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Notes

Simulated 'in-use' and 'mis-use' aspects of the delivery of terbutaline sulphate from Bricanyl Turbohaler™ dry powder inhalers

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Abstract

Using three different environmental conditions, patient 'use' of Bricanyl Turbohalers™ has been simulated over a 9 week period during which approx. 90% of the nominal number of doses were discharged. Qualitative assessment indicated dose metering efficiency remained within 15% of initial estimates. Drug dose obtained by drawing air at 60 l min^{-1} through the devices also remained constant, whereas at 28 l min^{-1} the emission was reduced to half the initial value obtained over the use period. A fall in fine particle fraction (0.4–5.8 μm) from 20 to 7% over use at 30°C/72% RH and to zero over use at 5°C was observed. Patient 'mis-use' involving incorrect loading orientation showed a small reduction in dose emission from a mean of 414 μg to 382 μg. Exhaling into the Turbohaler™ perturbed the fine particle fraction for the three subsequent shots although dose emission was restored after one shot.

Keywords: Terbutaline sulfate; Bricanyl Turbohaler™; Dry powder inhaler

The Turbohaler™ is the only multi-dose reservoir type dry powder inhaler (DPI) device to have substantial regulatory approval. We have previously described the intrinsic drug delivery characteristics of commercial batches of Bricanyl Turbohalers™ (Meakin et al., 1993, 1995). This work has now been extended to simulate its use under various environmental conditions and to examine some effects of patient non-compliance with package insert instructions (Duncan et al., 1990; Brown et al., 1992; Engel et al., 1992).

Drug delivery was determined at through-DPI flow rates of 28.3 l min^{-1} (Andersen Sampler) or 60 l min^{-1} (TSI, Apparatus A, BP 1993, App. XVIIC). Bricanyl Turbohalers™ (200×500 μg doses) were drawn from commercial lot K and gave unperturbed values for mean emitted dose and (with the exception of device K48, Table 1), mean fine particle fractions at 60 l min^{-1} within the range previously reported for lot K devices ($\pm$SD) of 387 ± 58 μg and 55 ± 7% (Meakin et al., 1995).

In order to simulate use devices were held at 30 ± 1.5°C/72 ± 3% RH, similar to international zone IV kinetic conditions (CPMP Guidelines),

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5 ± 1.5°C/uncontrolled RH, mimicking wintry conditions and ambient (21.5°C, range 13–30°C; RH, 63% range 39–84%) for 2–9 calendar weeks with caps secured. Following the recommended dose regimen, four times per working day devices were exposed to the test environment for 2 min by removing the cap and a shot then discharged to waste at 60 l min^{-1}. The Turbohaler™ metering system allocates drug into six dosing holes (Wetterlin, 1988); the device was loaded with the mouthpiece removed and loading efficiency assessed on a three-point scale per dosing hole (full = 2, part full = 1, empty = 0, maximum = 12). Discharge efficacy was scored empty = 2, part full = 1, full = 0. Single dose emission ($n = 5$) was determined at time zero and after 10, 21 and 40 days use simulation using the TSI; 180 shots were fired from each DPI tested (10 per condition). In a second study at 30°C/72% RH and 5°C/uncontrolled RH, emitted dose and fine particle fraction was followed over 9 calendar weeks with the Andersen Sampler. At time zero and intervals of 5–6, 10–11, 19–21 and 38–40 working days, a five shot cumulative sequence from each of five devices was collected.

Dosing hole scores were summed daily for each device, expressed as a percent of the maximum score of 48 and the mean dose metering efficiency rating (DMER) for the given set of devices calculated. In general, the five data sets shown in Fig. 1 imply that discharge from the dosing holes remains reasonably consistent and is slightly more efficient than loading. Baseline DMER was obtained by summing scores for shot 1 (which was unperturbed), for the 40 devices involved in the use-simulation study, giving values of 90% for loading and 95% for discharge. These are commensurate with the mean emitted dose plus mouthpiece recovery of 89% nominal previously reported for this batch of Turbohalers™ (Meakin et al., 1995). The data at 5°C suggest some loss of loading efficacy over time although the DMER remains within 15% baseline. At 30°C/72% RH, set 5 devices showed a clear downward trend although loading score again held within 15% of baseline. The result for ambient storage conditions showed an anomalous deterioration in DMER for both loading and discharge followed by recovery between days 20 and 30 of use which was not readily attributable to differences in observer or change in the laboratory environment. DMER data for 5°C and 30°C/72% RH (all determined at 60 l min^{-1}) do not predict the dramatic reduction in dose emission at 28.3 l min^{-1} which occurs in-use under these conditions.

Fig. 2 shows the effect of cumulative exposure to the various conditions on mean emitted dose per DPI. At 60 l min^{-1} the emitted dose remains consistent over the exposure time periods studied, with all values lying within the range of unperturbed device means for this batch (Meakin et al., 1995). In contrast at 28.3 l min^{-1}, the mean emitted dose is halved after 10–20 days at 5°C and 39 days at 30°C/72% RH.

The effect of the simulated in-use protocols on fine particle fraction was followed using the Andersen Sampler to allow estimation of mass median aerodynamic diameter (MMAD) of the particle cloud collected within the impactor (0.4–10 μm), together with fine particle fraction (0.4–5.8 μm, Andersen Stages 2–7 + after filter). Fig. 3 shows the latter remained constant at approx. 20% emitted dose for at least 10 days 'usage' at 30°C/72% RH but then fell to approx. 7% of emitted dose. At 5°C, reduction in fine particle fraction was exponential, approaching zero (4/5 devices) at 39 days and was accompanied by a 60% loss in total emission (Fig. 2 and 3). This devastating effect is probably due to the condensation of ambient moisture on the device surfaces which occurred when devices were removed from their 5°C storage environment for testing. It is clear that Turbohaler™ should not be held at low temperatures.

Zero time MMADs for the 10 devices were similar, ranging from 3.9 to 4.6 μm, mean 4.5 ± 0.2 μm; this did not change during use at 30°C/72% RH (5.5, 10.5, 20, 39 days; 4.3 ± 0.4, 4.2 ± 0.2, 4.3 ± 0.1, 4.2 ± 0.4 μm: $n = 5$). By 20 days use at 5°C, so little drug was deposited on the sampler plates that meaningful estimation of MMAD was impossible although at 5.5 and 10.5 days MMADs had remained unchanged at 4.4 ± 0.1 and 4.2 ± 0.2 μm, respectively. These findings would suggest that presentation of multi-stage

Table 1
Emitted dose and respirable fraction delivered from Bricanyl Turbohalers before and after exhaling into devices (air flow rate 60 l min^{-1} through the device)

	TBH code										
	K48 [a,d]	K49 [a,d]	K50 [a,d]	K51 [a,d]	K52 [a,d]	K53 [a,e]	K54 [b]	K55 [b]	K56 [b]	K57 [b]	K58 [b]
Shot no.	Emitted dose (μg)										
1–5: Mean (±SD)	395 (±43)	434 (±28)	386 (±42)	387 (±82)	393 (±42)	371 (±38)	434 (±46)	360 (±35)	390 (±19)	374 (±49)	369 (±73)
Range	331–442	404–479	321–422	260–472	358–461	329–426	380–498	320–402	377–422	318–430	273–458
Exhalation	After loading shot 6					Before loading shot 6					
6	29	89	nil	40	67	205	94	4	71	nil	54
7	396	475	396	368	376	455	nil	343	465	403	325
8	474	405	416	446	396	455	473	390	413	489	388
9	480	434	436	351	355	501	466	427	437	413	386
10	369	446	439	475	366	485	427	416	446	466	423
11	394	438	421	340	349	510					
8→: Mean (±SD)	429 (±56)	431 (±18)	428 (±11)	403 (±68)	367 (±21)	488 (±24)	452 (±22)	411 (±19)	432 (±17)	456 (±39)	399 (±21)
$t_{pre/post}$ [e]	1.03	0.18	1.92	0.31	1.12	5.33 [f]	0.62	2.28	3.13 [f]	2.42	0.68
Shot no.	Fine particle fraction (%)										
1–5: Mean (±SD)	25 (±8)	51 (±6)	58 (±10)	60 (±6)	50 (±7)	45 (±4)	55 (±6)	60 (±5)	59 (±2)	54 (±4)	55 (±3)
Range	18–38	44–56	48–70	53–69	45–60	39–49	48–64	53–66	56–61	49–59	51–60
Exhalation	After loading shot 6					Before loading shot 6					
6	nil	4	nil	27	nil	19	6	nil	13	nil	nil
7	26	33	57	62	49	21	nil	57	44	41	62
8	30	51	49	54	53	23	45	55	47	53	59
9	25	35	59	56	57	41	59	48	56	55	57
10	33	52	61	54	48	40	55	51	52	49	53
11	20	42	56	58	61	41					
8→: Mean (±SD)	27 (±6)	45 (±8)	56 (±5)	56 (±2)	55 (±6)	41 (±1)	53 (±7)	51 (±4)	52 (±5)	52 (±3)	56 (±3)
$t_{pre/post}$ [e]	0.47	1.32	0.28	1.40	1.09	1.28	0.41	2.62	2.89	0.57	0.56

[a] Shots 6–8 collected immediately after exhaling.
[b] Shots 6–10 collected immediately after exhaling.
[c] Shots 9–11 collected 4 h after exhaling.
[d] Shots 9–11 collected approx. 15 min after exhaling.
[e] $t_{pre/post}$ 1–5 vs 8–11.
[f] Significant $p < 0.05$.

impactor data in terms of MMAD and its geometric standard deviation (here 1.5–2.0), without recourse to a fine particle fraction statement could be unhelpful, at least in consideration of delivery efficacy from dry powder systems where, as in this study, very large proportions (46–97%) of the emitted dose are trapped in the pre-separator 'stage' of the impactor. The independence of MMAD from fine particle dose/fraction values suggests, that with Turbohaler™ the air turbulence primarily dislodges singlet particle units from the drug aggregate surface rather than multiplet particles with large unit aggregation numbers. If this were the norm for all DPI drug-aggregate or drug-carrier systems, then it is arguable that simple impingers like the TSI but re-designed to exhibit a lower size cut off than 6.4 μm could be used to advantage in DPI stability testing programmes.

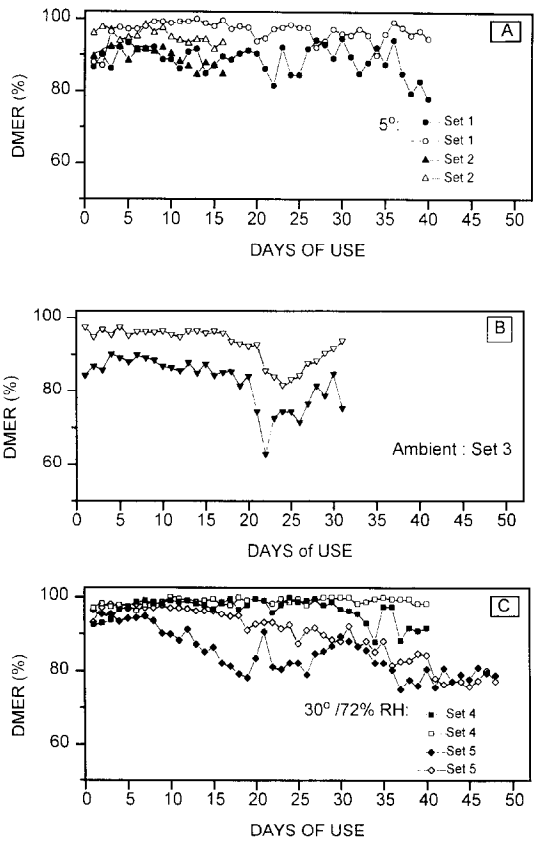

Fig. 1. Dose metering efficiency rating (DMER) score for Bricanyl Turbohalers™ during 'in-use' simulation. (A) Wintry conditions (5°C); (B) ambient conditions; (C) zone IV conditions (30°C/72% RH). Baseline scores prior to test (first shot, 40 devices); dose loading, 90%; dose discharge, 95%: set 1, $n = 5$ (●,○); set 2, $n = 10$ (▲,△); set 3, $n = 10$ (▼,▽); set 4, $n = 5$ (■,□); set 5, $n = 10$ (◆,◇). Closed symbols, dose loading; open symbols, dose discharge. Ordinate, DMER (%); abscissa, days of use.

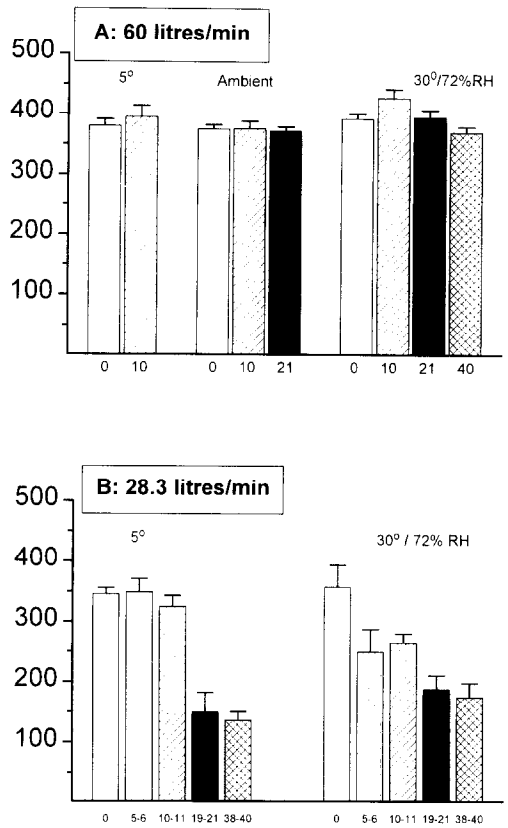

Fig. 2. Effect of in-use simulation on drug dose emitted from Bricanyl Turbohalers™ (bars are standard errors). (A) Air flow rate 60 l min^{-1} ($n = 10$); (B) air flow rate 28.3 l min^{-1} ($n = 5$). Ordinate, emitted dose (μg); abscissa, days of simulated use.

Patients may fail to follow instructions to hold the Turbohaler™ vertically when loading the dose or may exhale into the device (Brown et al., 1992). To investigate the probable worst case of the former, 2 × 5 single shot sequences were collected into the TSI from five DPIs following either vertical (V) or horizontal (H) loading. Incorrect orientation reduced emitted dose by about 8%; mean single shot values were V = 414 ± 54

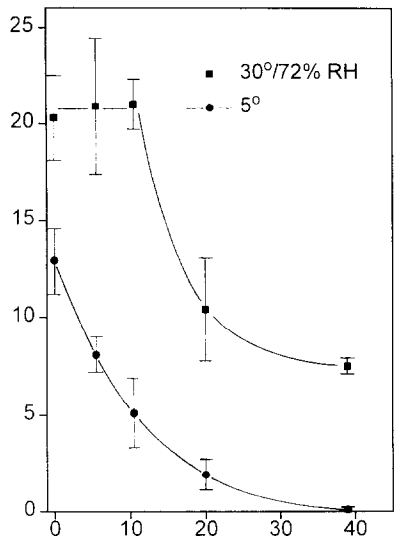

Fig. 3. Effect of in-use simulation on fine particle fraction delivery from Bricanyl Turbohalers™. Air flow rate, 28.3 l min^{-1}. (bars are standard errors). Ordinate, fine particle fraction; abscissa, days of simulated use.

μg and H = 382 ± 51 μg. Although statistically significant this difference is relatively small and probably accounts for the non-dependent clinical findings of Brown et al. (1992).

Patients do breathe into the device, despite the package insert instruction (Brown et al., 1992). This will displace drug from the dosing holes and drug feed plate; the moisture could also influence particle aggregation-deaggregation and thus fine particle fraction (Plomp et al., 1987). This was investigated by obtaining individual shot TSI data before and after a single exhalation into the DPI, pre- or post-loading shot 6. A fresh set of DPIs was used for each experimental mode to ensure comparability of treatment.

Table 1 shows that drug delivery from the shot immediately after exhalation into the device was both poor and erratic in either mode with emitted dose varying from 0 to 40% nominal; fine particle dose was negligible ranging from zero for 6/11 devices to a maximum of 38 μg (mean 6 ± 11 μg). However, with the exception of device K54, emitted dose values had recovered for shot 7 to lie within the general range found for initial shots from this batch of devices. *t*-test comparison of baseline emitted dose (shots 1–5) against values for shots 8 et seq. was significant only for devices K53 and K56, the former being particularly so with a 30% increase over baseline. Exhalation resulted in visible condensation on the inhalation channels resulting in drug material from shot 7 adhering to the damp walls. With device K53 only, shots 9–11 were sampled 4 h after exhalation. It is considered possible that desiccant action over this period reduced the wall adhesion forces thus allowing material originating from shot 7 to be drawn into the particle clouds generated by later shots.

It is apparent from Table 1 that perturbation of fine particle fraction usually extends to two shots post-exhalation, one more than for the emitted dose and is similar whether exhalation precedes or occurs after dose loading. Attention has been previously drawn to the low fine particle fraction value generated by device K48 (Meakin et al., 1995). Because Turbohaler™ contains pure drug, successful dose emission is not discernable by the typical 'taste' of drug-lactose carrier systems. Therefore, advice to patients to inspect the dosing holes in case of uncertainty (Astra, 1991) would not alleviate the problem of dose respirability resulting from this mode of mis-use.

The results from these simulated mis-use studies clearly confirm the importance of product package insert warnings on mis-use; such warnings should be re-inforced by verbal counselling of patients without which non-compliance becomes more problematical. The results overall serve to highlight in-use problems facing the use of dry powder reservoir DPI systems.

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