Relative lung dose from antistatic valved holding chambers Reply

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Correspondence and Reply

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To the Editor:

We read with interest the data of Hagedoorn et al[1] looking at the *in vitro* performance of antistatic valved holding chambers (VHCs), suggesting that some devices are more efficient than others and may not be interchangeable. Crucially, their *in vitro* technique does not account for the unique real-life interaction between the device and the patient in addition to effects of altered airway geometry in asthmatic airways.

We have previously reported on *in vivo* delivery of inhaled hydrofluoroalkane suspension formulation of fluticasone propionate (FP) pressurized metered dose inhaler (pMDI: Flixotide Evohaler; GlaxoSmithKline, Brentford, United Kingdom) via 3 antistatic VHCs, namely, 280 mL polyamide plastic Zerostat-V (Cipla, Mumbai, India), 250 mL stainless steel Nebuchamber (AstraZeneca, Cambridge, United Kingdom), and 197 mL plastic Aerochamber Max (Trudell Medical, London, Canada).[2] The spacers were all used new out of the box without washing or priming and without delay between actuation and inhalation in 18 patients with mild to moderate asthma. The relative lung dose of FP as bioavailability was calculated from the suppression of overnight urinary cortisol. Compared with pMDI alone, the relative lung bioavailability of FP was increased by 48% by Zerostat-V, 57% by Nebuchamber, and 71% by Aerochamber Max.

In another study using new out of box unprimed unwashed conventional plastic holding chambers, the relative lung delivery of the same dose of hydrofluoroalkane FP/salmeterol pMDI (Seretide Evohaler; GlaxoSmithKline) was compared with pMDI alone.[3] The relative lung dose of FP was 62% higher via 149 mL Aerochamber plus (Trudell Medical) and 49% higher via 750 mL Volumatic (GlaxoSmithKline). In a third study, a primed prewashed 750 mL Volumatic with the same dose of FP/salmeterol resulted in a 40% greater lung dose for FP versus pMDI alone.[4]

Hence, all the VHCs, whether they were antistatic or not, primed/prewashed or not, resulted in appreciable improvements in the relative lung dose of FP pMDI *in vivo*. This would be likely to have an impact in not only improving antiasthmatic airway efficacy but also worsening systemic adverse effects. Comparing the best and worst devices for relative lung dose, namely, Aerochamber Max (71%) and Volumatic (40%-49%), the difference in relative lung dose of FP was marked, bearing in mind that these devices were used under optimal conditions using single puffs along with deep inhalation and without delay. In a real-life clinic setting, we believe that such differences would be obviated because of poor spacer technique.

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Reply

To the Editor:

It is with interest that we have read the correspondence of Lipworth et al[1] in response to our recent communication on drug dose delivery from 5 antistatic valved holding chambers (VHCs).[2] To some extent we agree with their points of view, but we feel compelled to argue for the importance of an inhalation delay after actuation of pressurized metered dose inhalers (pMDIs) into VHCs during *in vitro* and *in vivo* experiments. Furthermore, we feel that some of their arguments, although true, may not be relevant when regarding therapy of the individual patient.

With reference to their *in vivo* studies, Lipworth et al[1] suggest that VHCs are likely to improve the lung deposition achieved with pMDIs regardless of their antistatic behavior, and that the variation in lung deposition caused by differences in antistatic behavior of VHCs may be much lower and therefore less important than the variation in lung deposition that is brought about by poor spacer technique and variation in (diseased) airway geometry. Indeed, these factors are not accounted for in our *in vitro* study. The authors further argue that with respect to lung deposition, higher is not always better, because a delicate balance has to be found between therapeutic and adverse effects.

However, as noted by the authors, they did not apply an inhalation delay after pMDI actuation in the VHCs during their *in vivo* studies. Consequently, the considerable effect of differences in antistatic behavior of the VHCs on aerosol half-life[3] is excluded from their end points. Even a delay as short as 1 second may already reduce the aerosol output from an untreated nonconducting Babyhaler by 40%, whereas the output from antistatic VHCs may remain similar for at least 5 seconds.[4] Because VHCs are often used to prevent actuation-coordination problems, a delay between actuation and inhalation is to be expected with their use in practice. We therefore argue that the lack of an inhalation delay is not representative of clinical practice and that the *in vitro* studies referenced by

Lipworth et al underestimate the clinical effect of differences in antistatic behavior between VHCs.

More importantly, we are of the opinion that a clear differentiation between inter- and intrapatient variability in lung deposition is in order for the current discussion. Differences in inhalation technique and (diseased) airway geometry are relevant especially to interpatient variability. However, to a single patient, having a reproducible inhalation technique (however poor) and a particular airway geometry, interpatient variability does not matter. Because for this patient the delicate balance between therapeutic and adverse effects, once achieved, will be shifted only by a change in delivered dose from the mouthpiece of the inhalation device. Such a change in the delivered dose may be an increase or a decrease and with our *in vitro* experiments we have irrefutably shown that this may very well result from switching between (antistatic) VHCs. Hence, although the use of antistatic VHCs is advisable, switching between them should be discouraged when no change in drug delivery is desired.

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