

Calibration of aerosol output from the Mefar dosimeter: implications for epidemiological studies

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ABSTRACT: Standardized methods for the measurement of airway responsiveness may use the Mefar MB3 inhalation dosimeter to generate standard doses of methacholine aerosol. The manufacturer provides calibrated output data for every nebulizer, so that a standard output may be achieved by varying nebulization time. This output is, however, measured by weight loss (WL), which may over-estimate true aerosol output (AO) because of concomitant evaporation.

We have used a chemical (fluoride) tracer method to measure AO directly from two batches of Mefar nebulizers (batch 1 $n=5$, batch 2 $n=10$) and compared results with manufacturer's quoted WL. Mean AO from batch 1 was $10.56 \text{ mg}\cdot\text{s}^{-1}$ (range $9.50\text{--}11.63$, $\text{SD}=0.92 \text{ mg}\cdot\text{s}^{-1}$), and mean AO from batch 2 was $5.66 \text{ mg}\cdot\text{s}^{-1}$ (range $4.92\text{--}6.58$, $\text{SD}=0.57 \text{ mg}\cdot\text{s}^{-1}$), implying that AO varied little within, but substantially between, the two nebulizer batches. Manufacturer's quoted WL does not reflect this near two fold difference: mean WL batch 1 $=14.0 \text{ mg}\cdot\text{s}^{-1}$ (range $13\text{--}15 \text{ mg}\cdot\text{s}^{-1}$); mean WL batch 2 $=11.1 \text{ mg}\cdot\text{s}^{-1}$ (range $11\text{--}12 \text{ mg}\cdot\text{s}^{-1}$). The median aerosol fractions (AO/WL) for batches 1 and 2 were 76% (range 65–83%) and 50% (range 43–60%), respectively. Similar results were obtained with our own measurement of weight loss. This implies that if the median nebulizers of batches 1 and 2 were calibrated (as recommended) by the manufacturer's WL to deliver a presumed $100 \mu\text{g}$ methacholine dose, the actual doses delivered would be $76 \mu\text{g}$ and $50 \mu\text{g}$, the range for all 15 nebulizers being 43–83 μg .

We recommend that mean AO is measured for each nebulizer batch (or, where the batch source is not known, each dosimeter), and that measurements of airway responsiveness in multicentre studies are corrected accordingly.

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Success of multi-centre, cross-sectional studies examining the prevalence of asthma will depend in part on the degree of standardization achieved in equipment and methodology among the participating investigators. An important diagnostic tool is the measurement of airway responsiveness which is increasingly performed using the Mefar MB3 inhalation dosimeter. Doubling incremental doses of the bronchoconstricting drug methacholine are sequentially delivered as aerosol, over the possible range 3–4,000 μg , to each test subject. Each delivery is followed by measurements of ventilatory function. The test is completed when the fall in the forced expiratory volume in one second (FEV_1) exceeds 20% or the maximum dose in the sequence has been given without producing this positive outcome. For positive tests, airway responsiveness is quantified by the provocative dose of methacholine (μg) estimated to cause a 20% fall in FEV_1 (PD_{20}) [1]. The greater the degree of asthmatic activity, the smaller is the PD_{20} .

In order to standardize PD_{20} measurements, it is desirable that participating investigators use the same standardized protocols and the same nebulizer equipment. The commercially produced Mefar MB3 dosimeter has been chosen for the latter role (Mefar s.r.l., Bovezzo, Italy). It uses an electrical pump to compress air within a small internal air tank. According to the manufacturer, this produces an initial driving pressure of 1.75 bar (25.4 psi), which is used to activate one of a series of Mefar jet nebulizers. The resulting airflow rates within the nebulizers vary between 9–11 $\text{l}\cdot\text{min}^{-1}$. Although aerosol size has been reported to vary between different Mefar nebulizers, the majority (>80%) of the aerosol droplets released under these conditions are respirable, *i.e.* $< 5 \mu\text{m}$ in mass median diameter [2]. Nebulizer output may be varied through an adjustable timing mechanism by increments of 0.1 s. Each nebulizer is supplied by the manufacturer with a calibration chart, which relates nebulization time to nebulizer output as measured by

total weight loss. Thus, a nebulizer with an output rate of $5.0 \text{ mg}\cdot\text{s}^{-1}$ according to the chart can be calibrated to produce a desired output of, e.g. 10 mg of solution using an activation time of 2 s.

However, measurement of the weight loss of a nebulizer following activation does not truly reflect its output of aerosolized solute, because weight lost through jet nebulization is known to contain two distinct components: aerosol (the reservoir drug solution suspended as respirable particles) and water vapour (which contains no drug solute) [3–6]. Of these, only aerosol output is of clinical relevance. Calibration based on weight loss will necessarily over-estimate the true dose of delivered drug solute (e.g. methacholine) [4].

In this investigation we, therefore, used a chemical tracer method to measure true aerosol output from the Mefar dosimeter directly, using nebulizers from two production batches of Mefar jet nebulizers. We compared the results with: 1) weight loss data derived from the manufacturer's calibration charts; and 2) weight loss measured by ourselves. Because nebulization causes temperature change which is known to affect vapour loss, we also investigated the effect of reservoir temperature on weight loss and on aerosol output.

Methods

Nebulizer output from the Mefar dosimeter was examined from each of 15 Mefar jet nebulizers purchased separately in two batches. Nebulizers nos 1–5 (batch 1) had been supplied with a new Mefar dosimeter, and nebulizers 6–15 (batch 2) had been purchased approximately 6 months later.

Measurement of aerosol output

Aerosol output (AO) from each nebulizer was assessed using a fluoride tracer method [4]. Five millilitres of a 1% NaF solution was added to the nebulizer reservoir. The nebulizer was then activated through the Mefar dosimeter for 1 s. During activation of the nebulizer, ambient air was drawn at $15 \text{ l}\cdot\text{min}^{-1}$ through a fitted T-piece over the nebulizer by means of a vacuum pump. This entrained and impacted aerosol on to a 25 mm Whatman glass fibre (GF/A) filter held within a metal cassette, positioned 5 cm from the nebulizer head. After collection, filters were removed and placed in 25 ml Universal bottles. Fluoride residues were subsequently dissolved in an appropriate buffer and quantified electrochemically as described previously [4]. The quantity of fluoride measured is directly related to the total volume of aerosol released from the nebulizer. For each nebulizer in batch 1, aerosol output from each of 12 activations was collected. For batch 2 nebulizers, a total of 8 activations was used for each nebulizer.

Measurement of weight loss

Two separate estimates of weight loss (WL) were used. One data set was derived from the manufacturer's calibration charts accompanying each nebulizer. These defined the weight loss to the nearest mg after 0.5, 1 and 1.5 s activation. For the purposes of this study, only the weight loss at 1 s was used.

We obtained the second set of weight loss measurements as follows. Each nebulizer was filled with 5 ml 0.9% saline, which had equilibrated to room temperature ($20\text{--}22^\circ\text{C}$). The nebulizer (plus solution) was weighed on an analytical balance ($\pm 0.01 \text{ mg}$) before five activations of 1 s duration. Each activation was separated by a 5 s pause to allow the compressed air tank within the dosimeter to refill fully. Upon completion of the fifth activation, the nebulizer was reweighed. Weight loss per second was calculated as the total weight lost divided by the activation time (5 s). Measurement of weight loss was repeated in triplicate for each of the 15 nebulizers.

Effect of reservoir temperature on weight loss and aerosol output

The effect of reservoir temperature on weight loss and aerosol output was assessed in a single Mefar nebulizer (nebulizer no.1, batch 1). A prewarmed (30°C) 5 ml aliquot of 1% NaF was allowed to equilibrate to ambient room temperature ($20\text{--}22^\circ\text{C}$) over an approximately 5 min period. During this period, the temperature of the reservoir solution was monitored using a detachable thermocouple ($\pm 0.1^\circ\text{C}$). At periodic intervals between 0.2 to 2 min, the reservoir temperature was recorded and the Mefar dosimeter activated for 1 s. For each activation, aerosol output and weight loss were measured as described above. Measurements of WL and AO were made similarly whilst a precooled (5°C) solution was allowed to equilibrate to room temperature.

Results

The measurements of mean aerosol output (AO) from each nebulizer are presented in table 1. There was a clear difference in the magnitude of aerosol output between the two batches examined. Batch 1 nebulizers had an overall mean aerosol output of $10.56 \text{ mg}\cdot\text{s}^{-1}$, whereas mean aerosol output from batch 2 nebulizers was $5.66 \text{ mg}\cdot\text{s}^{-1}$; about half that of batch 1. Within each batch, the variation in aerosol output between nebulizers was relatively small, standard deviations of 0.92 and $0.57 \text{ mg}\cdot\text{s}^{-1}$ respectively.

Table 1 also presents the weight loss data for each nebulizer. A much smaller difference in output between the two nebulizer batches was suggested by the manufacturer's calibration data, the average weight loss being $14.0 \text{ mg}\cdot\text{s}^{-1}$ (range $13\text{--}15 \text{ mg}\cdot\text{s}^{-1}$) for batch 1 and $11.1 \text{ mg}\cdot\text{s}^{-1}$ (range $11\text{--}12 \text{ mg}\cdot\text{s}^{-1}$) for batch 2.

Table 1. — Aerosol output and weight loss characteristics of 15 Mefar jet nebulizers

Nebulizer no.	Mean AO		WL-1		WL-2	
	mg·s ⁻¹	SD	Mefar data mg·s ⁻¹	our data mg·s ⁻¹	SD	
Batch 1						
1	11.28	0.35	14	13.50	1.18	
2	9.50	0.43	13	14.28	0.38	
3	11.63	0.18	14	13.08	0.68	
4	10.59	0.20	14	11.57	0.66	
5	9.79	1.26	15	13.57	0.24	
Mean	10.56		14.0	13.21		
SD	0.92			1.14		
Batch 2						
6	6.58	0.18	11	10.16	0.12	
7	5.31	0.22	11	9.66	0.11	
8	5.15	0.20	12	9.36	0.36	
9	6.37	0.29	11	9.99	0.41	
10	5.55	0.14	11	7.28	0.09	
11	5.93	0.36	11	9.12	0.23	
12	5.56	0.27	11	8.58	0.43	
13	5.65	0.15	11	9.19	0.17	
14	4.92	0.22	11	8.33	0.37	
15	5.58	0.54	11	9.00	0.24	
Mean	5.66		11.1	9.07		
SD	0.57			0.85		

AO: aerosol output; WL: weight loss.

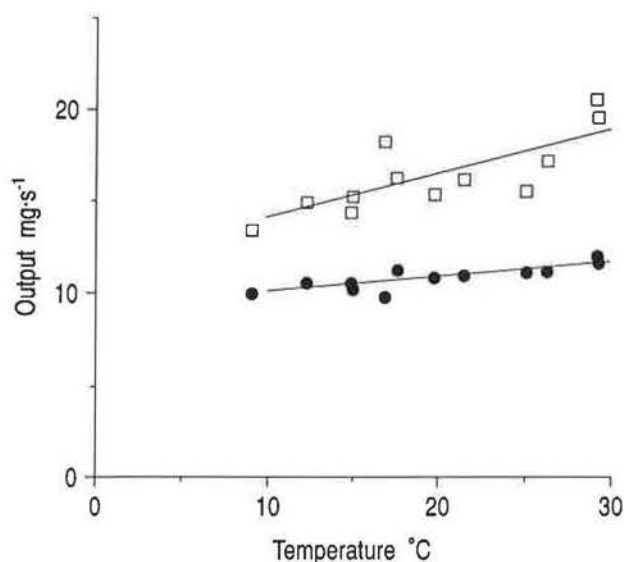


Fig. 1. — The effect of nebulizer reservoir temperature on nebulizer output. Simultaneous measurements of weight loss and aerosol output were made at reservoir temperatures between 10° and 30°C from a Mefar jet nebulizer activated for 1 s. Temperature (°C) affected WL strongly ($WL=11.52+0.247\text{temperature}$) and AO weakly ($AO=0.16+0.082\text{ temperature}$). □: weight loss (WL); ●: aerosol output (AO).

The aerosol fraction (AO/WL) for batch 1 nebulizers consequently ranged from 65–83% (median 76%) compared with a range of 43–60% for batch 2 (median 50%). Our own weight loss data at 20–22°C were of similar order, 13.21 mg·s⁻¹ (range 11.57–14.28 mg·s⁻¹) for batch 1 and 9.07 mg·s⁻¹ (range 7.28–10.16 mg·s⁻¹) for batch 2.

The relationship between reservoir solution temperature and nebulizer output is shown in figure 1. Over the operating range 10–30°C, the increase in both WL and AO was approximately linear. Temperature (°C) affected WL ($WL=11.52+0.247\text{ temperature}$; $F_{1,9}=10.8$; $p=0.009$) more strongly than AO ($AO=9.16+0.082\text{ temperature}$; $F_{1,9}=16$; $p=0.003$), resulting in increases of 35% and 16% for WL and AO, respectively.

Discussion

It has previously been reported that weight loss during activation of certain jet nebulizers considerably over-estimates drug aerosol output due to concomitant evaporation of its solvent (water) [3–6]. We have now confirmed that this is also true for the Mefar jet nebulizer. In addition, we have found distinct differences in aerosol output between different production batches of Mefar nebulizers, differences which are much less evident from weight loss estimates of output. This is of concern, since this nebulizer is being used in a multicentre cross-sectional study of asthma prevalence and risk factors within the European Community (EC). If the 15 nebulizers tested in this work were calibrated from the manufacturer's weight loss data and randomly used within the EC study, to quantify airway responsiveness, individual doses of administered methacholine aerosol would range from as little as 43% (nebulizer no. 8) to 83% (nebulizer no. 3) of the doses intended by the test protocol. This is likely to greatly affect the accuracy of PD₂₀ measurements.

However, our data suggest that the degree of variation of inaccuracy of drug aerosol output is likely to be much less within a particular batch of nebulizers and, hopefully, within any particular study centre, assuming all its nebulizers were supplied from a single production batch. This allows the possibility of using correction factors based on the mean aerosol output for the relevant nebulizer batch (if this is known). Without the use of a correction factor, there will be not only a diminished accuracy in PD₂₀ measurement (which will seriously impair the power to detect risk factors for asthma) but a confounding influence by batch type when results are eventually compared between centres.

The observed relationship between reservoir temperature and weight loss is a consequence of compressed air becoming fully saturated with water vapour as it passes through the nebulizer. The higher the temperature, the greater the water content in the saturated air. By contrast, increasing temperature exerted relatively little effect on AO. Thus, if nebulizers are calibrated

by AO (but not WL) little loss of accuracy in the measurement of airway responsiveness will result from subsequent variations in operating temperature of a few degrees. These conclusions are in agreement with earlier work [4]. The temperature dependence of WL (and AO/WL), however, does imply a loss of precision if measurements are recorded without knowledge of the operating temperature of the nebulizer reservoir. Reservoir temperature may be well below room temperature if the nebulizer solution has been refrigerated or the nebulizer successively activated (cooling effect caused by evaporation) - and room temperature may vary appreciably during the course of a calendar year. Without knowledge of the operating temperature, WL measurements must be relatively imprecise and can not be converted to accurate values of AO.

We recommend that correction factors (derived from measurements of AO) are established for each centre participating in the EC study. If the batch source of each nebulizer is known, it would be practical to obtain an accurate measure of the mean rate of true aerosol output from random samples of nebulizers from each production batch. Little variation in AO is to be expected between nebulizers within each batch, and so this mean value could be used by all centres using the particular nebulizer batch. Existing data would identify the mean period of activation used for all nebulizers supplied with the dosimeter, and this would allow the true dose of methacholine delivered to be calculated; dose (mg) = [mean AO (mg·s⁻¹) × mean activation period (s)]. A correction factor could then be obtained by comparing the true dose with the dose assumed initially. The initial value for PD₂₀ could then be corrected by the same factor.

Where the batch source is not known, it will be necessary to measure AO from every nebulizer (or a sample of nebulizers) from each centre. Provided all nebulizers were purchased together, it is likely that only one batch will be represented within each centre, and so the mean rate of AO could be used in calibration.

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