

# The output of budesonide from nebulizers

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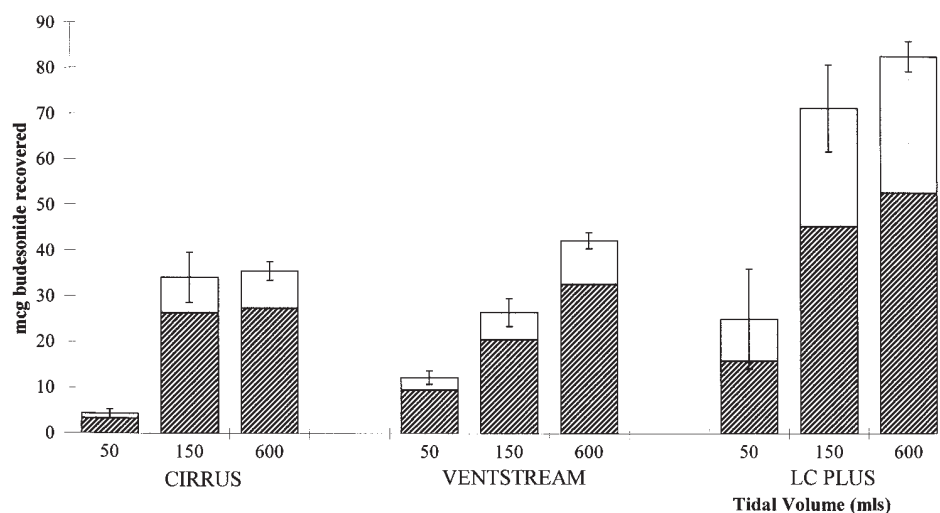


**FIG. 1.** Amount of budesonide recovered from filters placed between nebulizer and sinus flow pump. Dead space of filter housing was 11 mL. Parameters for simulated breathing pattern were (tidal volume, rate) 50 mL, 30 breaths per minute; 150 mL, 20 breaths per minute; and 600 mL, 16 breaths per minute. Inspiratory fraction was 40%. Error bars represent 95% confidence intervals for mean recovery. Amount of drug recovered on filters was multiplied by fraction recovered in particles below 4.3 µm in diameter in multistage liquid impinger to give calculated amount of drug in particles smaller than 4.3 µm (hatched bars), and larger than 4.3 µm (open bars).

Despite recent reports of side effects from inhaled steroid therapy,<sup>1</sup> no information is currently required by regulatory authorities on the dose of steroid actually reaching the patient from different nebulizers. As new, more efficient nebulizer designs are marketed, this information is essential to allow both therapeutic effects and side effects to be evaluated.

We have studied the amount of a steroid suspension, budesonide, available for inhalation from a conventional jet nebulizer and from two newer designs. These "breath enhanced, open vent" nebulizers incorporate a system of valves to increase the gas flow through the nebulizer during inspiration, increasing drug delivery to the patient. Such nebulizers have been shown to double the delivery of a bronchodilator to the lung<sup>2</sup> and have been suggested for use with nebulized steroids.

We measured the output of budesonide from a conventional nebulizer, the Intersurgical Cirrus (Intersurgical Ltd, Wokingham, UK), which has a constant output throughout inspiration and expiration, and two breath-enhanced open-vent nebulizers, the Medicaid Ventstream (Medicaid Ltd, Bognor Regis, UK) and the Pari LC Plus (Pari GmbH, Starnberg, Germany), which have enhanced output during inspiration only. In the laboratory part of our study, each nebulizer was charged with 2 mL (250 µg/mL) of budesonide suspension and operated for 5 minutes while attached to a sinus flow pump driven at different rates and volumes to represent breathing patterns of children. Budesonide was collected onto a filter and assayed with high-performance liquid chromatography. Each nebulizer type was tested 6 times. The particle size of budesonide released from each of the nebulizers was measured separately by using a glass multistage liquid impinger.<sup>3</sup>

In a parallel clinical study we measured the output of budesonide onto filters from different nebulizers when used by patients. Ten children with asthma aged 4 to 14 years used both the Ventstream and LC Plus nebulizers in random order for 5 minutes. The nebulizers contained 2 mL (500 µg) of budesonide nebulizer suspension, and drug that would have been inhaled was collected onto a

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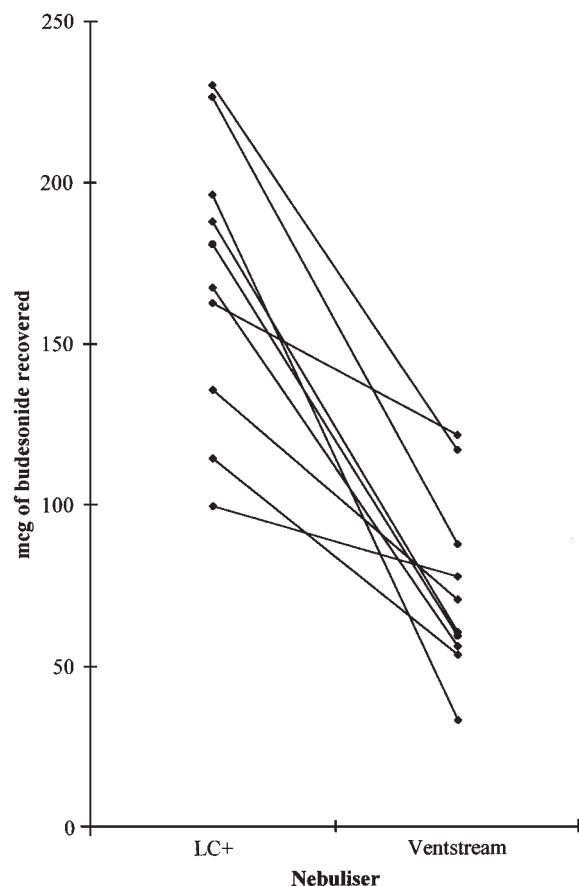


**FIG. 2.** Amount of budesonide (in micrograms) deposited on inspiratory filters when Pari LC Plus or Medicaid Ventstream nebulizers are used by children with asthma. Paired data are joined by lines.

filter placed between the nebulizer and the patient. The study was approved by the Leicestershire Ethical Review Committee, and informed parental consent was obtained.

Our data (Fig. 1) showed dramatic differences in the output of budesonide from the different nebulizers (analysis of variance,  $P < .001$ ) and were different from results predicted from studies in which solution medications were used in adults.<sup>2</sup> Multiple  $t$  tests with

Bonferroni's correction indicated that the LC Plus nebulizer delivered significantly more budesonide than the Cirrus and Ventstream nebulizers at the 150 mL and 600 mL tidal volumes. The Ventstream delivered more than the Cirrus at the 50 mL and 600 mL tidal volumes (all  $P < .05$ ). The in vitro data were supported by the patient study (Fig. 2) in which more drug was recovered when the LC Plus nebulizer was used ( $t$  test,  $P < .001$ ). Budesonide recoveries were higher from the filters used with the patients than from those used with the breathing simulator, possibly because of differences between the patient and machine breathing pattern. The Ventstream nebulizer produced a finer aerosol than the LC Plus (mass median aerodynamic diameter  $3.1 \mu\text{m}$  vs  $4.1 \mu\text{m}$ ), and the lower output of the Ventstream may have resulted from more of the larger particles remaining in the nebulizer compared with the LC Plus nebulizer.

There should be some caution in inferring clinical effect from measurements of drug deposited on filters, as these represent drug delivered to the mouth rather than to the lung. Although delivery to the mouth was higher with the LC Plus nebulizer compared with the Ventstream, deposition of budesonide in the mouth may also be higher with the LC Plus because of its larger particle size. We remain ignorant of the dose of drug that patients are likely to receive from different delivery devices despite the importance placed on the therapeutic ratio of clinical effectiveness to possible side effects. Our results suggest that nebulized delivery of budesonide may vary significantly between devices. This variability should be taken into account when designing clinical studies or treating patients with nebulized budesonide.

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