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PHARMACOKINETICS OF DEXKETOPROFEN AND TRAMADOL GIVEN IN COMBINATION: AN OPEN-LABEL, RANDOMIZED, 3-PERIOD CROSSOVER STUDY IN HEALTHY SUBJECTS

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Introduction

Dexketoprofen trometamol (DKP.TRIS) and tramadol hydrochloride (TRAM.HCl) are well known analgesics. The rationale of their combination is based on the different mechanism of actions leading to balanced analgesia from NSAID+opioid activity, and the different pharmacokinetics (PK) leading to the DKP.TRIS rapid onset and TRAM.HCl long lasting effect.

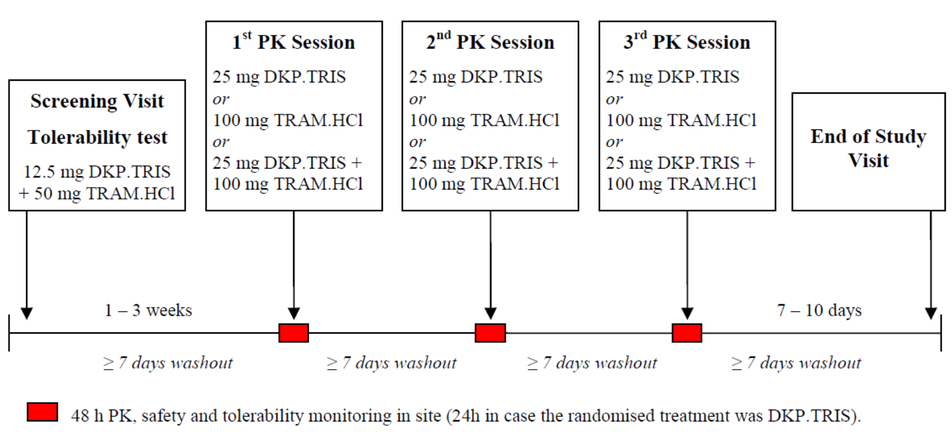
Objectives

- To investigate any effects on the pharmacokinetics of DKP.TRIS and TRAM.HCl when concomitantly administered in healthy subjects.
- To evaluate the safety and tolerability of the co-administration of DKP.TRIS and TRAM.HCl.

Methods

- An open, randomized, 3 period, 3 sequence, crossover study in healthy subjects.
- Subjects received a single doses of DKP.TRIS 25 mg (Enantyum™ 25mg tablet), TRAM.HCl 100 mg (Contramal™ 50mg tablet) and a combination of DKP.TRIS 25 mg + TRAM.HCl 100 mg separated by a minimum 7 days washout period (Figure 1).
- Plasma samples collected up to 48 hours post-dose were analyzed for each enantiomer of ketoprofen, tramadol and its O-demethyl-metabolite (M1) using chiral HPLC methods.
- The PK parameters were determined by non-compartmental analysis of each analyte.
- Geometric mean ratios (GMRs) of the PK parameters Cmax and AUCs of the Test treatment (combination) versus the Reference treatment (single agents) and 90% confidence interval (CI) were calculated after log-transformation of within-subject ratios (Phoenix WinNonLin 6.3).
- Safety assessments were performed: Safety Population defined by subjects who received at least one administration of study treatment including dose tolerability test.

Figure 1 *Study Outline*



Results

- Thirty-five (35) healthy Caucasian volunteers, of which 19 males and 16 females, were included in the study. Five subjects performed a tolerability test but did not take any study medication. Thirty subjects (17 male and 13 females) were randomized to three sequences.
- Mean (range) age and Body Mass Index were 33.8 (18-54) years and 23.30 (18.88- 28.04) kg/m^2, respectively.
- The plasma concentration-time profiles of Tramadol and DKP administered as single agents or in combination are shown in Figures 2 and 3. The point estimates of the exposure PK parameters (Cmax, AUC and Tmax) are reported in Tables 1 and 2. The 90% CIs of geometric mean ratio of AUC and Cmax of all analytes were within the accepted bioequivalence range (80.00-125.00%), when DKP.TRIS and TRAM.HCl were given alone or in combination. Other relevant PK parameters (Vz/F CL/F, t1/2 and MRT) were not affected by the co-administration.
- Inter-individual variability of Cmax and AUC was similar between test and reference formulations (Figure 3 and Figure 5) and in line with historical data for the single agents therapy.
- No serious adverse events (SAEs) reported. Among the Safety Population (n=35), 32 events occurring in 12 subjects were considered to be at least “possibly” related to the administered treatment. These AEs were all classified as being of “mild” or “moderate” severity. No subject experienced an AE leading to a premature withdrawal.

Tramadol

Figure 2 *Tramadol and M1 mean chiral plasma concentration time profile*

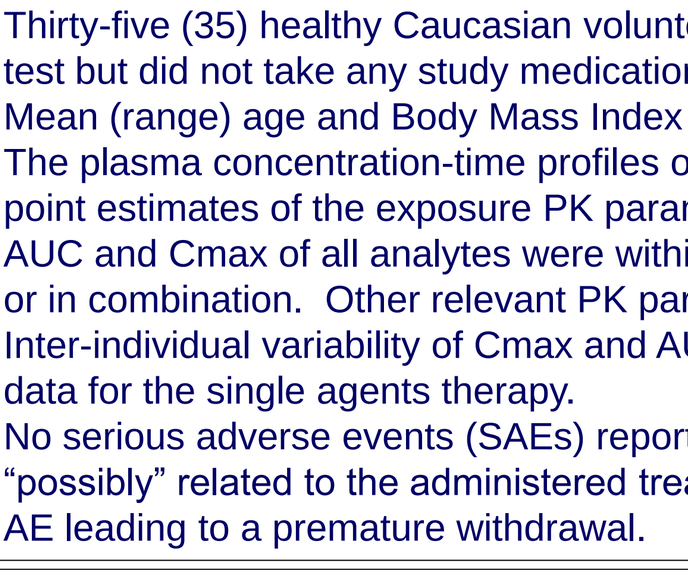
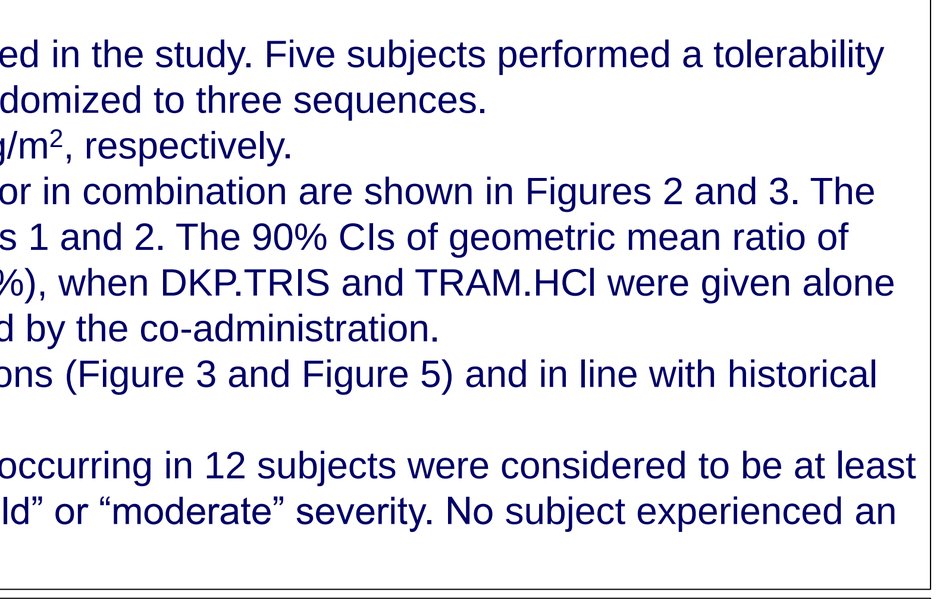


Table 1 *Pharmacokinetic parameters of Tramadol*

Analyte	Parameters	Geometric LSM (N=30) Test	Geometric LSM (N=30) Reference	Ratio (T/R) (%)	90% CI (Lower, Upper) (%)
(+)-TRAM	C_{max} (ng/mL)	196.9	183.36	107.40	(96.67, 119.33)
	$AUC_{(0-t)}$ (ng*hr/mL)	1501.8	1497.98	100.25	(96.79, 103.85)
	Tmax (hour)	1 (0.5-3.0)	1 (0.5-3.5)	n/a	n/a
(-)-TRAM	C_{max} (ng/mL)	177.7	164.56	107.99	(96.96, 120.28)
	$AUC_{(0-t)}$ (ng*hr/mL)	1213.6	1215.5	99.84	(96.62, 103.17)
	Tmax (hour)	1 (0.5-3)	1 (0.5-3.5)	n/a	n/a
(+)-M1	C_{max} (ng/mL)	22	19.61	112.01	(104.22, 120.39)
	$AUC_{(0-t)}$ (ng*hr/mL)	250.5	236.57	105.88	(101.05, 110.94)
	Tmax (hour)	2 (0.75-6)	3 (0.5-12)	n/a	n/a

Test = TRAM.HCl (100 mg) + DKP.TRIS (25 mg)
Reference = TRAM.HCl (100 mg)
n/a = not applicable; median and range for Tmax

Figure 3 *Individual $AUC_{(0-t)}$ and C_{max} of Tramadol*



Dexketoprofen

Figure 4 *DKP plasma concentration time profile*

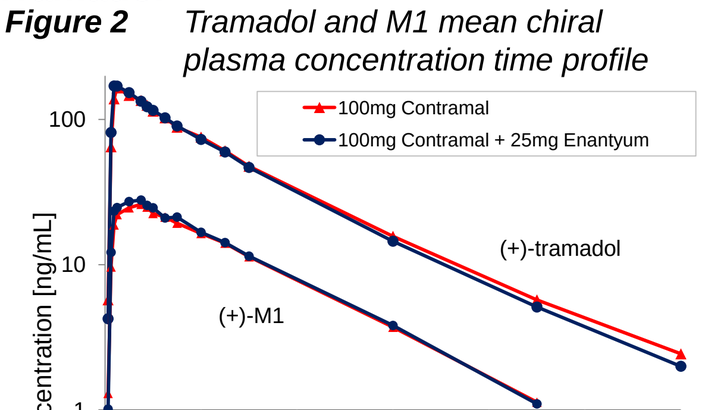
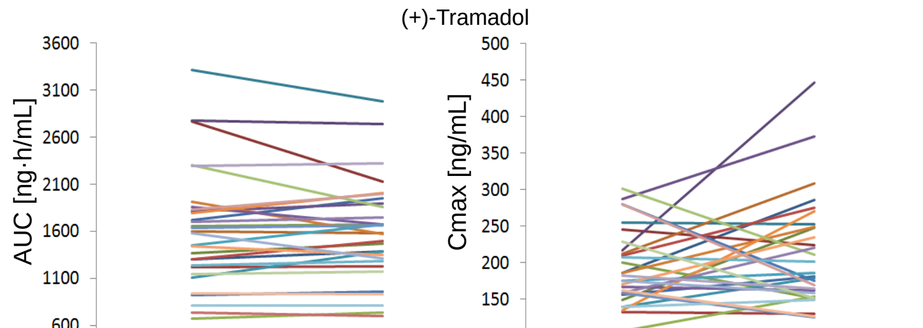


Table 2 *Pharmacokinetic parameters of DKP*

Analyte	Parameters	Geometric LSM (N=30) Test	Geometric LSM (N=30) Reference	Ratio (T/R) (%)	90% CI (Lower, Upper) (%)
DKP	C_{max} (ng/mL)	2816.5	2854.9	98.66	(88.15, 110.41)
	$AUC_{(0-t)}$ (ng*hr/mL)	3935.7	3875.8	101.55	(98.16, 105.05)
	Tmax (hour)	0.5 (0.3-4)	0.5 (0.3-1.5)	n/a	n/a

Test = TRAM.HCl (100 mg) + DKP.TRIS (25 mg)
Reference = DKP.TRIS (25 mg)
n/a = not applicable; median and range for Tmax

Figure 5 *Individual $AUC_{(0-t)}$ and C_{max} of DKP*



Conclusions

- Co-administration of DKP.TRIS 25mg and TRAM.HCl 100mg does not change the pharmacokinetics of either drugs.
- The combination of DKP.TRIS 25mg and TRAM.HCl 100mg is safe and well tolerated.