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Raltegravir Penetration in Seminal Plasma of Healthy Volunteers

Andrea Calcagno, Stefano Bonora, Antonio D'Avolio, Marco Siccardi, Marco Simiele, Mattia Chiesa, Daniel Gonzalez de Requena and Giovanni Di Perri
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Penetration of antiretroviral drugs into the genital tract is crucial for virological efficacy in this compartment and impacts the transmission of the virus. Anti-HIV drugs showed different degrees of passage into the male and female genital systems, and their efficacy appeared related to the concentrations reached at the site of action (2, 5).

Raltegravir (RGV) is a novel drug whose target is the HIV preintegrase complex. Jones and colleagues demonstrated a significant passage in the cervicovaginal fluid of female healthy volunteers, with concentrations around 93% of plasma and a longer elimination half-life (17 versus 7 h) (4). A paper recently published in this journal showed that males treated with RGV-containing regimens had undetectable viral loads in seminal plasma and showed variable but high drug penetration in such compartment. The median RGV concentration in semen measured at 5 h postdose was 345 (range, 83 to 707) ng/ml with a median semen-to-plasma RGV concentration ratio of 1.42 (range, 0.52 to 6.66) (1). However, no data of RGV penetration in seminal plasma over the whole dosing interval are currently available.

We performed a multiple-dose, one-way, open-labeled, noncontrolled, single-center study. Eight healthy male volunteers were enrolled after we obtained written informed consent. Median (interquartile range [IQR]) age, weight, and body mass index (BMI) were 31 (28 to 39) years, 79 (75 to 89) kg, and 24.5 (22.3 to 26.3) kg/m^2, respectively. Subjects were considered healthy according to history, physical examination, electrocardiogram, and standard laboratory tests, including a test for hepatitis viruses and an HIV screen. Subjects were administered RGV (400 mg twice daily) in fed state for 4 days plus a single dose on day 5. On day 5, peripheral blood and semen (after 5 days of sexual abstinence) were concomitantly collected within 11 to 12 h (4 subjects) or 2 to 4 h (4 subjects) after last RGV dose intake. RGV blood plasma and seminal plasma levels were measured by a validated high-performance liquid chromatography (HPLC-PDA) method with limit of detection of 11.7 ng/ml (3). Results were expressed as geometric mean (95% confidence interval).

In the group with measurements performed at the end of the dosing interval, blood and semen RGV concentrations were 151 (51 to 443) and 937 (212 to 3,582) ng/ml, respectively, with a semen-to-blood plasma concentration ratio of 6.45 (3.78 to 9.37) (Fig. 1). In the group where RGV was measured after recent drug intake (2 to 4 h), plasma and semen concentrations were 651 (438 to 1,020) and 953 (541 to 1,706) ng/ml, respectively, with a semen-to-blood plasma ratio of 1.62 (1.33 to 2.06). All samples were found to be above the 95% inhibitory concentration of wild-type HIV-1 strains (14.6 ng/ml).

Our study confirmed a high and variable degree of RGV penetration in seminal plasma. However, we showed for the first time that the magnitude of penetration significantly varies over the dosing interval. The semen-to-blood plasma concentration ratio, in fact, was higher at the end of the dosing interval (6.45) than at 2 to 4 h after drug intake (1.62). This finding suggests a possible delay of drug penetration from plasma to semen and/or a slower RGV clearance in the compartment, leading to increasing levels in semen over time compared to stable plasma concentrations (equivalent mean plasma levels in the two groups). The

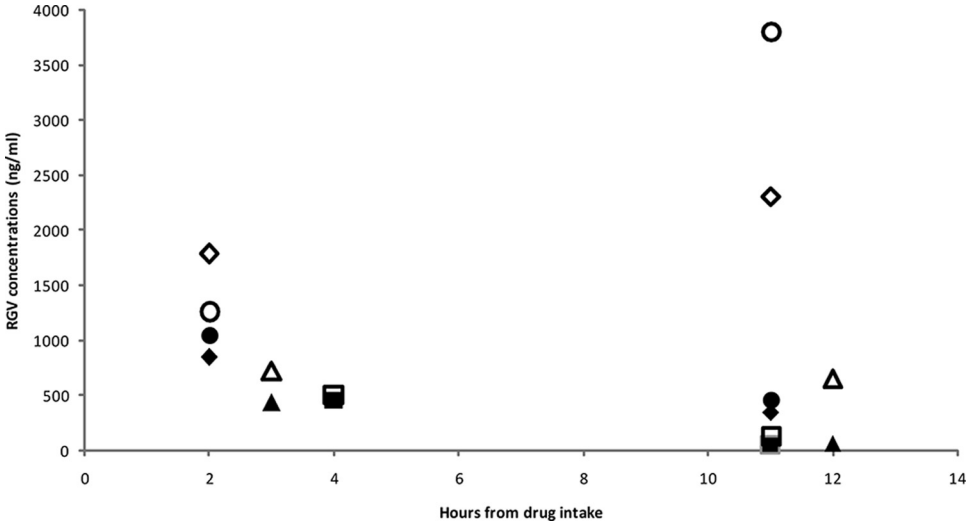

FIG. 1. Scatter-dot representation of plasma (filled markers) and seminal (empty markers) concentrations (ng/ml) over time. A single patient's concentrations are represented with the same symbol.

possible therapeutical and prophylactic implications warrant study in the clinical setting.

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Andrea Calcagno*
Stefano Bonora
Antonio D'Avolio
Marco Siccardi
Marco Simiele
Mattia Chiesa
Daniel Gonzalez de Requena
Giovanni Di Perri
Clinica Universitaria c/o Ospedale Amedeo di Savoia
University of Torino
C.so Svizzera 164
Torino, Italy 10149

*Phone: 39-0114393856
Fax: 39-3384447633
E-mail: andrea.calcagno@unito.it

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