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Poster presentation

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An open-label multicentre pilot study evaluating the pharmacokinetics (PK) of co-administered lopinavir (LPV) and nevirapine (NVP) in HIV+ adults

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Purpose of the study

Co-administration of LPV/r SGC with NVP, an inducer of CYP3A, necessitates a LPV/r dose increase. The objectives of "The NRTI Sparing Study" were to evaluate the PK of co-administered LPV/r and NVP in HIV-infected subjects at week 4 and to assess any changes in these PK parameters at 48 weeks follow-up.

Methods

In this prospective, 48-week (wk), multicentre study, 40 patients (39 ART-naive) were recruited to receive LPV/r SGC (533/133 mg BID) plus NVP (200 mg BID) and undergo PK sampling (0–12 hr) at wk 4 and wk 48. In one of the two participating centres, switches to the LPV/r tablet formulation (400/100 mg BID) were allowed between wk 4 and 48, once HIV-RNA was <50 copies/ml. LPV concentrations were determined by HPLC-MS/MS and NVP concentrations via HPLC-UV. PK parameters were calculated via non-compartmental analysis and within-subject changes assessed by geometric mean ratios (GMR) with 95% confidence intervals (95% CI).

Summary of results

Wk 4 PK data were available on 35 patients. Geometric mean (95% CI) LPV AUC and C were 92012 ng.h/ml (81237–104215) and 3979 ng/ml (3159–5011), respectively. For NVP these values were 62749 ng.h/ml (55621–70790) and 4594 ng/ml (4023–5246), respectively. At wk 24, five individuals had HIV-RNA >50 copies/ml. Wk 4 PK data was available on 4/5 of these patients, all of whom had LPV and NVP concentrations greater than the proposed trough concentration desirable in patients with wild-type HIV-1 (1000 and 3000 ng/ml, respectively). Twenty-five patients also underwent wk 48 PK sampling; of these 10 remained on SGC, while 15 switched to the tablet formulation (400/100 mg BID). No significant intra-individual changes in PK were observed over 48 wks for patients remaining on SGC ($p > 0.24$). In those switching to the tablet, PK parameters were not significantly different ($p > 0.68$), although there was a trend towards lower LPV C at wk 48 (see Table 1).

Conclusion

This study explored an NRTI sparing strategy. We recognise that one limitation is that some patients were switched to the LPV/r tablet formulation. The issue of whether, if starting with this strategy, a dose of 400/100 mg or 600/150 mg tablet would be used, has not been addressed here. PK parameters at wk 4 and 48 did not differ significantly in patients receiving co-administered LPV/r and NVP. However, there was a trend towards lower LPV C in patients who switched to LPV/r tablet. Therefore, there is a need for caution and a consideration for TDM-guided dose adjustment depending on the population.

Table 1:

PK [patients remaining on LPV/r SGC (n = 10)]	Wk 4	Wk 48	GMR (95% CI)	CV% wk 4; wk 48
LPV AUC0–12, ng.h/ml	102951 (85318, 130692)	91589 (84050, 101101)	0.89 (0.70, 1.13)	34; 15
LPV Ctrough, ng/ml	4848 (3615, 7952)	5230 (4347, 6794)	1.08 (0.67, 1.75)	60; 35
LPV Cmax, ng/ml	12307 (10659, 14663)	11115 (10209, 12251)	0.90 (0.75, 1.08)	26; 15
NVP AUC0–12, ng.h/ml	71850 (67089, 90850)	68793 (58059, 86236)	0.96 (0.83, 1.10)	45; 33
NVP Ctrough, ng/ml	5254 (4933, 6676)	4932 (4032, 6527)	0.94 (0.76, 1.16)	45; 40
NVP Cmax, ng/ml	6924 (6440, 8741)	6830 (5846, 8385)	0.99 (0.85, 1.15)	46; 30
PK [patients switching to LPV/r tablet (n = 15)]	Wk 4	Wk 48	GMR (95% CI)	CV% wk 4; wk 48
LPV AUC0–12, ng.h/ml	77332 (68401, 87428)	67853 (60277, 85324)	0.88 (0.67, 1.14)	26; 34
LPV Ctrough, ng/ml	3171 (2355, 4271)	2164 (2013, 3688)	0.68 (0.37, 1.24)	62; 58
LPV Cmax, ng/ml	9393 (8619, 10518)	8706 (7618, 10846)	0.93 (0.76, 1.12)	20; 35
NVP AUC0–12, ng.h/ml	55289 (49589, 64356)	57231 (50758, 64528)	1.04 (0.88, 1.21)	26; 26
NVP Ctrough, ng/ml	3984 (3842, 4947)	4063 (3540, 4665)	1.02 (0.86, 1.21)	28; 29
NVP Cmax, ng/ml	5447 (4918, 6251)	5576 (5004, 6469)	1.02 (0.88, 1.20)	24; 25

Values given as geometric mean (95% CI); CV% = coefficient of variation (%).