples were also collected at 30, 36, 48, 72 and 96 h after dosing (for the 30-mg dose group blood was sampled up to 72 h only). In addition, blood samples were collected before dosing on days 4,

10 and 12. Blood samples were stored on ice and protected from light until centrifugation to separate the plasma. Plasma samples were subsequently frozen and stored at −20°C or lower until analysis.

Analytical methodology

Fiduxosin plasma concentrations were determined using a validated HPLC tandem mass spectrometric (MS/MS) method. Briefly, human plasma samples (500 μL) supplemented with internal standard and adjusted to basic pH with 0.75 mL of an aqueous solution of sodium hydroxide (0.1 N) were extracted with 6 mL of ethyl acetate. The extract was evaporated to dryness and the residue was reconstituted in a solution consisting of acetonitrile–0.1% trifluoroacetic acid in water, 40:60 v/v. Resolution of the analyte peaks was achieved with a Kromasil 100 C18 analytical column (100×3.0 mm) with a YMC Basic Direct Connect guard cartridge. The mobile phase consisted of acetonitrile–1% glacial acetic acid in water, 45:55 v/v, at a flow rate of 1.0 mL min^{-1}. The column effluent was ionized by atmospheric pressure chemical ionization via the heated nebulizer source. Mass analysis and analyte detection was achieved in the positive ion mode using MS/MS under multiple reaction monitoring conditions. Reactions monitored were (Q1 → Q3) m/z 514 → 255 and m/z 556 → 297 for the internal standard and fiduxosin, respectively. Calibration standard levels ranging from approximately 1.08 to 507.14 ng mL^{-1} were used in the assay. Quality control samples with theoretical concentrations of 4.99, 46.59 and 379.37 ng mL^{-1} were included during each run batch. The lower limit of quantitation was 1.08 ng mL^{-1}, and the assay was unbiased with coefficients of variation (CVs) $\leqslant$ 7%.

Pharmacokinetic analyses

Fiduxosin pharmacokinetic parameters were calculated using standard non-compartmental methods (Gibaldi & Perrier 1982). For the day 1, 7 and 14 data, the maximum plasma concentration (C_{max}), and the time to maximum plasma concentration (T_{max}) were determined from the observed plasma-concentration-versus-time data, and the area under the plasma-concentration-versus-time curves from time zero to 24 h after dose administration (AUC_{24}) were determined using linear trapezoidal method. Additionally, for day 7 and day 14 data, the minimum plasma concentration (C_{min}) was determined from the observed plasma-concentration-versus-time data and the apparent oral clearance (CL/F) was determined by dividing the dose by the day 7 and 14 AUC_{24} values, respectively. The terminal elimination rate constant (β) was estimated from day 14 washout data by linear regression of the natural log-transformed plasma concentrations in the apparent linear terminal phase using at least 3 time points. The data points determining the apparent linear phase were selected from visual inspection. The corresponding elimination half-life ($t_{1/2}$) was calculated as $\ln(2)/\beta$. Apparent volume of distribution (V_β/F) was determined by dividing the oral clearance (day 14) by β.

Safety and tolerability

Safety was evaluated through adverse event monitoring, clinical laboratory and non-laboratory testing and physical examinations. Tolerability was assessed in terms of stopping rules designed to estimate the maximum tolerated dose.

Statistical analysis

Mean and standard deviation were calculated for all pharmacokinetic parameters, except $t_{1/2}$. For $t_{1/2}$, the harmonic mean and pseudo-standard deviation were calculated (Roe & Karol 1997).

Dose proportionality and linear kinetics were assessed using analyses of covariance. Analyses of covariance with classification by dose level were performed on T_{max}, β (day 14 only), V_β/F (day 14 only) and dose-normalized C_{max}, C_{min}, and AUC_{24} for day 7 and day 14 separately. Body weight and age were included in the model as covariates. The primary test of the hypothesis of invariance with dose was a test on a contrast in dose level effects within the framework of the analysis of covariance with good power for a monotonic function of dose.

To assess time dependence of fiduxosin pharmacokinetics, the pharmacokinetic parameters (T_{max} and dose-normalized C_{max}, C_{min} and AUC_{24}) from day 7 were compared with their respective estimates from day 14 using analyses of variance on the changes in a parameter estimate. The factor in these analyses of variance was dose level and a test was performed on the average of the mean changes for the four dose levels. Additionally, the pre-dose concentrations from day 4 and later, and day 7 and later, were analysed separately to assess the attainment of steady state.

PROC GLM of SAS version 6.12 with Type III sums of squares was used for the analysis of covariance and analysis of variance models. $P \leqslant 0.05$ was considered statistically significant.

Results and Discussion

Forty-six male subjects who completed the study received either fiduxosin or placebo. The mean age, weight and height of the 31 subjects who received fiduxosin were 66 years (range 60–78 years), 81.6 kg (range 56.7–97.0 kg) and 176.4 cm (range 165.0–186.0 cm), respectively. Two subjects (one active and one placebo) assigned to the 60-mg dose group did not participate in the study, as they had protocol violations after being randomized to a dose group.

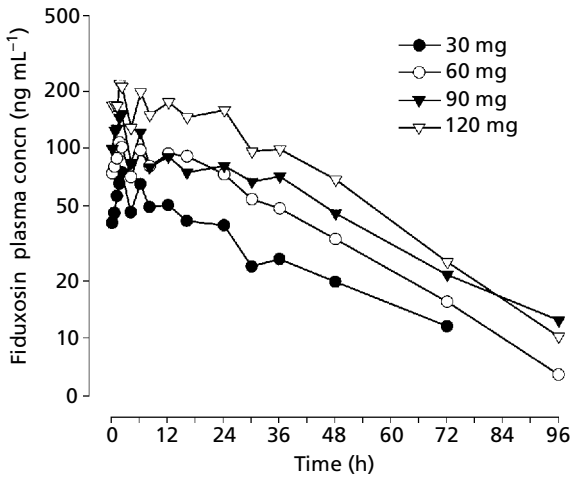

Figure 1 Mean fiduxosin plasma concentration–time profiles obtained after multiple-dose administration of fiduxosin on study day 14. Indicated doses were given once daily to elderly healthy male subjects.

Mean fiduxosin plasma-concentration-versus-time profiles obtained on day 14 after multiple-dose administration are illustrated in Figure 1. The mean (s.d.) fiduxosin pharmacokinetic parameters are presented in Table 1. The pre-dose concentrations from day 4 and later, and from day 7 and later were assessed separately for a linear trend with time. A significant ($P = 0.02$) linear trend with time was observed when pre-dose concentration from day 4 was included in the analysis; no trend with time ($P > 0.05$) was observed when the day 7 and later pre-dose concentrations were analysed. Therefore, steady state was achieved by day 7.

The harmonic mean half-life ranged from 17.3 to 25.5 h. As expected for a drug that is dosed at intervals approximating the half-life, the concentrations at steady state were approximately double the concentrations after the first dose. The mean accumulation ratios calculated as mean of the day 14 AUC_{24} and day 1 AUC_{24} ratios were 2.0, 2.2, 1.8 and 3.0 for the 30, 60, 90 and 120 mg/day dose groups, respectively. At steady

Table 1 Fiduxosin pharmacokinetic parameters in healthy elderly subjects.

Parameters	30 mg (n = 8)	60 mg (n = 7)	90 mg (n = 8)	120 mg (n = 8)
C_{max} (ng mL^{-1})				
Day 1	42.6 (21.0)	66.1 (22.6)	80.8 (37.9)	95.0 (39.4)
Day 7	72.5 (22.6)	124.9 (58.6)	156.3 (54.0)	208.2 (50.2)
Day 14	77.1 (25.0)	116.8 (40.8)	158.3 (66.1)	234.5 (48.8)
T_{max} (h)				
Day 1	6.7 (3.9)	11.4 (9.9)	11.9 (10.6)	16.8 (10.1)
Day 7	5.3 (4.6)	7.8 (7.7)	1.8 (0.5)	4.8 (5.8)
Day 14	3.5 (2.1)	4.3 (5.4)	2.2 (1.6)	5.4 (7.8)
AUC_{24} (ng h mL^{-1})				
Day 1	606 (204)	971 (405)	1263 (669)	1378 (460)
Day 7	1223 (392)	2152 (921)	2509 (830)	3585 (1054)
Day 14	1162 (440)	2083 (910)	2201 (1023)	3914 (840)
C_{min} (ng mL^{-1})				
Day 7	33.6 (13.4)	62.9 (29.3)	80.1 (29.6)	106.2 (33.7)
Day 14	34.5 (14.7)	63.0 (24.9)	70.1 (31.3)	115.5 (25.9)
CL/F (L h^{-1})				
Day 7	27.3 (10.6)	34.7 (21.5)	39.3 (12.3)	35.9 (9.6)
Day 14	29.7 (12.6)	35.4 (21.0)	47.2 (16.5)	32.0 (7.1)
$t_{1/2}$[b] (h)	25.5 (10.5)	20.4 (4.6)	20.4 (6.2)[a]	17.3 (2.9)
V_{β}/F (L)	1145 (397)	1110 (785)	1399 (682)[a]	846 (343)

Mean (s.d.) are reported. [a]n = 7; β could not be estimated in one subject probably due to protracted absorption or dissolution. [b]Harmonic mean and pseudo-standard deviation.

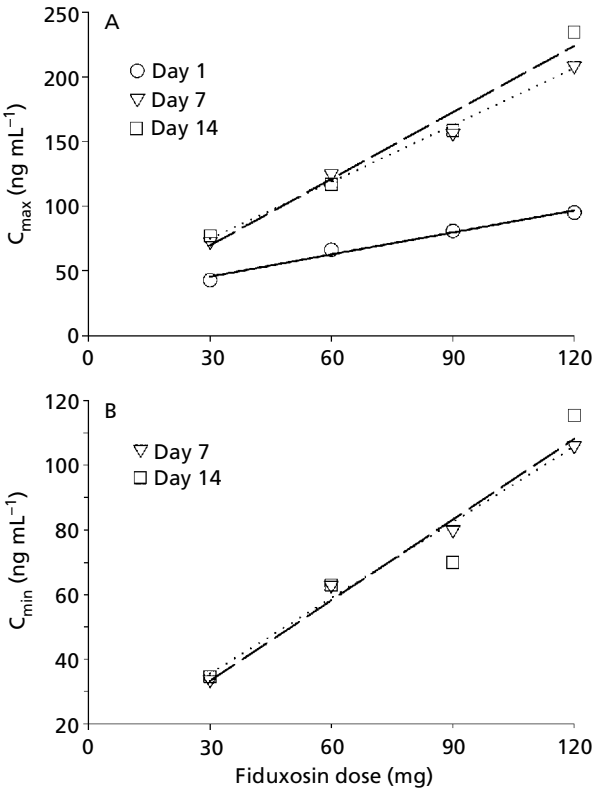

Figure 2 Mean C_{max} (A) and C_{min} (B) values obtained after multiple once-daily dosing of fiduxosin in elderly healthy male subjects. The lines represent the linear regression of the C_{max} or C_{min} values versus fiduxosin dose. The *P* values for testing the slope of the regression line being equal to zero were less than 0.05 for all regressions. A. Day 1 C_{max}: continuous line, y = 0.573x+28.15 (r^2 = 0.9833), day 7 C_{max}: dotted line, y = 1.4617x+30.85 (r^2 = 0.9911), and day 14 C_{max}: dashed line, y = 1.7123x+18.25 (r^2 = 0.9715). B. Day 7 C_{min}: dotted line, y = 0.7833x+11.95 (r^2 = 0.9912) and day 14 C_{min}: dashed line, y = 0.8337x+8.25 (r^2 = 0.9261).

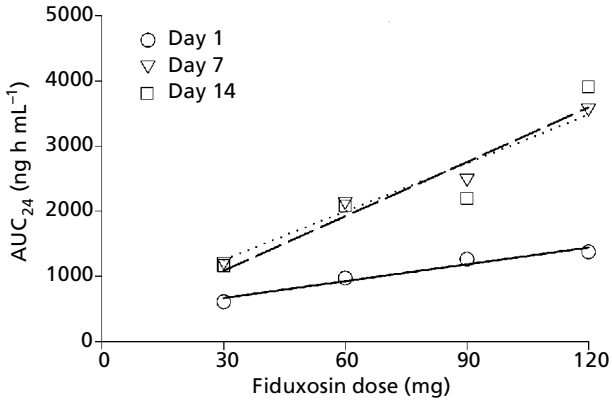

Figure 3 Mean AUC_{24} versus fiduxosin dose after administration to elderly healthy male subjects. The lines represent the linear regression of the data. The *P* values for testing the slope of the regression line being equal to zero were less than 0.05 for all regressions. Day 1 AUC_{24}: continuous line, y = 8.6933x+402.5 (r^2 = 0.9546), day 7 AUC_{24}: dotted line, y = 24.81x+506.5 (r^2 = 0.969) and day 14 AUC_{24}: dashed line, y = 27.913x+246.5 (r^2 = 0.8875).

state the maximum concentrations were approximately twice the minimum concentrations during a dosing interval at all dose levels.

The relationships between mean C_{max} and C_{min} values versus fiduxosin dose are illustrated in Figure 2, and between mean AUC_{24} values versus fiduxosin dose in Figure 3. Visual examination of these plots suggests that fiduxosin pharmacokinetics are linear. The mean T_{max} increased with dose on day 1, but was relatively constant at steady state (day 7 and 14) across the 30–120 mg/day dose range (Table 1). The increase in T_{max} with dose on day 1 is consistent with previous observations in a single dose study (Dutta et al 2001a). Dose-dependent alterations in absorption or dissolution kinetics could account for the increase in T_{max} with dose on day 1. The absorption characteristics of fiduxosin are consistent with its chemical characteristics as a lipophilic agent with relatively low water solubility at pH 7 ($< 10\ \mu g\ mL^{-1}$). With low doses, it would appear that dissolution is rapid and complete, but with successively higher doses, solubility limitations may prolong dissolution, resulting in the observed controlled-release characteristics in the absorption profile. However, it appeared that at steady state T_{max} was relatively constant across the studied dose range. Overall, there was no statistically significant effect ($P > 0.05$) of dose on T_{max}.

Assessment of dose proportionality and linear kinetics

Fiduxosin multiple-dose pharmacokinetics were independent of dose. The T_{max}, β (day 14 only), V_β/F (day 14 only) and dose-normalized C_{max}, C_{min} and AUC_{24} were assessed separately for a linear trend with dose using analyses of covariance for day 7 and 14 data. The test statistic (linear trend with dose) was not significant ($P > 0.05$) for any of the pharmacokinetic parameters except for the elimination rate constant. The elimination rate constant was found to be dose dependent (P = 0.03) across the 30–120 mg/day dose range. However, subsequent comparison of β from the 60, 90 and 120 mg/day dose groups revealed no statistically significant differences (P = 0.34). The differences in half-lives between dosing groups may be due to randomness, or may be due to the shorter blood sampling schedule for the 30-mg group in association with a complex time course of protracted absorption or dissolution.

After single oral dosing under fasting conditions, the plasma concentration–time profiles have an initial peak with subsequent secondary maxima (Dutta et al 2001a). With dosing under non-fasting conditions, C_{max} and AUC_{∞} were substantially increased, and the secondary maxima were generally not observed (Dutta et al 2001b). Since the aqueous solubility of fiduxosin at neutral pH is $< 10\ \mu g\ mL^{-1}$, these observations of longer $t_{1/2}$ and secondary maxima under fasting conditions are taken as indications of sustained dissolution or absorption of drug occurring in the terminal phase. Accordingly, the longer sampling in the 60, 90 and 120 mg/day dose groups is believed to more accurately characterize the true β value.

Assessments of time dependence

Fiduxosin multiple-dose pharmacokinetics were time invariant. The time dependence of fiduxosin pharmacokinetics was assessed using two approaches. First, the T_{max} and dose-normalized C_{max}, C_{min} and AUC_{24} from day 7 were compared with their respective estimates from day 14. The test statistic (change in pharmacokinetic parameter value) was not significant ($P > 0.05$) for any of the pharmacokinetic parameters. Second, the pre-dose concentrations from day 4 and later, as well as from day 7 and later were assessed for a linear trend with time. Results of these tests suggested that although a linear trend with time was observed when the pre-dose concentration from day 4 was included in the analysis, no trend in time was observed when the day 7 and later pre-dose concentrations were analysed. This is not surprising, since by day 4 only 3–4 half-lives (harmonic mean half-life was 17–25 h) had elapsed and steady state was probably not achieved in some of the subjects with longer fiduxosin $t_{1/2}$ values. These results also suggested that fiduxosin pharmacokinetics were time invariant.

Safety and tolerability

Fiduxosin was well tolerated and safe when administered in daily doses of 30, 60, 90 or 120 mg for 14 consecutive days. No deaths or serious adverse events occurred during the study. The most commonly reported adverse event in both the fiduxosin and the placebo-treated subjects was headache; all were of mild intensity. Episodes of dizziness were reported in 5 subjects receiving fiduxosin. No dose-related patterns in the occurrence of adverse events or in changes in laboratory variables were observed. No clinically significant changes in vital signs or physical examinations occurred. Two cases of postural hypotension, one mild and one of moderate intensity, were reported during the study. These rapidly resolved and were not dose related. The safety and tolerability of fiduxosin in healthy elderly male subjects was established for multiple doses of 30–120 mg administered once daily for 14 consecutive days; the maximum tolerated dose of fiduxosin was not attained.

Conclusion

Fiduxosin multiple-dose pharmacokinetics were dose independent and time invariant over the 30–120 mg/day dose range under fasting conditions. Steady state was achieved by day 7. T_{max} and V_{β}/F were dose independent. C_{max}, C_{min} and AUC_{24} for days 7 and 14 were linearly proportional with dose over the 30–120 mg/day dose range and were unchanged from day 7 to day 14.

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