Low First-Spray Drug Content in Albuterol Metered-Dose Inhalers

Terry D. Cyr,[1,2] Susan J. Graham,[1] K. Y. Robert Li,[1] and Edward G. Lovering[1]

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INTRODUCTION

There are no USP requirements for the amount of drug in single sprays from metered-dose inhalers. Unit spray, as defined in individual monographs, is based on means determined from pooled samples of 4 to 12 sprays (1). In view of this, work was begun to determine the amount of drug in individual, single sprays from albuterol metered-dose inhalers. Shortly after this work began, it became apparent that the drug content of the first spray after a period of rest as short as 1 hr was substantially less than that of subsequent sprays. An investigation of this observation is described in this report.

MATERIALS AND METHODS

Sample Collection

Single sprays from the albuterol inhaler products were collected in a 500-ml separatory funnel mounted horizontally on a retort stand. The stopcock end of the funnel was plugged with a wad of absorbent cotton wet with methanol, and air was drawn through the apparatus at 8 liters/min by a vacuum pump. Immediately prior to sample collection the inside of the funnel and the cotton wad were moistened with methanol. To collect a sample, the canister, with actuator, was shaken for 5 sec, valve down, the funnel stopcock opened for 2 sec, the inhaler valve depressed for 1 sec, and the stopcock closed. The drug collected in the funnel was quantitatively transferred to a 25-ml volumetric flask by rinsing with several portions of methanol. The flask was made up to volume with methanol. The weight of each spray was determined by difference, based on the weight change of the canister.

Sample Analysis

Albuterol samples were analyzed by a liquid chromatographic method developed in this laboratory (2). The concentration of albuterol in the standard solution was reduced to 0.004 mg/ml. The relative standard deviation of five injections of the standard at this concentration was less than 3%.

Equipment

The Varian Star liquid chromatograph consisted of a Model 9010 ternary pump, a Model 9095 autosampler equipped with a 10-μl loop (Valco Instruments Co. Inc.), a Model 9050 variable-wavelength UV-VIS detector, and a Varian Star 9020 Workstation with Revision B software. A Doerr Electric Corporation vacuum pump (Model 0322-V4B-G18DX) was used for sample collection.

Chemicals

HPLC-grade acetonitrile, methanol, *o*-phosphoric acid (85%), and USP Reference Standard albuterol (primary standard) were used. Purified water was prepared using a Sybron Barnstead system.

Test Samples

Albuterol metered-dose inhalers were obtained directly from the manufacturer or purchased in a local pharmacy. They are coded by a capital letter to represent the manufacturer, a number to represent the lot, and after the hyphen, another number to distinguish between individual canisters of the same lot.

Experimental Design

Sample collection intervals and conditions were chosen to approximate patient usage. Recommended dosage for each product is one or two sprays, up to four times a day (3); one package insert states that a dose should last at least 4 hr. Preliminary experiments had shown that the amount of drug in the first spray after a period of quiescence depended on the rest position, the greatest deviation from the label claim being observed when the rest position was with the valve down. In practice, the canister might be stored horizontally, as in a purse, or valve up or down, as in a shirt pocket. Based on these considerations, the following protocol was followed. After firing unneeded sprays to waste, canisters were stored for 3 hr, valve down. Five groups of three individual sprays were collected through the actuator, after shaking, over the total labeled spray content of each canister (all were labeled to contain 200 sprays), beginning at sprays 10, 50, 100, 150, and 198. The time between the first and the second sprays, and the second and the third sprays, in each group of three sprays, was about 2.5 min. The albuterol content of the individual sprays was determined.

RESULTS

Table I gives results obtained on 19 canisters representing eight lots from three manufacturers. For each canister, the mean of the first sprays of the five groups of three (sprays 10, 50, 100, 150, and 198) is given under spray 1. Also given are the relative standard deviation (RSD) and the highest and lowest drug contents of the five individual first sprays. Table I also includes the mean drug content and RSD of the second (sprays 11, 51, 101, 151, and 199) and third sprays (sprays 12, 52, 102, 152, and 200) for each canister. The means of the first, second, and third sprays over all groups and all canisters are depicted by manufacturer in Fig.

[1] Bureau of Drug Research, Health Protection Branch, Tunney's Pasture, Ottawa, Ontario, Canada K1A 0L2.
[2] To whom correspondence should be addressed.

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Table I. Mean Albuterol Content in the First, Second, and Third Sprays (μg)[a]

Canister	Spray 1 (RSD) [range][b]	Spray 2 (RSD)	Spray 3 (RSD)
A1-5	65 (14) [51–76]	86 (6)	86 (11)
A1-6	75 (26) [50–95]	96 (7)	93 (12)
A2-5	71 (19) [61–93]	101 (6)	99 (9)
A2-6	79 (21) [63–109]	97 (12)	103 (27)
B3-2	59 (17) [42–68]	94 (4)	90 (7)
B3-3	65 (12) [55–75]	91 (8)	86 (4)
B3-4	80 (47) [50–146]	90 (10)	92 (11)
B3-5	91 (74) [33–208]	89 (4)	92 (6)
B3-6	60 (25) [35–71]	95 (10)	95 (8)
B4-1	53 (26) [33–71]	92 (5)	88 (5)
B4-2	76 (34) [48–119]	94 (12)	90 (8)
B5-1	112 (50) [64–196]	92 (12)	87 (7)
B5-2	86 (44) [56–150]	90 (7)	88 (8)
C4-1	46 (29) [27–53]	103 (8)	95 (11)
C4-2	36 (38) [28–51]	105 (10)	100 (6)
C5-1	32 (23) [24–43]	122 (5)	106 (6)
C5-2	33 (26) [23–46]	115 (9)	113 (13)
C6-1	31 (33) [23–49]	103 (5)	94 (5)
C6-2	44 (31) [28–65]	104 (7)	102 (10)

[a] The results are the average drug contents in the first, second, and third sprays of five groups of three sprays beginning at sprays 10, 50, 100, 150, and 198.

[b] As an example, for canister A1-5, the drug content in sprays 10, 50, 100, 150, and 198 was 63, 76, 68, 66, and 51 μg, respectively. Thus the mean is 65 μg, the RSD 14%, and the range 51 to 76 μg.

1. The drug content in spray 1 varies erratically (Table I). Usually it contains substantially less drug than the 100 μg claimed on the label. However, some first sprays contain very high levels of drug, for example, spray 198 from canister B3-5 contained 208 μg albuterol, and similarly, sprays 100 and 150, canister B5-1, contained 196 and 141 μg, respectively. The mean drug contents of the second and third sprays are more consistent with the label claim and are less variable, as indicated by the RSD. Drug remaining on the actuator, usually 10 to 15 μg per spray, was not analyzed and is not included in the data reported.

The possibility of using the weight of individual sprays to assess the drug content of individual sprays from metered-dose inhalers was investigated. Representative results are given in Table II. There is no observable difference among the first, second, and third sprays and the RSD are 2% or less. Similar weight change data were obtained for all canisters. There was no evidence of loss of prime, as defined in a recent study (4).

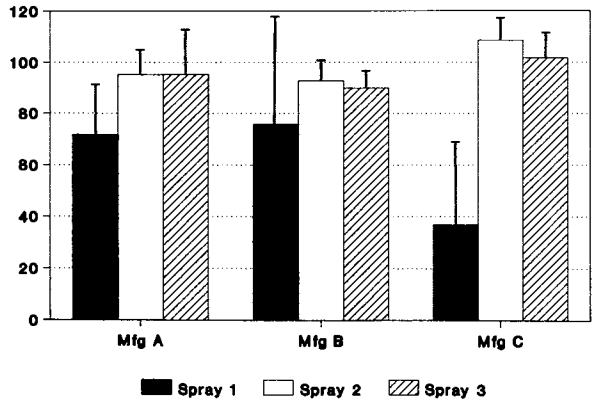

Fig. 1. Grand means of the albuterol content in the first, second, and third sprays, by manufacturer, based on data from all groups of three sprays and all canisters. Relative standard deviations are shown by the error bars.

DISCUSSION

The data were subjected to statistical analysis to establish that the problem of low drug content in the first spray exists. The plan was as follows.

1. Examine each manufacturer (Mfg) independently of the others (spray 1 differs from sprays 2 and 3), noting differences due to lot, canister and spray number, between spray 1 and spray 200.
2. Identify differences between manufacturers.
3. Examine spray 1 outliers in all manufacturers and identify differences between them.

As expected, the drug content in spray 1 was significantly different from that in sprays 2 and 3 ($P < 0.05$ for manufacturer B and $P < 0.01$ for manufacturers A and C). The difference was attributable largely to that between the first spray and the other two, but for manufacturer C, comparison between spray 2 and spray 3 gave a nearly significant result ($P = 0.0545$).

Lot-to-lot variations and differences among canisters from the same lot were not observed to be significant. However, with the small number of lots and cans used in this design, and the relatively high fluctuation in measured drug content, particularly in spray 1, the power for detecting such differences was not high. The difference between manufacturers, which is significant ($P = 0.0178$), is attributable to the difference between Mfg C and the other two ($P < 0.01$).

On an arbitrary categorization of outliers as being less than 50 μg (low) or over 150 μg (high), the number of canisters that gave at least one outlying datum with one of the first sprays from the five groups of three sprays is given in Table III, by manufacturer. One of the canisters from Mfg B gave both a low and a high first-spray value. Analyses of the proportion of canisters with outliers indicate that Mfg C was not significantly different from Mfg B, but Mfg A was significantly different from Mfg B ($P < 0.05$).

Since, for each canister, five groups of three sprays

Table II. Mean Weight of Representative First, Second, and Third Sprays (mg)[a]

Code	Spray 1 (RSD)	Spray 2 (RSD)	Spray 3 (RSD)
A1-5	89.0 (0.6)	88.5 (0.5)	87.8 (1.3)
A2-5	88.8 (0.8)	87.9 (0.9)	87.6 (1.2)
B3-3	83.9 (2.0)	82.5 (1.8)	81.5 (0.9)
B4-2	84.9 (1.5)	84.1 (0.5)	83.7 (0.6)
C4-1	88.1 (2.6)	86.3 (1.7)	86.6 (1.9)
C5-1	91.1 (0.8)	91.3 (1.2)	91.1 (0.6)

[a] Average weights of the first, second, and third sprays from five groups of three sprays beginning at sprays 10, 50, 100, 150, and 198.

Table III. First-Spray Outliers by Canister

Mfg B		Mfg A		Mfg C	
Low	High	Low	High	Low	High
5/9	3/9	0/4	0/4	6/6	0/6

were analyzed, the data were recast in terms of tests with outliers (Table IV). Analyses indicate that Mfg C and Mfg A were significantly different from Mfg B ($P < 0.01$ and $P = 0.05$, respectively).

Although inconsistent first-spray drug content is a problem for all manufacturers, the problem is most apparent in product from Mfg C. Judging from their physical appearance, valves used by manufacturers A and B are the same, but that used by C is different in design.

The data suggest the need for specifications for first-spray drug content in pharmacopeial monographs for metered-dose inhalers. Existing standards for loss of prime do not address this problem, as the data in Table II demonstrate. It would be appropriate to base first-spray drug content requirements on data collected in a manner which approximates patient usage. Thus, for albuterol, a practical and effective test would consist of sampling five sets of three consecutive discharges spread over the total number of doses in the test canister, with a sampling time between sets of at least 3 hr. The results identify the need for better valves and/or formulations for metered-dose inhalers.

Table IV. First-Spray Outliers by Sets of Three Sprays

Mfg B		Mfg A		Mfg C	
Low	High	Low	High	Low	High
6/45	3/45	0/18	0/18	26/30	0/30

The unit spray drug content uniformity test procedure for other drugs should be based on the pattern of patient usage. In no case should it be based on the assay of pooled samples. The albuterol results suggest the first-spray problem may be due to separation of suspended particles from propellant fluid in the valve. If this is the case, there may not be a first-spray effect for solution aerosols and it may be possible to determine the unit spray drug content by weight.

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