ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2002, p. 3684–3685 Vol. 46, No. 11
0066-4804/02/$04.00+0 DOI: 10.1128/AAC.46.11.3684–3685.2002

Lopinavir Measurement in Pleural Effusion in a Human Immunodeficiency Virus Type 1-Infected Patient with Kaposi's Sarcoma

Human immunodeficiency virus type 1 (HIV-1) infection is highly compartmentalized within various organs. Tissue dissemination is evident in the lung (1), the male (3) and female (8) genital tracts, the lymph nodes (12), and especially in the brain (5, 12). This process may contribute to the increase in systemic HIV-1 heterogeneity.

Although multiple antiretroviral drug regimens have led to a dramatic decline in HIV-related morbidity and mortality (6), viral eradication is not yet achievable with existing regimens, a failure likely to be attributable to poor drug penetration into critical tissues. Despite adequate plasma drug concentrations and associated systemic virological efficacy (7), poor drug diffusion into particular body sites is thought to be responsible for the selection of drug-resistant HIV quasispecies which keep on seeding the systemic compartment, thus eventually leading to emergence of HIV-1 variants resistant to antiretroviral drugs.

Limited data available on drug concentrations of highly bound protease inhibitors show that penetration of these drugs into semen (10) and brain (4) is poor. In addition to considerations of protein binding, passage into body compartments is likely related to limited lipid solubility, high molecular weight, extensive binding to plasma proteins, or affinity for ATP-dependent efflux membrane transporters (11). Recently, high viral load values were found in the pleural space, and these were shown to be responsible for HIV quasispecies migration from the pleural space to the blood (2).

As no data exist on the penetration of antiretroviral drugs in pleural fluid, we measured concentrations of lopinavir, a highly specific HIV-1 protease inhibitor, in plasma and pleural fluid of an HIV-1-infected male admitted to our ward for cutaneous and pulmonary Kaposi's sarcoma associated with bilateral pleural effusion. The subject had a good response to antiretroviral therapy (consisting of stavudine, 40 mg twice a day [BID]; lamivudine, 150 mg BID; and lopinavir-ritonavir, 400 and 100 mg BID) with a CD4 cell count increase from 70 to 352 cells mm^{-3} and a plasma viral load decrease of 2.7 $\log_{10}$ after 3 months of treatment. When blood and pleural fluid were collected for drug analysis, the patient had been on lopinavir-ritonavir for 19 days and was about to initiate a specific treatment for Kaposi's sarcoma.

Lopinavir concentrations were assessed 12 h after a dose of lopinavir-ritonavir by high-performance liquid chromatography–dual mass spectrometry (9) and were seen to be similar in pleural fluid and plasma (12,439 and 12,691 $ng \cdot ml^{-1}$, respectively). As lopinavir is coformulated with low-dose ritonavir to enhance plasma lopinavir concentrations, ritonavir concentrations in pleural fluid and plasma were also assessed and were 352 and 214 $ng \cdot ml^{-1}$, respectively.

In normal conditions, lower concentrations of lopinavir may be expected in pleural fluid, since passage of highly bound drug, such as lopinavir, through parietal and visceral pleura is limited. However, as suggested by laboratory findings (pleural protein content, 3.7 $g \cdot dl^{-1}$; pleural fluid protein/serum protein ratio, 0.6; pleural fluid lactate dehydrogenase [LDH], 544 $IU \cdot liter^{-1}$; pleural fluid LDH/serum LDH ratio, 2), the presence of acute inflammation in the pleural space with significant exudative effusion can account for the comparable concentrations of lopinavir and ritonavir that we found in pleural fluid and plasma. However, drug concentrations were here measured at a single time point which may not reflect the pleural fluid/plasma ratio over the 12-h dosing schedule since the penetration of a drug like lopinavir-ritonavir into a closed space such as the pleura may be relatively slow.

To what extent the rate of penetration of antiretrovirals into pleural fluid may be of therapeutic concern is presently unknown. However, since enhanced HIV replication may result (both systemically and locally) from immune activation by opportunistic pathogens, the presence of suppressive concentrations of antiretrovirals in the site where the concomitant process is ongoing does appear to be important.

Further studies are clearly needed to investigate the relevance of HIV replication and antiretroviral drug penetration into pleural effusions and other tissue compartments.

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