

Pregabalin-codeine-disease interactions in patients with acute herpetic or postherpetic neuralgia



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AIM:

To understand the implications of neuropathic pain in herpes zoster on pregabalin and codeine interaction to guide suitable dose regimens in the clinical practice considering that a different drug-drug interaction profile may exist in patients with acute herpetic neuralgia (AHN) or postherpetic neuralgia (PHN) compared with healthy participants (HP). Pregabalin pharmacokinetics were assessed in plasma and urine, whereas codeine and its active metabolites morphine and morphine-6-glucuronide (M6G) were assessed in plasma.

METHODS:

- Group 1: eligible HP (n=10);
 - Group 2: AHN (n=7);
 - Group 3: PHN (n=7).
- Clinical Study*
- All participants were previously phenotyped as CYP2D6 normal metabolizers (NM) following a single oral dose of metoprolol (10mg) as a probe (log plasma concentrations ratios of metoprolol and its alpha hydroxylated metabolite lower than 1.5);
 - In the morning, under fasted condition, all participants received a single oral dose of pregabalin (75mg) and codeine (30mg) with 250 mL of water;
 - Serial plasma samples and urine up to 24h after drug administration;
 - Pregabalin, codeine, morphine and M6G were analyzed using validated LC-MS/MS methods;
 - Pharmacokinetic parameters were calculated using the Phoenix WinNonlinTM software employing a noncompartmental analysis;
 - Pharmacokinetic parameters are presented in Tables 1 and 2 as geometric means (95%CI).

Drug-drug-disease interaction

Table 1 - Pharmacokinetic parameters of pregabalin in plasma and urine in healthy participants (HP; n=10), acute herpetic neuralgia (AHN; n=7), and patients diagnosed with postherpetic neuralgia (PHN; n=7) after oral administration of a single dose of 75 mg pregabalin.

	acute herpetic neuralgia (AHN; n=7)	postherpetic neuralgia (PHN; n=7)	healthy participants (HP; n=10)
C _{max} (µg/mL)	4.70 (3.28-6.72) *	3.76 (2.97-4.76)	2.73 (2.25-3.33) *
t _{max} (h)	1.5 (0.5-3)	2 (0.5-3)	1.5 (1-3)
AUC _{last} (h*µg/mL)	34.13 (25.79-45.17) *	27.09 (20.81-35.26) ^Δ	18.89 (16.12-22.14) * ^Δ
AUC _{0-inf} (h*µg/mL)	37.00 (28.91-47.35) *	29.26 (22.25-38.50) ^Δ	20.21 (17.20-23.74) * ^Δ
Cl/F (L/h)	2.17 (1.66-2.83) *	2.75 (2.12-3.56)	3.93 (3.38-4.56) *
t _{1/2} (h)	5.42 (3.82-8.51)	5.16 (4.54-8.63)	5.32 (4.35-6.97)
K _{el} (h ⁻¹)	0.13 (0.08-0.18)	0.13 (0.08-0.15)	0.13 (0.1-0.16)
Vd/F (L)	18.09 (11.49-28.49) *	23.03 (17.13-30.95)	30.09 (25.72-35.2) *
Ae (mg)	64.29 (55.03-75.11) *	68.19 (61.76-75.28) ^Δ	36.97 (29.10-46.98) * ^Δ
Fel (%)	85.72 (73.37-100.14) *	90.92 (82.35-100.38) ^Δ	49.3 (38.80-62.63) * ^Δ
Cl _{renal} (L/h)	1.86 (1.35-2.56)	2.50 (1.82-3.43)	1.94 (1.50-2.50)
Cl _{creatinina} (mL/min)	95.72 (85.87-106.71)	95.41 (80.21-113.5)	103.93 (95.23-113.43)

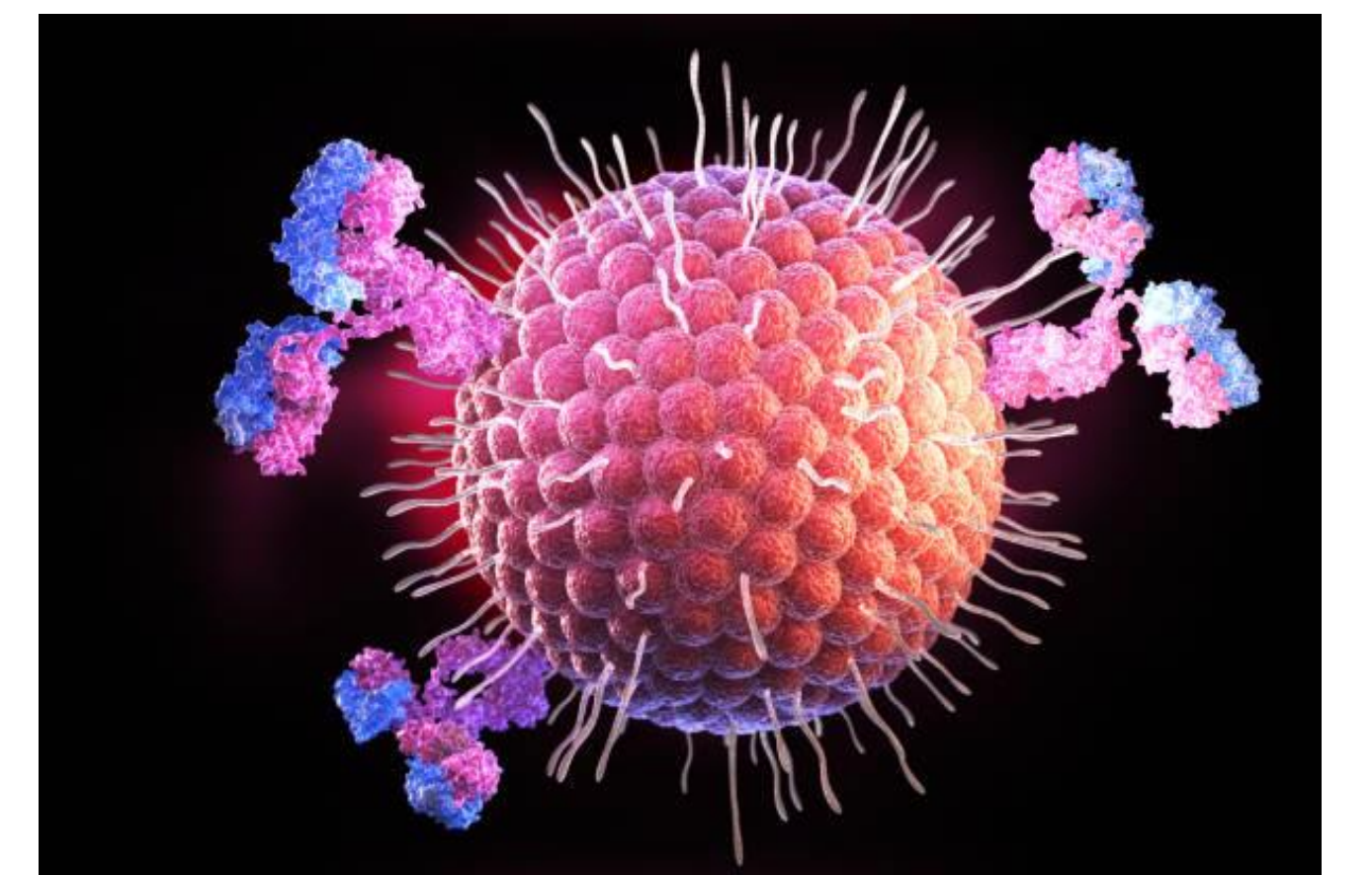
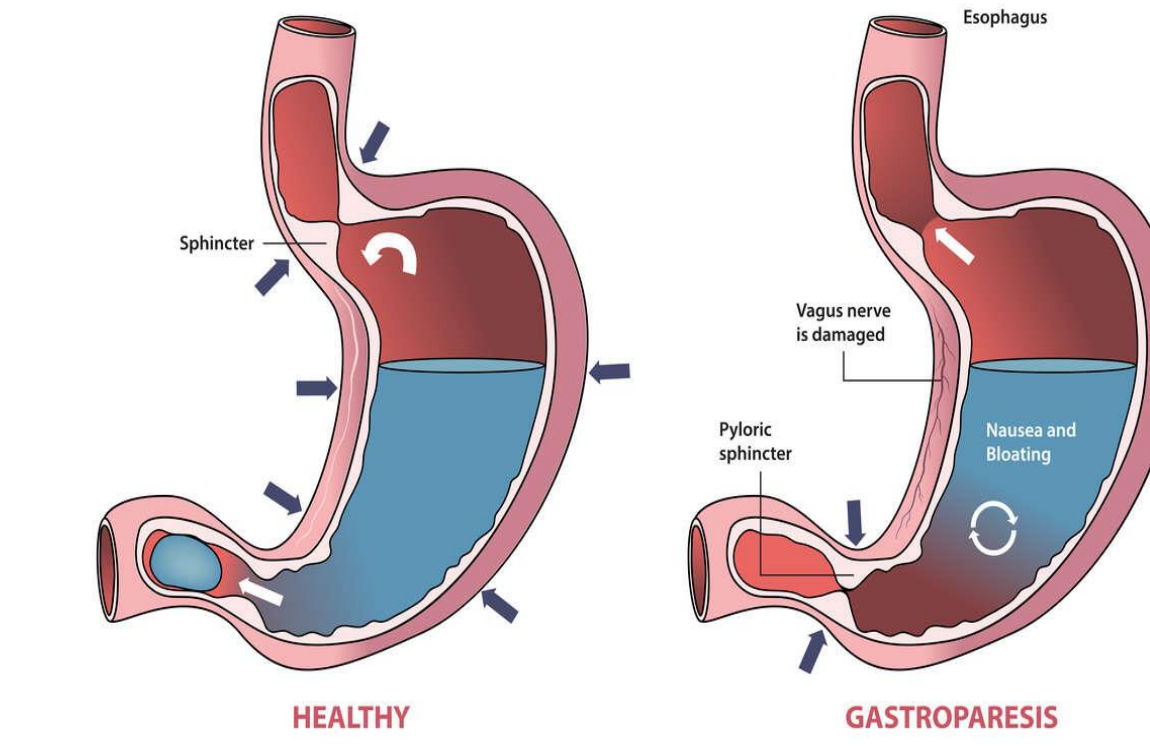
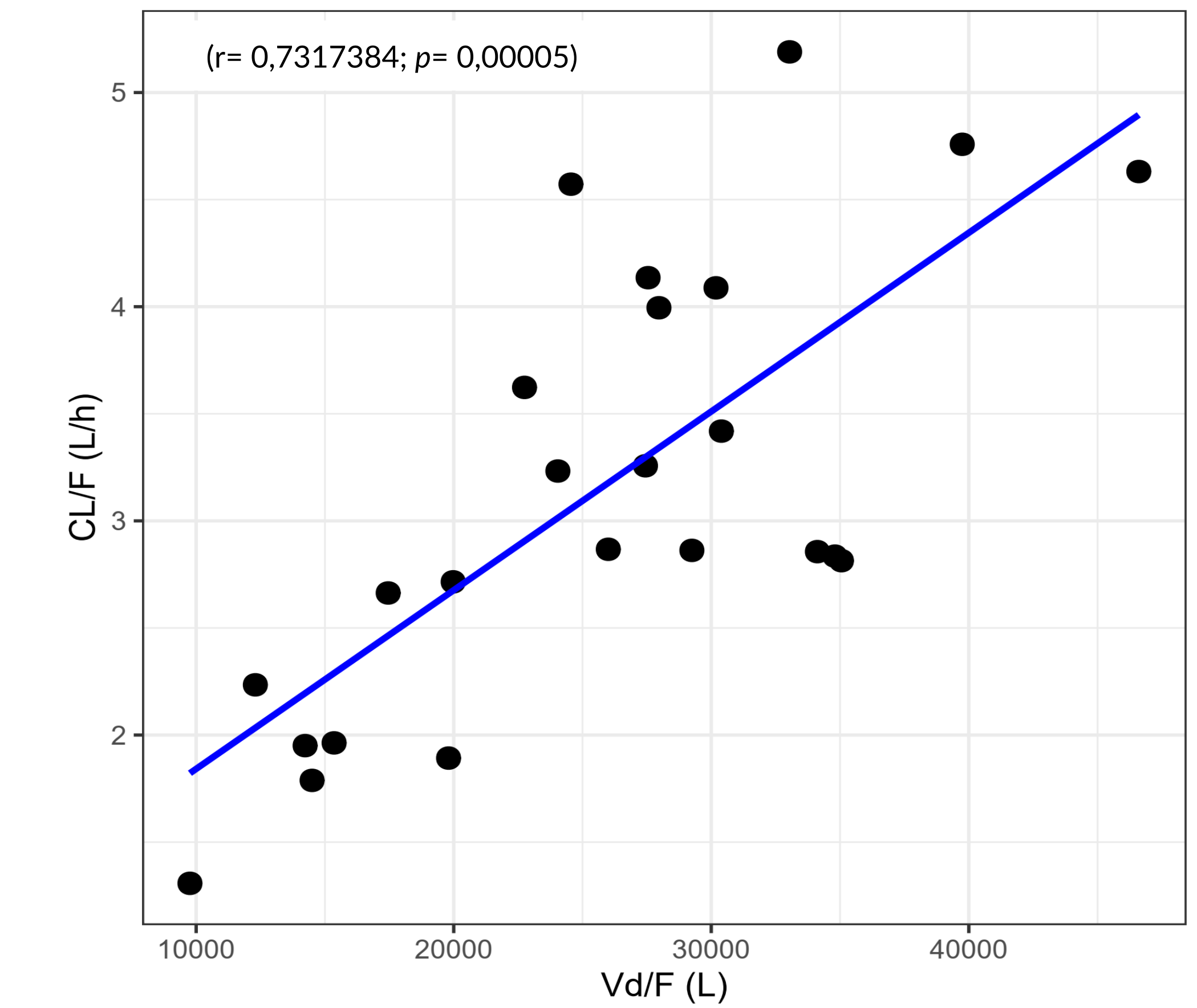
* p<0,05 Tukey's Honest Significant Difference test: HP vs AHN; ^Δp<0,05 Tukey's Honest Significant Difference test: HP vs PHN; data are presented as geometric means and 95%CI; ^Δ data are presented as median (minimum-maximum).

Table 2 - Pharmacokinetic parameters of codeine and its metabolites morphine and morphine-6-glucuronide (M6G) for the healthy participants (HP; n=10), acute herpetic neuralgia (AHN; n=7), and patients diagnosed with postherpetic neuralgia (PHN; n=7) after oral administration of a single dose of 30 mg codeine.

	Codeine		
	acute herpetic neuralgia (n=7)	postherpetic neuralgia (n=7)	healthy participants (n=10)
K _{el} (h ⁻¹)	0.10* (0.12-0.19)	0.28*# (0.20-0.36)	0.18# (0.15-0.23)
t _{1/2} (h)	5.12* (3.57-5.83)	2.43*# (1.92-3.51)	3.83# (3.01-4.73)
t _{max} (h)	1.00 (0.50-1.50)	2.00 (1.00-3.00)	1.25 (0.50-2.00)
C _{max} (ng/mL)	55.62 (32.05-96.53)	41.5 (28.78-59.86)	54.69 (39.63-75.48)
AUC _{last} (h*ng/mL)	190.77 (112.98-322.12)	167.26 (106.29-263.19)	200.05 (148.75-269.05)
AUC _{0-inf} (h*ng/mL)	193.28 (114.24-327.01)	168.98 (107.52-265.57)	202.32 (150.59-271.83)
CL/F (L/h)	157.26 (93.13-265.53)	178.23 (113.76-279.25)	149.75 (111.58-200.98)
Vd/F (L)	1035.76 (541.42-1981.43)	659.42 (486.55-893.72)	827.60 (610.43-1122.05)
	Morphine		
	acute herpetic neuralgia (n=7)	postherpetic neuralgia (n=7)	healthy participants (n=10)
K _{el} (l/h)	0.13* (0.04-0.25)	0.22*# (0.11-0.26)	0.12# (0.06-0.16)
t _{1/2} (h)	5.21* (2.78-18.61)	3.21*# (2.65-6.06)	5.85# (4.44-10.68)
t _{max} (h)	1.00 (0.50-1.50)	1.50 (0.50-3.00)	1.00 (0.50-2.00)
C _{max} (ng/mL)	4.83 (2.97-7.85)	3.26 (2.34-4.55)	4.38 (2.79-6.89)
AUC _{last} (h*ng/mL)	17.47 (10.83-28.20)	15.92 (11.30-22.42)	18.86 (11.98-29.68)
AUC _{0-inf} (h*ng/mL)	19.14 (11.74-31.20)	16.78 (11.95-23.56)	20.76 (13.32-32.36)
AUC _{0-inf} morphine/codeine	0.10 (0.06-0.16)	0.10 (0.07-0.13)	0.10 (0.08-0.14)
	Morphine-6-glucuronide		
	acute herpetic neuralgia (n=7)	postherpetic neuralgia (n=7)	healthy participants (n=10)
K _{el} (l/h)	0.09 (0.04-0.19)	0.12# (0.08-0.25)	0.06# (0.05-0.10)
t _{1/2} (h)	7.88 (3.67-18.11)	5.58# (2.80-8.34)	12.61# (6.83-15.36)
t _{max} (h)	2.00 (1.00-3.00)	2.00 (1.50-4.00)	1.50 (1.00-2.00)
C _{max} (ng/mL)	6.01 (2.80-12.92)	8.05 (5.60-11.56)	9.12 (5.76-14.44)
AUC _{last} (h*ng/mL)	23.47 (11.33-48.63)	36.86 (17.63-77.07)	53.58 (31.22-91.97)
AUC _{0-inf} (h*ng/mL)	26.52 (12.34-57.00)	39.95 (19.13-83.44)	68.39 (42.02-111.33)
AUC _{0-inf} M6G/codeine	0.14* (0.08-0.24)	0.24 (0.13-0.43)	0.34* (0.23-0.49)

#p<0,05 Bonferroni/Dunn test HP vs PHN; *p<0,05 Bonferroni/Dunn test AHN vs PHN; *p<0,05 Tukey's Honest Significant Difference (HSD) test HP vs AHN; data are presented as geometric means and 95%CI; ^Δ data are presented as median (minimum-maximum).

Figure 1 - Correlation between pregabalin apparent total clearance (Cl/F) and pregabalin apparent volume of distribution (Vd/F).



CONCLUSION:

- Acute herpetic neuralgia and postherpetic neuralgia do not alter the plasma exposure of codeine, morphine and M6G;
- The administration of a single oral dose of codeine 30 mg reduces pregabalin bioavailability and, consequently, its plasma exposure in healthy participants, but not in patients with herpetic neuralgia, inferring an example of drug-drug-disease interaction.

