Lung tissue distribution of drugs as a key factor for COVID-19 treatment

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Abstract

Lopinavir combined with ritonavir were reported to benefit the patients with SARS by reducing the viral loads. However, in the latest clinical trials, no benefit was observed with lopinavir-ritonavir treatment beyond standard care in patients with COVID-19. We comment here that this disappointed result of clinical trial might result from the low volume of the lung distribution of lopinavir. The major reasons were listed below: 1) The binding affinity of ACE2 with SARS-CoV-2 spike protein is ˜10- to 20-fold higher than the binding affinity of ACE2 with SARS-CoV spike protein, indicating that SARS-CoV-2 can enter AT2 cells in lung much easier than SARS-CoV. Therefore, the viral loads of SARS-CoV-2 might be much higher than viral loads of SARS-CoV in the lung tissue. 2) The concentration of lopinavir in the lung tissue was 1.18 μg equiv/ml in rats. The low volume of the lung distribution of lopinavir might not be enough to inhibit the coronavirus replication due to the high viral loads in the lung tissue. 3) In contrast, the concentration of chloroquine in the lung tissue was much higher (30.76 ± 0.85 μg equiv/ml) in rats, which might lead to its clinical and virologic benefits in the treatment of COVID-19 patients. Together, we proposed here that anti-SARS-CoV-2 drug repurposing studies should pay more attentions to the lung tissue distribution of antiviral drugs. The efficacy of antiviral drugs might depend on their lung tissue distributions

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Over 72,000 people around the world was killed by Coronavirus Disease 2019 (COVID-19). COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is impossible to create novel drugs against the coronavirus in very short time, as it often takes years; therefore, the best strategy is to find new antiviral uses from approved drugs [1]. Not surprisingly, SARS-CoV-2 shares a highly similar viral genome sequence with SARS-CoV [2], suggesting that the effective treatments for SARS may also work for COVID-19 treatment.

Lopinavir, a human immunodeficiency virus type 1 (HIV-1) protease inhibitor, showed a good inhibitory effect on SARS-CoV replication in cell-based assays. In clinical trials, lopinavir combined with ritonavir benefited the patients with SARS by reducing the viral loads [3]. According to molecular docking and

dynamics analysis, lopinavir has been identified as a main protease inhibitor of SARS-CoV, and approved for inhibiting the SARS-CoV replication [4]. Recent docking simulation studies showed that lopinavir can also directly bind to catalytic pocket of SARS-CoV-2 main protease, indicating its potential to reduce the viral loads in patients with COVID-19 [5]. However, in clinical trials, no benefit was observed with lopinavir-ritonavir treatment beyond standard care in patients with COVID-19 [6].

Both SARS-CoV and SARS-CoV-2 can attach to angiotensin-converting enzyme 2 (ACE2) and then enter host cells [2]. Given that ACE2 is highly expressed in AT2 cells in lung [7], lung becomes a major organ under the coronavirus attack. Interestingly, ACE2 bound to the SARS-CoV-2 spike protein with ˜15 nM affinity, which is ˜10- to 20-fold higher than ACE2 binding to SARS-CoV spike protein [8]. It is indicated that SARS-CoV-2 can enter AT2 cells in lung much easier comparing with SARS-CoV. The viral loads of SARS-CoV-2, in turn, might be much higher than viral loads of SARS-CoV in the lung tissue. Therefore, the anti-SARS-CoV-2 drugs should target against the lung rather than other tissues.

In a previous study, the tissue distribution of isotope-labeled lopinavir was examined in rats. The peak radioactivity levels in plasma were achieved at 4 h post-administration. At 4 h after administration (10 mg/kg), liver (52.24 μg equiv/ml), adrenals (4.80 μg equiv/ml), and thyroid (4.41 μg equiv/ml) exhibited greater radioactivity levels than plasma. The lung (1.18 μg equiv/ml) exhibited less radioactivity levels than plasma, indicating that the distribution of lopinavir in the lung tissue is relatively low [9]. We guess the concentration of lopinavir in the lung is too low to inhibit SARS-CoV-2 replication well. It might explain why lopinavir did not benefit the patients with COVID-19.

Unlike lopinavir, chloroquine exhibited clinical and virologic benefits in the treatment of COVID-19 patients, including improving lung image findings and reducing viral loads. In preclinical studies, chloroquine showed a strong inhibitory effect on SARS-CoV-2 replication in cell-based assays (EC_{50} = 1.13 μM) [10]. Lung is one of the major target tissues as evidenced in tissue distribution studies of oral administration of chloroquine in rats. After an oral administration of ^{14}C-chloroquine (20 mg/kg) to albino and pigmented rats, the lung tissue concentrations were similar (30.76 ± 0.85 and 34.76 ± 1.56 μg equiv/ml, respectively) [11]. In a 32-weeks treatment (16.8 mg/kg/day), the lung tissue concentrations of chloroquine were 51.7 ± 3.1 and 104 ± 7.0 μg/mg in male and female rats, respectively [12]. Both these two pharmacokinetics studies showed that the distribution of chloroquine is high in the lung distribution. We believed that chloroquine can take an advantage of the high volume of the lung distribution to inhibit the viral replication in the lung.

Together, we proposed that anti-SARS-CoV-2 drug repurposing studies should pay more attentions to the lung tissue distribution of antiviral drugs. The low volume of the lung distribution of antiviral drugs might not be enough to inhibit the coronavirus replication due to the high viral loads in the lung tissue. Among the anti-SARS-CoV-2 drugs in the clinical trials, hydroxychloroquine is likely to be a promising drug that benefit COVID-19 patients because of its high volume of the lung distribution. In a 32-weeks treatment (19.4 mg/kg/day), the lung tissue concentration of hydroxychloroquine is 55.7 ± 3.4 μg/mg [12]. So far, the most potent inhibitor of SARS-CoV-2 *in vitro* is remdesivir (EC_{50} = 0.77 μM) [10], which lacks of the tissue distribution data in public. Although remdesivir was reported to reduce MERS-CoV viral lung loads in animals [13], we are eager to see its lung tissue distribution data. It would help to choose an appropriate dosing and route of administration of remdesivir.

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