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A single-dose, randomised, crossover study to compare the rate and extent of absorption of lisinopril solution versus tablets in healthy volunteers

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***Objectives*: The aim of this study was to compare the main pharmacokinetic characteristics and bioavailability profile of a new formulation of lisinopril solution with that of a commercially available tablet formulation.**

***Methods*: Twenty healthy volunteers participated in a single dose (lisinopril 10 mg), balanced, randomised, two period crossover study. The following formulations were studied: 10 ml of 5 mg in 5 ml lisinopril solution (Rosemont Pharmaceuticals Ltd) and 2 × 5 mg lisinopril tablets (Zestril®, AstraZeneca). The primary variables were the AUC from 0–t hours after drug administration ($AUC_{0\text{-}tlast}$), the area under the plasma concentration time curve extrapolated to infinity ($AUC_{0\text{-}\infty}$) and the maximum plasma concentration (C_{max}). Additional variables were the time to maximum plasma concentration (t_{max}) and the terminal elimination half-life ($t_{1/2}$). Further to this, adverse events data were collected.**

***Results*: The lisinopril solution achieved a mean ± sd C_{max} of 43.1 ± 17.5 ng/ml, compared to 51.0 ± 19.1 ng/ml for lisinopril tablets. Results for $AUC_{0\text{-}\infty}$ were 582.5 ± 194.4 ng/ml.h and 691.4 ± 250.0 ng/ml.h respectively. The 90% confidence intervals for the point estimates for the ratios of the log transformed data did not fall within the limits for bioequivalence. Differences between treatments were not statistically significant.**

***Conclusion*: The new formulation of lisinopril tested in this study, a solution, was less extensively absorbed after a single oral dose in healthy volunteers than an equivalent dose of the tablet reference formulation. While clinicians should be aware of the difference between these formulations, the likely impact on therapeutic use is minimal.**

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Introduction

Lisinopril is a long-acting angiotensin converting enzyme (ACE) inhibitor that has been shown to be effective in the treatment of hypertension and congestive heart failure[1]. Given once daily, lisinopril is absorbed slowly, variably and incompletely from the gastrointestinal tract after oral administration. The parent drug does not undergo metabolism, and is excreted entirely unchanged in the urine. ACE inhibitors are commonly used in the treatment of hypertension in infants and children, and lisinopril has been shown to be safe and effective in this patient group[2].

The pharmacokinetics of lisinopril in solid formulations has been extensively studied, and tablet formulations given at the same dose have been shown to be bioequivalent[3,4]. No data are available, however, on the absorption of lisinopril presented as a solution. Rosemont Pharmaceuticals Ltd has developed such a formulation to facilitate the treatment of hypertension in children and other patients who require or prefer a liquid dose. The objective of this study was to discover the main pharmacokinetic characteristics and bioavailability profile of this new formulation of lisinopril, and to compare these characteristics with a commercially available tablet formulation.

Methods

This was a single-dose (lisinopril 10 mg), randomised, crossover study in 20 healthy volunteers. The study was conducted in accordance with the International Conference of Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the recommendations of the World Health Organization, and the Declaration of Helsinki. Prior to study initiation, approval was obtained from the Research Ethics Committee of the Cork Teaching Hospitals and written informed consent was obtained from all participants. Volunteers (male and female) were eligible if they were aged between 18 and 50 years (yr), had a body mass index ≤ 30 kg/m^2, were non-smokers or smokers of less than 10 cigarettes per day, had a clinically normal medical history, and had normal clinical and laboratory findings, including physical examination, electrocardiograph, urinalysis, drugs of abuse screen and haematology, biochemistry and virology (Hepatitis B and C, HIV) testing. Concomitant medication was not permitted from 14 days prior to or for the duration of the trial. The contraceptive pill was allowed as a method of contraception for female volunteers. Simple analgesia was permitted up to 72 hours (h) prior to the trial.

The following formulations were administered: Test = 10 ml of 5 mg/5 ml lisinopril oral solution (Rosemont) and Reference = 2 × 5 mg lisinopril tablets (Zestril®, AstraZeneca). Volunteers were required to fast overnight for at least 10 h prior to dosing on the study day. During the overnight fast, water could be taken *ad libitum*, up to 1 h pre-dosing. Each volunteer was given a single oral dose of one of the medications at approximately 08:00. In one treatment period, the tablets were swallowed, without chewing or crushing, with 240 ml water. In the other treatment period, 10 ml of solution was swallowed, followed by 230 ml water. A mouth check was carried out to ensure that the medication was swallowed. The two formulations were given to each volunteer in random order, separated by a washout period of at least 7 days. Water was restricted for 2 h after dosing; a light lunch was provided 4.5 h after dosing.

Blood samples of 6 ml were drawn at each of the following times by means of an indwelling catheter or venepuncture: pre-dose, and at 1.0, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 9.0, 10.0, 12.0, 24.0 and 36.0 h post dosing (n = 18 blood samples per period). The total volume of blood taken over the entire study did not exceed 240 ml. The blood samples were collected into labelled lithium-heparin tubes (Sarstedt, Germany) and centrifuged at 3,000 rpm for 10 min at 4°C in a refrigerated centrifuge. Plasma samples were frozen immediately and stored at –20°C until analysed. Adverse events or abnormal clinical, blood haematological or biochemical values were also recorded.

Analytical details

Plasma concentrations of lisinopril were measured using a sensitive, specific, validated LC/MS/MS procedure using a PE Sciex API system with a Turbo-ionspray source and mass scanning by MRM (multiple reaction monitoring). The method involved the extraction of lisinopril and internal standard from acidified plasma using C18 Solid Phase Extraction (SPE) before injection onto the LC/MS/MS system. Lisinopril was identified by the following MRM transitions 406.4→84.3. The internal standard enalapril was identified by the MRM transition 377.2→234.3. The limit of quantification (LOQ) was set at 1 ng/ml for lisinopril; the validation range was 1–500 ng/ml. The intra-assay precision ranged from 2.63 to 7.01% and intra-assay mean % accuracy ranged from 100.56 to 110.64%. The inter-assay precision ranged from 4.68 to 11.23% and the inter-assay accuracy ranged from 100.07 to 103.81%. The lowest reported concentration of lisinopril in the study was 1.00 ng/ml; the highest reported concentration of lisinopril was 99.23 ng/ml.

Table 1 Pharmacokinetic parameters of lisinopril solution (Rosemont Pharmaceuticals Ltd) and lisinopril tablets (Zestril®, AstraZeneca, UK)

Parameter	Solution		Tablets		*P* value
$AUC_{0\text{-tlast}}$ (ng/ml.h)	553.0 ± 191.1	[34.6]	657.6 ± 248.3	[37.8]	0.079
$AUC_{0\text{-}\infty}$ (ng/ml.h)	582.5 ± 194.4	[33.4]	691.4 ± 250.0	[36.2]	0.067
C_{max} (ng/ml)	43.1 ± 17.5	[40.6]	51.0 ± 19.1	[37.6]	0.100
$t_{½}$ (h)	7.2 ± 0.9	[12.6]	7.1 ± 1.1	[16.3]	0.382
t_{max}* (h)	6.0	[18.4]	7.0	[9.8]	0.154

Data shown are mean (± standard deviation) [coefficient of variation]; * median

Pharmacokinetic parameter calculations were conducted using WinNonlin® (Version 4.0.1, Pharsight Corporation, Cary NC USA). The primary variables were the AUC from time 0 to the last measurable plasma concentration after drug administration ($AUC_{0\text{-tlast}}$), the area under the plasma concentration time curve extrapolated to infinity ($AUC_{0\text{-}\infty}$) and the maximum plasma concentration (C_{max}). Additional variables were the time to maximum plasma concentration (t_{max}), the terminal elimination half-life ($t_{1/2}$), mean residence time (MRT) and terminal elimination rate constant (k_{el}).

AUC was calculated using the mixed log linear (linear up/log down) trapezoidal rule. Using this method the AUC was calculated by the trapezoid method between the first (data) point and t_{max}, and then by the logarithmic method between t_{max} and the last data point. Values below the LOQ were assumed to be zero when they occurred before t_{max}. Values below the LOQ occurring after t_{max} were ignored for calculation of the terminal regression line. There was interpolation between data points if a value below the limit of quantification, or a missing value, occurred between two values above the LOQ. Extrapolation of AUC was carried out using linear regression on the logarithmic (ln) transformed data points of the curve.

Statistical analysis

For the purposes of this study, it was assumed that the Test/Reference ratio for C_{max} and AUC would fall between 0.95 and 1.05, with intra-subject CVs ≤ 21%. Given these assumptions, a study including 20 subjects should have at least 80% ($\alpha = 0.05\%$) power to show bioequivalence for C_{max} and AUC with 90% confidence intervals set between 80 and 125%. Analyses of variance (ANOVA) were performed after logarithmic transformation of C_{max}, $AUC_{0\text{-tlast}}$ and $AUC_{0\text{-}\infty}$ values for lisinopril. The effects considered in the ANOVA model were treatment, sequence, study period, and subject within sequence. Parametric point estimators for the ratio and the shortest 90% confidence intervals were calculated using the LSMEANS for treatment effects from the ANOVA of log-transformed data with subsequent exponential transformation. If the 90% CI calculated for the log transformed data of $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max} for lisinopril fell within the limits of 80–125% the test formulation was to be considered bioequivalent to the reference formulation with respect to rate and extent of absorption. Statistical analyses were performed using SAS® Version 8.2 (SAS® Institute, Cary NC USA).

Results

Twelve healthy males and nine healthy females aged between 18 and 36 yr (mean 22.4 yr) volunteered to take part in this study. One subject withdrew from the study before dosing in the first period following an episode of vaso-vagal syncope; the results for all 20 subjects who completed the study were included in the kinetic and statistical analyses.

No discordant values (outlier data) were observed for the pharmacokinetic parameters. Both the C_{max} and AUC were lower with the lisinopril solution than the tablet, although this difference was not statistically significant (Table 1). The comparative bioavailability of the lisinopril solution compared to tablets is shown in Table 2. These results indicate that the solution cannot be considered bioequivalent to the tablet formulation using generally recognised limits of 80 to 125%. Mean lisinopril plasma concentrations *vs.* time for 24 h following dosing are depicted in Figure 1.

Total individual drug exposure over the whole study was 20 mg (10 mg in two periods of treatment). No clinically significant alterations in vital signs, physical findings or haematology/biochemistry results were found in any of the volunteers. Four cases of headache and two of light-headedness (out of eight mild adverse events recorded during this study) were considered by the Investigator to be possibly related to the study

Table 2 Comparative bioavailability of the two formulations studied

Parameter	Ratio of means	90% confidence interval	Intra-subject CV (%)
$AUC_{0\text{-tlast}}$ (ng/ml.h)	85.0	73.1 – 98.9	28.0
$AUC_{0\text{-}\infty}$ (ng/ml.h)	85.0	73.6 – 98.2	26.8
C_{max} (ng/ml)	84.1	70.8 – 100.0	32.4

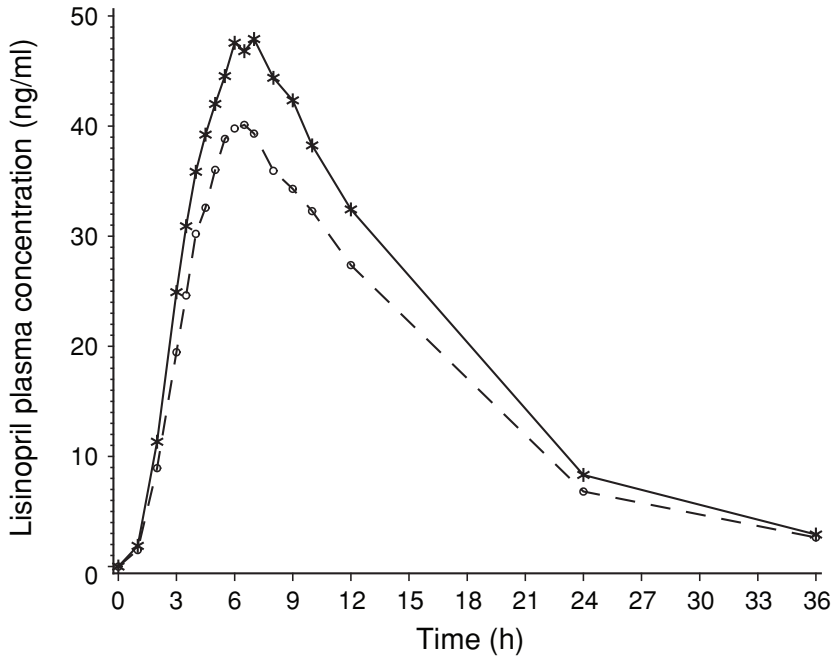

Figure 1 Mean lisinopril plasma concentration versus time curves following a single 10 ml dose of lisinopril solution, Rosemont Pharmaceuticals Ltd (○) or a single 2 × 5 mg dose of Zestril® tablet, AstraZeneca, UK (*).

medication. One case of nausea was treated with a non-prescription medication (Alka Seltzer). The overall examination of laboratory results showed no significant changes or trends between screening and final examination. The study medication appears to be safe and well tolerated in healthy volunteers at the dose given.

Discussion

The principal finding of this study is that 5 mg/5 ml lisinopril solution (Rosemont) is less extensively absorbed than lisinopril tablets. These two formulations cannot be considered to be bioequivalent, as the confidence intervals for the point estimates for AUC and C_{max} (primary parameters) were outside the acceptance limits of 80 to 125%. The Rosemont product is currently available for prescription within the United Kingdom as a "special". Clinicians should be alerted to these findings; also, their possible implications for efficacy and safety should be considered.

ACE inhibitors are safe and effective in the treatment of hypertension in children[2,5]. They are particularly effective for the treatment of hypertension in infants; the reasons for this are unclear. Based on adult studies, these agents also have possible beneficial effects on cardiac function, peripheral vasculature and end organ damage[6-8]. The Summary of Product Characteristics (SPC) for Zestril® states that "Efficacy and safety of use in children has not been fully established. Therefore, use in children is not recommended". Despite this fact, lisinopril is used "off label" in paediatric patients. Normal therapeutic practice is to begin with a low dose (usually 2.5 mg), and then titrate upwards according to clinical response. In a randomised, placebo-controlled clinical study examining the safety and efficacy of lisinopril in children aged 6 to 16 y, investigators found that a dose of 70 microg/kg offered consistent antihypertensive efficacy[2]. Higher doses were associated with additional antihypertensive efficacy, and the authors recommended that upward titration be considered for those children who respond inadequately to the starting dose. The maximal dose used in this study was 610 microg/kg. Lisinopril was well tolerated by these children in this dosage range.

This study shows that following a single dose, lisinopril solution is absorbed less extensively than lisinopril tablets, falling just outside the usual acceptance limits for bioequivalence. In theory, the efficacy of the solution may be compromised compared to tablets dose for dose. In clinical practice, however, the dose of lisinopril used in an individual patient is generally titrated according to response. Furthermore, lisinopril is given as a daily dose; any potential pharmacodynamic differences between these formulations will be minimised at steady state. For these reasons, therapeutic failure of the lisinopril solution is unlikely. The solution has the added advantage of allowing for more flexibility when titrating against efficacy in a particular patient. Clinicians planning to change an individual patient from the solution to tablets should be aware that this is akin to a potential dose increase of approximately

19%. When first changing from solution to tablets, clinicians might be advised to choose a tablet dose a little lower than that calculated on a mg/kg basis from the dose of solution.

The reasons for the less extensive absorption of the Rosemont lisinopril solution are unclear. There are a number of reports in the literature of instability of ACE inhibitors in extemporaneously manufactured liquid formulations[9-11]. Lisinopril shows much greater stability than others in this class (data on file, Rosemont Pharmaceuticals); furthermore, the fact that this is a true solution ensures uniformity of dose. This is backed by stability data generated by the manufacturer which supports a shelf-life of 12 months. While it is theoretically possible that the fact that volunteers were fasted may have influenced the absorption of the solution, this seems unlikely as the SPC for the Reference product specifically states that the absorption of Zestril® tablets is not affected by food[12].

The safety of the test formulation should not be in question; toxicity is highly unlikely in the context of a formulation which is less well absorbed. Furthermore, the flexibility in dose delivery accorded by using a liquid formulation means that the possibility of inadvertent overdose may be reduced. The adverse events experienced by volunteers in this study were few. One volunteer complained of transient light-headedness some hours after dosing with the solution; this same volunteer experienced the same symptoms following dosing with the tablets. The Rosemont product has been available in the United Kingdom as a "special" since 2004. To date, no adverse events have been reported to the UK Medicines and Healthcare Regulatory Authority on this product.

In conclusion, a Rosemont Pharmaceuticals lisinopril solution (5 mg/5 ml) has been shown to be somewhat less extensively absorbed than lisinopril tablets. While it is important that this information is communicated to clinicians, it is unlikely that it will have any significant implications for therapeutic use.

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