Poster 579

Unexpected drug-drug interaction between Tipranavir/ritonavir (TPV/RTV) and Enfuvirtide (T20).

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BACKGROUND. New compounds should be evaluated for drug interactions. Association of TPV and T20 has become an option in the salvage setting. ***Aim of our study was to investigate the effect of T20 co-administration on both TPV and RTV plasma concentrations.***

Material and methods. Pts placed on a TPV/RTV-based regimen (500/200 mg BID) at our department underwent TPV and RTV concentrations measurement by HPLC. Record of last dose intake and sampling timing and no concomitant interacting drug were criteria of selection. TPV and RTV concentrations were averaged at each time post dose point for each subject. Samples obtained from 11 to 13 hours after last TPV/RTV dose intake were considered as C_{trough}. Modelling of sparse plasma samples was made by using a first order absorption and elimination monocompartmental model without Tlag. Time averaged plasma concentrations from each patient were modelled as naïve pooled data according to T20 administration. T-Student Test was use as needed. Values were given as ng/ml.

Results. A total of 321 samples from 39 subjects (20 with T20, group A, and 19 without, group B) were considered. No differences in sex, weight, height or HCV co-infection were seen between groups. 133 C_{trough} were considered (71 from A and 62 from B). Higher mean TPV C_{trough} was observed in group A (40666 ng/ml +/-20230 vs 26522 ng/ml +/-16907, p=0.024), as well as higher mean RTV C_{trough} (410 ng/ml +/-379 vs 265 ng/ml +/-144, p=0.012). Modelling of all TPV concentrations gave a correlation coefficient R=0.47 for group A and R=0.65 for group B. Higher Vd/F (9.83 L vs 4.19 L), but lower Kel value (0.07 h-1 vs 0.17 h-1) were observed in A as compared to B, whereas Ka was similar in both groups. Half-life elimination of A was 9.57 h vs 4.1 h of B. Higher C_{min} were predicted in A (42770 ng/ml vs 28195 ng/ml), without differences on C_{max} (69106 ng/ml vs 80954 ng/ml), or AUC (701770 ng*h/ml vs 697781 ng*h/ml). Modelling of RTV concentrations gave similar results, being differences more pronounced in elimination half life (4.32 h in A vs 2.65 h in B), and in C_{min} (400 ng/ml in A vs 138 ng/ml). No appreciable difference in TPV and RTV CL/F was found.

Conclusions. Higher TPV and RTV C_{trough} were found in patients administered with T20. Mechanism of interaction is unknown, potentially affecting Vd (higher with T20) and elimination half-life (higher in T20 group) of TPV and RTV. Further studies are warranted to define the clinical significance of this funding.

PATIENTS AND METHODS

- Patients placed on a TPV/RTV-based regimen (500/200 mg BID) at our department underwent TPV and RTV concentrations measurement by HPLC.
- Record of last dose intake and sampling timing and no concomitant interacting drug were criteria of selection.
- TPV and RTV concentrations were averaged at each time post dose point for each subject.
- For C_{trough} study, only samples obtained from 11 to 13 hours after last TPV/RTV dose intake were considered.
- Modelling of sparse plasma samples was made by using a first order absorption and elimination monocompartmental model without Tlag.
  - Time averaged plasma concentrations from each patient were modelled as naïve pooled data according to T20 administration.
  - WinNonLin software was used for modelling and estimation of pharmacokinetic parameters.
- Evolution of of TPV C_{trough} in two sujects in whom T20 was either removed or introduced in a TPV/r based regimen are also shown.
- T-Student Test was use to study differences between groups. Values were given as ug/ml.

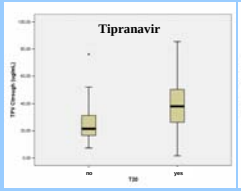
RESULTS

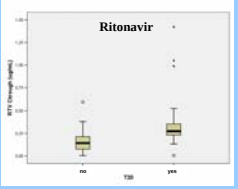
Population characteristics

	Total	+ T20	- T20	*P value*
N	39	20	19	
Sex (male)	31	16	15	*0.35*
HCV +	7	5	2	*0.4*
Age	44 [38.7-49]	47 [38-55]	42 [37-48]	*0.45*
Weight (Kg)	70 [62.6-75]	68.8 [60.7-76]	70 [63.5-75]	*0.87*
Height (cm)	175 [170-180]	175 [170-180.6]	175 [169-180]	*0.8*

Ctrough Analisys

	Total (±SD)	+ T20 (±SD)	-T20 (±SD)	*P value*
N° of samples	133	71	62	
TPV C_{trough} (ug/ml)	33.77 (19.78)	40.666 (20.238)	26.552 (16.907)	***0.024***
RTV C_{trough} (ug/ml)	0.277 (0.3)	0.41 (0.379)	0.165 (0.14)	***0.012***
T20 C_{trough} (ug/ml)	3.714 (1.330)	3.714 (1.330)		





Modelling Analisys

•A total of 321 sparse samples were considered for modelling.

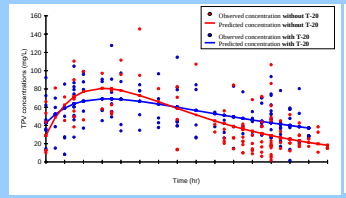
Final model pharmacokinetic parameters

Drug	Estimated PK parameters	+ T20	- T20
Tipranavir	*Coefficient of regression*	0.47	0.65
	Vd/F (L)	9.83	4.19
	Ka (h^{-1})	0.49	0.44
	Kel (h^{-1})	0.07	0.17
	Cmin (ug/ml)	42.77	28.195
	Cmax (ug/ml)	69.106	80.954
	*AUC (ug*h/ml)*	701.770	697.781
	T1/2 (h)	9.57	4.1
	CL/F (L/h)	0.712	0.717
Ritonavir	*Coefficient of regression*	0.44	0.63
	Vd/F (L)	115.35	74
	Ka (h^{-1})	0.2	0.3
	Kel (h^{-1})	0.16	0.26
	Cmin (ug/ml)	0.4	0.138
	Cmax (ug/ml)	0.884	1.08
	*AUC (ug*h/ml)*	8.52	7.85
	T1/2 (h)	4.32	2.65
	CL/F (L/h)	23.45	25.47

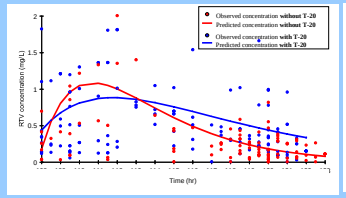
Predicted and observed concentration time curve

Weighted residuals vs Time

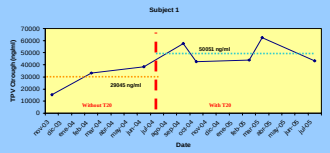
Tipranavir

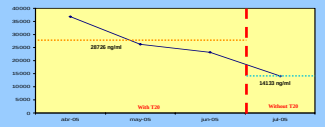


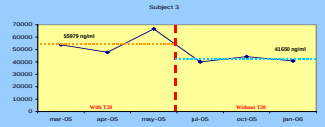
Ritonavir



Single Subjects case reports







CONCLUSIONS

- Significantly higher TPV and RTV C_{trough} were found in patients administered with T20 as compared to values observed in subjects with no concomitant T20 intake.
- In 3 representative case reports, discontinuation or addition of T20 to a TPV/r based regimen led to TPV plasma levels modification according to this trend.
- Mechanism of such interaction is unknown, but it seems to potentially affect volume of distribution (higher with T20) and elimination half-life (higher in T20 group) of both TPV and RTV.
- Further studies are warranted to define the clinical significance of this finding, given that both efficacy and, to a lesser extent, tolerability of TPV have been supposed to be concentration-related.

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