Comparative bioavailability of tetracycline and lymecycline

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1 The relative bioavailability of lymecycline and tetracycline hydrochloride was compared in 12 healthy volunteers in a double-blind cross-over study using a high performance liquid chromatographic method for plasma and urine analyses.

2 A statistical significant difference in favour of tetracycline hydrochloride was found concerning the mean AUC and the mean lag time. The relative bioavailability of lymecycline was only 70% compared with tetracycline in multiple dosing ($19.13 \pm 5.39 \mu\text{g ml}^{-1} \text{ h}$ and $27.22 \pm 6.26 \mu\text{g ml}^{-1} \text{ h}$ respectively) and 80% in a single dose ($21.88 \pm 4.23 \mu\text{g ml}^{-1} \text{ h}$ and 26.91 ± 6.01 respectively) and the mean lag time of tetracycline was only 60% compared with lymecycline.

Keywords tetracycline lymecycline bioavailability healthy volunteers

Introduction

A number of studies concerning the pharmacokinetic characteristics of tetracyclines have been performed during the past years (Adir & Barr 1978; Barr *et al.*, 1972; Brice & Hammer, 1969; de Carneri, 1961; Flatberg, 1973; Lovering *et al.*, 1975; Tuomisto & Männistö, 1973). Usually the methods for plasma and urine analysis have been microbiological or fluorimetric, methods which suffer from lack of selectivity. In this study this problem was overcome by use of a high performance liquid chromatographic technique (Hermansson, 1982).

Earlier experiments (Hermansson & Andersson, 1982) demonstrated that there is a fast degradation rate of lymecycline at acidic and neutral pH to tetracycline, lysine and formaldehyde. It was also recently demonstrated that only tetracycline and no trace of lymecycline could be detected in plasma after administration of a lymecycline capsule (Hermansson, 1982). These findings suggest that lymecycline is completely degraded to tetracycline in the gastrointestinal tract prior to absorption. Therefore, we were interested in comparing the bioavailability of the 'pro-drug' lymecycline with that of tetracycline.

Methods

Volunteers

Twelve healthy volunteers, eight women and four men (mean age 31 years and mean weight of 65 kg) participated in the study. All were considered to be healthy before and after the investigation as evidenced by clinical examination, urine analysis and routine laboratory tests. All subjects were informed about the nature of the study and of the possible side effects. Informed signed consent was given. The investigation protocol was approved by the Committee of Ethics of the University Hospital, Uppsala, Sweden.

Preparations, drugs

Identical capsules containing tetracycline hydrochloride or lymecycline corresponding to 300 mg of tetracycline base were given to the subjects according to the protocol. The differences in weight for the whole capsules were s.d. $\pm 3.63\%$ for tetracycline and s.d. $\pm 2.04\%$ for lymecycline. Tetracycline hydrochloride was kindly supplied by ACO Läkemedel AB (Solna, Sweden) and lymecycline was obtained from Carlo-Erba (Milan, Italy).

Study protocol

The study was double-blind crossover, so that all subjects received both preparations in single and multiple dosing randomized according to the Latin square design. The single dose study was carried out during the first week, when only one capsule was given. The subjects had fasted overnight for at least 8 h. Standardized breakfast was allowed 2 h after the capsule intake. The capsules were taken together with 250 ml of water.

The steady state study was performed during the second week where the capsules were taken twice a day (every 12 h) on the first, second and third day and once in the morning on the fourth day, when the blood samples were taken. During the first 3 days the subjects were instructed to fast at least 1.5 h after and before intake of the capsule (swallowed with 250 ml of water). The fourth day the routine was the same as for the single dose study.

After the steady state there was a 2 weeks' wash-out period. After completing both the single and steady state studies the volunteers were questioned if they had experienced any adverse reactions while taking the drugs. This was done before the code was broken.

Sampling

During the single dose study blood samples were taken from an arm-vein 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 h after dosing. Urine was collected for 24 h. During the steady state study blood samples were taken the fourth day at 0, 0.5, 1, 2, 4, 6, 8 and 12 h. The blood samples were collected in 10 ml heparinized Venoject tubes, the plasma immediately separated and frozen at -20°C until analysed. Urine samples were stored at -20°C until analysis.

Assays

The methods used for determination of tetracycline and lymecycline in plasma and urine was the high performance liquid chromatographic method described earlier (Hermansson, 1982).

Pharmacokinetic and statistical analysis

The pharmacokinetic analyses were performed using the IGPARM program (Gomeni & Gomeni, 1978).

The statistical significance of differences in the areas under the plasma concentration time

curve (AUC) were analysed according to analysis of variance for two way balanced data and Tukey's tests for non-additivity. The non-parametric Wilcoxon signed rank test was used for the analysis for the other pharmacokinetic parameters.

Results

The summary of pharmacokinetic parameters calculated are given in Table 1. Only tetracycline and no trace of lymecycline could be detected in the plasma and urine samples taken after administration of lymecycline. In the single dose study the mean AUC of lymecycline ($21.88 \pm 4.23 \mu\text{g ml}^{-1} \text{ h}$) was only 80% compared to that of tetracycline ($26.91 \pm 6.01 \mu\text{g ml}^{-1} \text{ h}$), ($P < 0.01$, Figure 1). The difference in mean AUC was more pronounced in the multiple dose study where mean AUC of lymecycline ($19.13 \pm 5.39 \mu\text{g ml}^{-1} \text{ h}$) was only 70% compared to that of tetracycline ($27.22 \pm 6.26 \mu\text{g ml}^{-1} \text{ h}$), ($P < 0.001$, Figure 2).

Mean peak plasma concentration for tetracycline was $2.50 \pm 1.58 \mu\text{g/ml}$ compared to $2.13 \pm 0.40 \mu\text{g/ml}$ for lymecycline. The difference is not significant ($P = 0.05$). The mean time to reach maximal concentration (t_{max}) was almost identical for the two preparations. Mean lagtime for tetracycline was $0.17 \pm 0.01 \text{ h}$ compared to lymecycline $0.29 \pm 0.05 \text{ h}$, the difference being statistically significant ($P < 0.01$). There was also a significant difference ($P < 0.01$) between the k_a -values for tetracycline and lymecycline 0.91 ± 0.22 and 0.71 ± 0.22 respectively.

The results of the urine samples were complete in five volunteers and are shown in Table 2. No statistical analysis was done of the urine parameters since the sampling was incomplete. The total amount of tetracycline and lymecycline measured as tetracycline excreted in 24 h urine is in agreement with the stated difference in AUC for the two drugs.

Adverse reactions

Eight out of the 12 volunteers had experienced a bad 'metallic' taste in their mouths during a period starting some 5-10 min after intake and lasting about 1 h after taking lymecycline, none while taking tetracycline hydrochloride. Two experienced 'heartburn' and two gastric upset while taking lymecycline, whereas none experienced that while taking tetracycline. Two persons noticed mild diarrhoea while taking both drugs.

Discussion

In this study we found a significant difference between tetracycline and lymecycline concerning the mean AUC with the relative bioavailability of lymecycline being 70% compared with tetracycline in multiple dosing and 80% in a single dose. We also found a significantly shorter lag time and higher k_a value for tetracycline.

Our findings are not in agreement with a previous study (de Carneri, 1961) where higher levels of lymecycline were obtained in the first hour plasma samples compared with tetracycline. However, in that study they used a microbiological method for analysing the plasma levels and it can be assumed that lymecycline was used for the preparation of the standard curve for quantitation of lymecycline in the plasma samples. It has been demonstrated that only tetracycline and no trace of lymecycline can be found in human plasma after administration of lymecycline (Hermansson, 1982). This means that all plasma concentrations determined after the administration of lymecycline are 36% too high if lymecycline is used as standard sample. Also that study lacks information about the formulation design which influences the bioavailability (Barr *et al.*, 1972; Brice & Hammer, 1969; Flatberg, 1973; Lovering *et al.*, 1975; Tuomisto & Männistö, 1973).

Lymecycline is degraded in the gastrointestinal tract to tetracycline, lysine and formaldehyde (Hermansson, 1982). When the solid drug reaches the stomach, dissolution, degradation and gastric emptying take place. Gastric emptying may result in the transfer of dissolved and degraded as well as undissolved and not degraded lymecycline into the duodenum where most of the absorption of tetracycline appears to take place (Colaizzi & Klink, 1969). The explanation of the findings in our study may be that the longer lag time for lymecycline reflects the time for degradation of lymecycline to tetracycline and the lower bioavailability measured as AUC for lymecycline is a reflection of the fact that lymecycline is not fully dissolved and degraded when reaching the duodenum and therefore not completely absorbed.

A daily dose of lymecycline corresponding to 600 mg tetracycline generates, if completely hydrolysed, about 40 mg formaldehyde in the gastro-intestinal tract. The toxic potential of formaldehyde in this dose is not known. However, when considering our findings of a lower bioavailability of lymecycline when compared with tetracycline together with the well-known

Table 1 Pharmacokinetic parameters (mean $\pm$ s.d.) calculated after oral administration of tetracycline hydrochloride 300 mg (base) and lymecycline 300 mg (base) in single and multiple dosing

Single dose	$AUC_{0-\infty}$ ($\mu\text{g ml}^{-1} \text{ h}$)	C_{max} ($\mu\text{g/ml}$)	t_{max} (h)	Lag time (h)	$t_{1/2}$ (h)	k_a (absorption rate constant)	k_{el} (elimination rate constant)
Tetracycline	26.91 $\pm$ 6.01	2.50 $\pm$ 1.58	3.04 $\pm$ 0.52	0.17 $\pm$ 0.11	7.85 $\pm$ 1.56	0.91 $\pm$ 0.22	0.09 $\pm$ 0.02
Lymecycline	21.88 $\pm$ 4.23	2.13 $\pm$ 0.40	3.03 $\pm$ 0.62	0.29 $\pm$ 0.05	8.06 $\pm$ 1.17	0.71 $\pm$ 0.22	0.09 $\pm$ 0.01
Multiple dose							
Tetracycline	27.27 $\pm$ 6.26						
Lymecycline	19.13 $\pm$ 5.39

Figure 1 Mean plasma concentrations of tetracycline, 0 to 24 h after single oral dose of tetracycline-hydrochloride 300 mg (●) and lymecycline 300 mg (○) in 12 healthy subjects.

Figure 2 Mean plasma concentrations of tetracycline, 0 to 12 h after multiple oral doses (fourth day) of tetracycline-hydrochloride 300 mg (●) and lymecycline 300 mg (○) in 12 healthy subjects.

Table 2 Percentage (%) of total amount of given drug (tetracycline-hydrochloride and lymecycline) excreted as tetracycline in 24 h urine

	Subjects				
	1	2	3	4	5
Tetracycline-hydrochloride	44.3	63.1	36.4	28.0	38.9
Lymecycline	30.0	24.1	34.3	17.1	25.9

allergenicity (Hendrick & Lane, 1977; Schorr *et al.*, 1974) and the recently discussed potential

carcinogenicity and mutagenicity of formaldehyde (Ariens *et al.*, 1982; Perera & Petito, 1982) the clinical use of lymecycline must be questioned.

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