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THE INFLUENCE OF FOOD INTAKE ON THE BIOAVAILABILITY OF TIMEGADINE, A NOVEL NON-STEROIDAL ANTI-INFLAMMATORY DRUG

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The effects of food ingestion on the absorption of timegadine, a recently synthesised non-steroidal anti-inflammatory drug, was studied in ten healthy volunteers. It was found that food enhanced the absorption of timegadine as shown by increased peak plasma concentrations (C_{max}), decreased time taken to achieve these concentrations (t_{max}), and increased area under the plasma concentration time curve (AUC).

Introduction

Timegadine (*N*-cyclohexyl-N''-4-(2-methylquinolyl)-*N'*-2-thiazolyl gluanidine hydrochloride: Leo Pharmaceutical Products) is a recently synthesised non-steroidal anti-inflammatory drug with unusual prostaglandin synthetase antagonism in that it inhibits both cyclo-oxygenase and lipo-oxygenase (Ahnfelt-Ronne & Arrigoni-Martelli, 1980). This inhibition prevents the formation of prostaglandins which produce pain and fever in inflammatory joint disease (Vane, 1974; Kuehl & Egan, 1980).

Preliminary studies with rheumatoid arthritis patients given timegadine 250 mg twice daily for periods of 2–3 weeks indicate that the drug is well tolerated with no serious side effects reported. Steady state plasma concentrations were achieved after 1–2 weeks treatment, with considerable variations in concentrations between patients, the reported ranges being 0.368–2.289 μg/ml and 0.192–1.636 μg/ml (Arrigoni-Martelli *et al.*, personal communication).

Food is known to affect the absorption of many drugs, including other non-steroidal anti-inflammatory drugs such as aspirin and indomethacin (Emori *et al.*, 1976; Mandelli & Tognoni, 1980). The effect of food on the absorption of timegadine was investigated to assess this as a possible factor in the wide variations in steady state plasma concentrations. Since dosing is likely to be once or twice daily, the first meal of the day seemed appropriate, and a substantial breakfast was chosen for investigation.

Methods

Ten healthy volunteers aged 22–32 years each received one 250 mg tablet of timegadine after a 12 h overnight fast and after a standard cooked breakfast. The breakfast consisted of bacon and egg and one slice of buttered bread with one cup of tea, and the order of fasting and fed was randomly allocated with at least 1 week between studies. Blood was withdrawn from a forearm vein at intervals via an indwelling cannula and the serum stored at −20°C prior to assay by h.p.l.c.

All chemicals with the exception of h.p.l.c. grade acetonitrile and dichloromethane (Rathburns), were AnalaR grade obtained from Fisons Ltd, Loughborough. Timegadine and internal standard (SR 1410) were gifts from Leo Pharmaceutical Products, Denmark.

Extraction of timegadine

To 1.0 ml of plasma in a 10 ml stoppered centrifuge tube were added 350 μl of 2 μg/ml SR1410 internal standard and 2.0 ml ethanol. The tube contents were vortex mixed for 30 s and centrifuged for 5 min at 3,000 rev/min. The supernatant was transferred to a 10 ml stoppered centrifuge tube, made alkaline with 500 μl 1 M sodium hydroxide and extracted with 4.0 ml of dichloromethane. Following vortex mixing for 30 s and centrifugation for 5 min at 3,000 rev/min, the aqueous phase was discarded and the dichloromethane evaporated to dryness under nitrogen at 35°C. The contents of the tube were reconstituted in 100 μl of methanol and 80 μl injected onto the chromatograph.

Chromatographic conditions

Analysis was performed on a reverse phase column (Lichrosorb R.P. 18–5 μm) 30 cm × 0.4 cm. Detection was at 360 nm, using a Pye Unicam variable wavelength detector. Column temperature was

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ambient, absorbance setting was 0.02 AUFS, flow rate was 2.5 ml/min; eluent was 60% acetonitrile in triethylammonium phosphate buffer pH 2.5.

Using this system the retention times of the drug and internal standard were 3.5 and 5.5 min respectively. Quantitation was by the internal standard method and was based on a standard curve over the concentration range 0–1.0 μg/ml. The assay was found to be linear over the range 0–3.0 μg/ml. Overall recovery was 88.1% and the coefficient of variation for replicate analyses of 50 and 200 ng/ml was 7.9% and 6.3% respectively.

Data analysis

The areas under each serum concentration/time curve (AUC) up to 9 h was determined using the trapezoidal rule. The final elimination half life ($t_{1/2}$) was calculated from semi-logarithmic plots of serum concentration *vs* time by a least squares linear regression analysis of the terminal exponential phase of the curve. Statistical analysis was by the paired two-tailed *t*-test.

Results

The mean plots of plasma concentration *vs* time are shown for both studies in Figure 1. Administration of timegadine with food led to higher drug plasma concentrations.

Maximum measured plasma concentrations (C_{max}), time to peak (t_{max}), and area under the curve (AUC) up to 9 h, are shown for all subjects in Table 1. The presence of food significantly increased both peak drug plasma concentration and absorption as reflected by the area under the plasma concentration/time curve. Absorption was also significantly faster as indicated by the decrease in t_{max}, however, there was no significant change in the elimination half-life $t_{1/2}$.

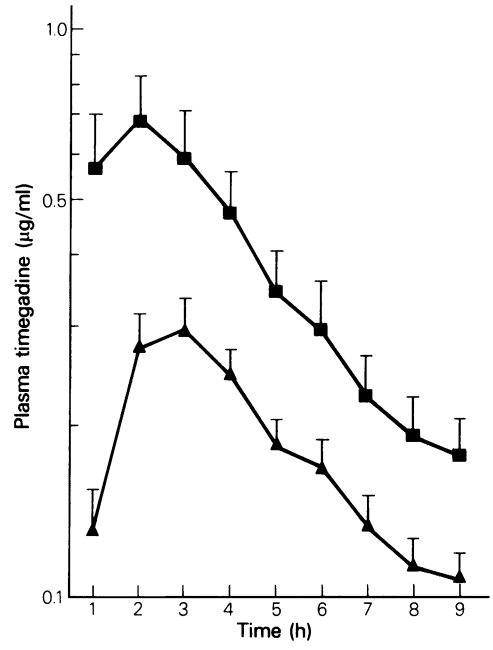

Figure 1 Mean (+ s.e. mean) plasma concentrations of timegadine after administration of a single 250 mg tablet fasting (▲), and non-fasting (■).

Table 1 Pharmacokinetic parameters for timegadine following a single 250 mg tablet fasting and non-fasting

	Fasting				*Non-fasting*			
Subject	t_{max} (*h*)	C_{max} (*µg/ml*)	*AUC*	$t_{1/2}$ (*h*)	t_{max} (*h*)	C_{max} (*µg/ml*)	*AUC*	$t_{1/2}$ (*h*)
1	4	0.145	0.817	3.9	2	0.342	1.143	1.6
2	1	0.205	1.217	4.9	2	0.728	2.596	3.2
3	3	0.195	1.117	4.8	3	0.258	1.377	4.4
4	4	0.180	0.682	1.4	2	0.414	1.933	2.6
5	2	0.243	1.182	4.3	2	0.273	1.609	3.0
6	2	0.435	2.065	2.0	1	0.897	4.407	3.2
7	3	0.559	2.747	3.9	2	1.121	5.409	3.2
8	3	0.676	3.321	3.8	2	2.171	11.173	3.2
9	4	0.303	1.811	5.2	4	0.399	2.215	3.1
10	4	0.273	1.479	4.8	4	0.520	2.562	4.8
Mean	3	0.321	1.634	3.9	2.4	0.712	3.442	3.2
s.d.	1.05	0.178	0.831	1.3	0.97	0.586	3.032	.88
P	<0.05	<0.01	<0.025	>0.05				

t_{max}: time to maximum measured serum concentration
C_{max}: maximum measured serum concentration
AUC: area under the serum concentration-time curve up to 9 h (units $\mu g\ ml^{-1}\ h$)
$t_{1/2}$: elimination half-life
P: probability value

Discussion

The effect of food on the bioavailability of any particular drug is unpredictable (Melander, 1978). Food may act by diluting or complexing with drug in solution (D'Arcy & Merkus, 1980), by altering the gastric emptying and intestinal transit time (Welling, 1977; Romankiewicz & Reidenberg, 1978), by increasing splanchnic blood flow (Toothaker & Welling, 1980), or by increasing liver blood flow in cases where a drug is subject to 'first pass' metabolism (George, 1979). Thus food enhances the bioavailability of propranolol and metoprolol (Melander *et al.*, 1977), and labetalol (Mantyla *et al.*, 1980), but decreases the bioavailability of diclofenac (Willis *et al.*, 1981). Alternatively, food may not affect the bioavailability, but may alter the peak blood concentration or the time taken to reach that peak, as in the case of digoxin (Johnson *et al.*, 1978).

This study shows that food enhances the bioavailability of timegadine, a finding in contrast to the situation with aspirin (Mandelli & Tognoni, 1980) and indomethacin (Emori *et al.*, 1976). Timegadine is likely to be given in a once or twice daily dosage and food may have an important effect, not just on the initial peak blood concentration, but also on the eventual 'steady state' blood concentration with repeated doses. Thus food may be one determining factor in efficacy, or dose related adverse effects.

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