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Title: Therapeutic drug monitoring of inhaled corticosteroids in exhaled breath for adherence assessment

Authors: Daiki Hira, PhD.^{a,1}, Satoshi Hamada, M.D., PhD.^{b,2}, Tomohiro Terada, PhD.^{a,3}

Affiliations: ^aDepartment of Clinical Pharmacology and Therapeutics, Kyoto University Hospital. 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, JAPAN.

^b Department of Advanced Medicine for Respiratory Failure, Graduate School of Medicine, Kyoto University, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, JAPAN.

E-mail: ¹ hira_d@kuhp.kyoto-u.ac.jp, ² sh1124@kuhp.kyoto-u.ac.jp, ³ teradat@kuhp.kyoto-u.ac.jp

Corresponding author: Daiki Hira, PhD.

Department of Clinical Pharmacology and Therapeutics, Kyoto University Hospital. 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, JAPAN.
hira_d@kuhp.kyoto-u.ac.jp, +81-75-751-3588.

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29 To the Editor:

30 We have read with great interest the article by Alahmadi et al, which demonstrated
31 the relationship of serum inhaled corticosteroid (ICS) levels and exacerbation rates in
32 severe asthma¹. As indicated in the article, therapeutic drug monitoring of serum ICS
33 level after inhalation may be a marker of treatment adherence. However, we have
34 concerns about the weakness of the relationship between the serum ICS level and
35 therapeutic efficacy. Therefore, we suggest paying attention to the difference between
36 serum and lung concentrations. In the article, marked variability in serum
37 pharmacokinetics was shown between patients, and the authors suggested that the main
38 sources of variation are deposition, oral bioavailability, lipophilicity, and volume of
39 distribution. Most ICS are metabolized by CYP3As in the liver. The systemic
40 pharmacokinetics of CYP3A substrates varies widely by genetic variation in CYP3As
41 and concomitant CYP3As inhibitors. CYP3As are mainly expressed in the liver and
42 intestine but rarely in the lungs^{2,3}. Therefore, there may be a difference between the
43 concentration in the lung and systemic circulation. Recently, Sadiq et al have reported
44 that the lung fluticasone concentration after inhalation was higher than plasma
45 concentration⁴. The gap between the lung and plasma concentrations could be a reason
46 for the weak correlation between serum concentration and therapeutic effects in

47 Alahmadi's study¹.

48 Since it is difficult to routinely perform lung biopsy for the assessment of
49 inhalation therapy adherence, a noninvasive method for estimating lung concentration
50 should be developed to evaluate the therapeutic effect in the lung. Our previous report
51 has demonstrated that ICS in exhaled breath could be detected immediately after
52 inhalation of dry-powder inhaler (DPI), and the exhaled drug amount increased,
53 depending on the participants' inhalation flow rate⁵. Other *in vitro* studies have
54 indicated that the deagglomeration rate and pulmonary deposition rate of DPI increase
55 depending on the inhalation flow rate⁶. In general, a high inhalation flow rate is required
56 for the deagglomeration of DPI. Then, submicron particles, which are likely to be
57 exhaled, are also generated by high inhalation flow rate. Therefore, the exhaled drug
58 amount after inhalation should correlate with the deagglomeration rate and pulmonary
59 deposition rate of DPIs. We propose a novel therapeutic drug monitoring method of ICS
60 in exhaled breath for monitoring treatment adherence. The drug amount in exhaled
61 breath is unlikely to be affected by individual variability of metabolic enzymes and
62 depends on inhalation techniques such as inhalation flow rate. In addition, since the
63 drug concentrations in exhaled breath immediately after inhalation are larger than the
64 reported serum concentrations, it can be quantified not only by liquid chromatography

with tandem mass spectrometry but also by high performance liquid chromatography with ultraviolet detection, which is a more clinically available method. Although further clinical studies should be conducted, the exhaled ICS monitoring may also be a good biomarker for the assessment of adherence to inhalation therapy.

Daiki Hira, PhD.^a, Satoshi Hamada, M.D., PhD.^b, Tomohiro Terada, PhD.^a

^aDepartment of Clinical Pharmacology and Therapeutics, Kyoto University Hospital. Kyoto, JAPAN. ^b Department of Advanced Medicine for Respiratory Failure, Graduate School of Medicine, Kyoto University, Kyoto, JAPAN.

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