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Commentary

Comment on: Inhaled antimicrobial therapy—Barriers to effective treatment, by J.Weers, Adv. Drug Deliv. Rev. (2014), http://dx.doi.org/ 10.1016/j.addr.2014.08.013☆

A.H. de Boer, M. Hoppentocht

Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Ant. Deusinglaan 1, 9713 AV Groningen, the Netherlands

We read the review of Weers: 'Inhaled antimicrobial therapy-Barriers to effective treatment' with great interest as it addresses the question whether infections with difficult to eradicate pathogens can be controlled or treated successfully with existing agents in new ways [1]. The manuscript gives a good review of the regulatory, economic and drug delivery barriers to overcome and discusses the strong and weak points of the various systems currently available or in development.

Regrettably, the manuscript contains a peculiar and highly arguable discussion about the strategy of using single dose disposable dry powder inhalers (DPIs). In a comparison between the Twincer™ and the TOBI® Podhaler™, both designed to deliver high dose antibiotics to the respiratory tract, it is claimed that the order of magnitude for lung doses of inhaled aminoglycosides is 100 mg. It is computed that achieving a 100 mg lung dose, as claimed for tobramycin from the TOBI® Podhaler™, would require inhalation of the contents of approximately 40 Twincer™ devices. This computation is based on approximately 20% lung delivery from the Twincer (2.5 mg) from a 12.5 mg dose of colistimethate sodium.

We consider this discussion incorrect and misleading for a number of reasons. First of all, reference is made to the efficiency of the Twincer™ in a proof of principle study (in cystic fibrosis patients) with colistimethate sodium. Different drugs, in different formulations, may behave rather differently and therefore, lung doses of tobramycin from the Twincer™ cannot be anticipated from a colistimethate study. Secondly, lung deposition data for colistimethate sodium from the Twincer™ have not yet been published. Most likely, Weers has made his computation based on the information given that the Twincer™ colistimethate sodium DPI showed 140% bioavailability based on delivered dose and 270% based on label claim (weighed dose) relative to nebulised colistin (mean of 205% improvement) [2]. In this manuscript of Westerman et al. 10% lung deposition efficiency for nebulised tobramycin was also mentioned [2]. Combination of this information would yield an estimated average lung deposition efficiency of 20.5% but this is an incorrect interpretation with different drugs, nebulisers and doses (delivered versus metered) involved. Thirdly, the colistimethate sodium dose given in the proof of principle study with the Twincer™ was 2 × 12.5 (=25) mg of colistimethate sodium instead of 12.5 mg [2]. Although this was not explained by Westerman et al., the 25 mg dose was split in two equal portions because of unknown safety and tolerability aspects of inhaled dry powder colistimethate sodium. However, in a previous in vitro study it was mentioned that further optimisation was expected to increase the dose to at least 50 mg [3]. More recently it could be shown that the delivered fine particle fraction (FPF) for colistimethate sodium from the Twincer™ is almost independent of the dose weight up to 50 mg indeed [4]. With increasing dose weight, inhaler losses are reduced and this increases the FPF effectively delivered. Inhaler losses of less than 5% were measured for this high dose weight and in combination with FPFs < 5 μm of an average of 80% of the delivered dose, this yields very high dose fractions available for lung deposition, even after correction for losses in the oropharynx.

The computation of Weers is misleading also because lung doses of 100 mg tobramycin cannot be obtained with the marketed TOBI® Podhaler™. Newhouse et al. reported whole lung doses from the Podhaler™ of an average of 34.3% (expressed as percent of total radioactivity) for a 25 mg dose of the tobramycin Pulmosphere™ formulation (TOBI®) [5]. For a TOBI® dose, comprising 4 capsules with 28 mg tobramycin each (112 mg), this results in a lung dose of only (0.343 × 112) 38.4 mg. Therefore, it has to be assumed that Weers referred to the target delivered dose of 102 mg mentioned for the Podhaler™ (at 60 L/min, inhaled volume of 2 L) in the 'Highlights of Prescribing Information' brochure for the TOBI® Podhaler™ [6]. This is 91% of the label claim (112 mg) which is an overestimation compared to the mean 78.3% (87.7 mg) emitted dose reported by Newhouse et al. Besides, the emitted dose has to be corrected for oropharyngeal deposition (43.6%, expressed as percent of total radioactivity, at 72 L/min in the same study of Newhouse et al.) [5]. This leaves a whole lung dose for tobramycin from the Podhaler™ of approximately 40 mg, based on a delivered dose of 88 mg (from four capsules with 28 mg active ingredient each).

Considering that the Twincer™ can deliver 50 mg doses of pure colistimethate sodium with FPFs < 5 μm of approximately 75% of the label claim, a delivered fine particle dose of at least 37.5 mg may be expected of which more than 20 mg (>53%) will be available for lung

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E-mail address: a.h.de.boer@rug.nl (A.H. de Boer).

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deposition at the relatively low flow rate though this inhaler (4 kPa corresponds with 54 L/min). In the comparison of Weers, it would therefore require only 2 Twincer™ devices per dose instead of 40 to achieve the same lung dose for tobramycin, providing that this aminoglycoside can be delivered equally efficient as colistimethate sodium. In contrast with the TOBI® Podhaler™ each of the two blisters can be administered in one single inhalation manoeuvre.

Meanwhile, a manuscript entitled 'The Cyclops for pulmonary delivery of aminoglycosides; a new member of the Twincer™ family' has been published [7] in which we show that in an improved Twincer™ concept the dispersion of pure spray dried tobramycin (base) can indeed be as efficient as that of colistimethate sodium. In fact, with a reduced air flow rate of only 35 L/min at 4 kPa, we may expect further reduction of the losses in the oropharynx and thus, a higher fraction of the dose being available for lung deposition. This puts the strategy with disposable inhalers for tobramycin in a completely different perspective as outlined by Weers.

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