Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.

Review: Pressurized metered-dose inhalers are as effective as other handheld inhalers for corticosteroid use in asthma

Brocklebank D, Wright J, Cates C, on behalf of the National Health Technology Assessment Inhaler Review Group. **Systematic review of clinical effectiveness of pressurised metered dose inhalers versus other hand held inhaler devices for delivering corticosteroids in asthma.** BMJ. 2001 Oct 20;323:896-900.

QUESTION

In patients with stable asthma, is the standard chlorofluorocarbon-containing pressurized metered-dose inhaler (PMDI) as effective as other handheld inhaler devices for delivering corticosteroids?

DATA SOURCES

Studies published from 1966 to July 1999 were identified by searching the Cochrane Airways Group trials database (derived from MEDLINE, EMBASE/Excerpta Medica, CINAHL; hand searches of 18 relevant journals and proceedings of 3 respiratory societies; and reviews of bibliographies of relevant studies). Pharmaceutical companies that manufacture inhaled asthma drugs were contacted for unpublished studies.

STUDY SELECTION

Studies in any language were selected if they were laboratory, hospital, or community-based randomized controlled trials of children or adults that lasted ≥ 4 weeks and compared a single drug delivered by a standard PMDI (with or without a spacer) with any other handheld inhaler. Trials comparing different doses of the same drug were also included.

DATA EXTRACTION

2 reviewers independently extracted data on study design, patient characteristics, details of the intervention, study duration, outcomes, and quality. Outcomes included lung function (FEV_1), quality-of-life measurements, symptom scores, drugs for additional relief, acute exacerbation, days off work or school, treatment failure, patient compliance, patient preference, adverse effects, bronchial hyperreactivity, and systemic bioavailibility.

MAIN RESULTS

24 articles describing 29 studies met the selection criteria. 14 studies compared PMDIs with dry-powder inhalers (DPIs): PMDIs were less effective than DPIs for improving FEV_1 and morning peak expiratory flow rate and for reducing use of additional relief drugs (Table). However, these differences either disappeared after adjustment for baseline variables or were within clinically equivalent limits. 11 studies compared chlorofluorocarbon PMDI with hydrofluoroalkane (10 studies used beclomethasone, and 1 study used fluticasone). Treatment effects did not differ. 1 study compared breath-actuated PMDI with PMDI but found no differences for any outcomes. 3 studies of children were included, but a meta-analysis of the results could not be done because of study differences. None of the studies of children found any differences in pulmonary function between the devices. However, 1 study found that the Turbohaler group reduced their use of relief drugs by 1 puff per week (95% CI 0.35 to 1.96) more than the PMDI group.

CONCLUSION

In patients with stable asthma, the standard chlorofluorocarbon-containing pressurized metered-dose inhaler is as effective as other handheld inhaler devices for delivering corticosteroids.

Source of funding: NHS Research and Development Health Technology Assessment Programme.

For correspondence: Dr. J. Wright, Bradford Hospitals NHS Trust, Bradford, England, UK. E-mail john.wright@bradfordhospitals.nhs.uk.■

Pressurized metered-dose inhaler vs dry-powder inhaler for delivering corticosteroids in asthma (parallel studies only)*

Outcomes at 4 wks	Number of studies *(n)*	SMD (95% CI)
FEV_1	7 (1404)	–0.14 (–0.25 to –0.03)
Morning peak expiratory flow rate	7 (1389)	–0.14 (–0.25 to –0.04)
Use of additional relief drugs	6 (967)	–0.18 (–0.31 to –0.05)

*SMD = standardized mean difference; minus sign means results favor the dry-powder inhaler. A fixed-effects model was used.

COMMENTARY

PMDIs have been used since the early 1900s to deliver aerosolized β_2-agonists and corticosteroids to the lung. In recent years, environmental concern over chlorofluorocarbon propellants has fueled interest in the development of alternative delivery systems. The reviews by Brocklebank and colleagues and Ram and colleagues found no difference between PMDIs and other handheld delivery systems in patients with stable mild-to-moderate asthma. They concluded that the standard PMDI remains the most cost-effective delivery device.

Both device and patient-specific issues influence the success or failure of a particular delivery system. Patient factors influencing drug delivery and therapeutic success include not only coordination but also breath-holding ability and inspiratory flow rate, both influenced by disease severity. Findings in patients with mild-to-moderate asthma may not be applicable to patients with more severe airway obstruction.

Proper education in the use of the various handheld delivery systems is crucial because substantial rates (between 12% and 90%) of incorrect metered-dose inhaler use have been reported (1). In the investigational setting—the "best-case scenario"—patients receive detailed instructions that are reinforced throughout the study. "Real-world" patients receive varying degrees of instruction, and adherence to correct technique, if not reinforced, often wanes in the long term. Psychosocial factors (cultural beliefs, education, and language skills) may also influence the ability to comprehend and follow instructions.

The available delivery systems each have advantages and disadvantages. PMDIs are portable and convenient, but effectiveness is technique dependent. Furthermore, excessive oropharyngeal deposition may lead to local side effects with inhaled corticosteroids. Spacer devices can improve PMDI efficiency and decrease toxicity by decreasing particle size and increasing the lung-throat deposition ratio, but they are cumbersome to use and vary in the efficiency of drug delivery. Their main advantage is in reducing problems with lack of coordination between actuation and inhalation.

(continued on page 111)

Review: Pressurized metered-dose inhalers are as effective as other handheld inhalers for β_2-agonist bronchodilator use in asthma

Ram FS, Wright J, Brocklebank D, White JE, on behalf of the National Health Technology Assessment Inhaler Review Group. **Systematic review of clinical effectiveness of pressurised metered dose inhalers versus other hand held inhaler devices for delivering β_2 agonist bronchodilators in asthma.** BMJ. 2001. Oct 20;323:901-5.

QUESTION

In patients with stable asthma, is the standard chlorofluorocarbon-containing pressurized metered-dose inhaler (PMDI) as effective as other handheld inhaler devices, including chlorofluorocarbon-free PMDIs, for delivering β_2-agonist bronchodilators?

DATA SOURCES

Studies published from 1966 to December 2000 were identified by searching the Cochrane Airways Group trials database (derived from MEDLINE, EMBASE/Excerpta Medica, CINAHL; hand searches of 20 relevant journals and proceedings of 3 respiratory societies; and review of the bibliographies of included trials). MEDLINE, EMBASE/Excerpta Medica, CINAHL, and 17 online respiratory Web sites were also independently searched, and pharmaceutical companies that manufacture inhaled asthma drugs were contacted for unpublished studies.

STUDY SELECTION

Studies in any language were selected if they were laboratory-, hospital-, or community-based randomized controlled trials of children or adults that compared delivery of β_2-agonist bronchodilators by standard PMDI (with or without a spacer) with any other handheld inhaler. Trials comparing different doses of inhaled drug and those that used challenge testing were also included.

DATA EXTRACTION

2 reviewers independently extracted data on study design, patient characteristics, details of the intervention, study duration, outcomes, and quality. Outcomes included lung function (FEV_1), quality-of-life measurements, symptom scores, drugs for additional relief, steroid requirements, nocturnal awakening, acute exacerbations, days off work or school, treatment failures, patient compliance, patient preferences, adverse effects, bronchial hyperreactivity, and systemic bioavailability.

MAIN RESULTS

89 articles describing 84 studies met the selection criteria. 71 trials involved adults, and 13 involved children. In most trials, patients had mild-to-moderate asthma (baseline FEV_1 > 50% of predicted). Meta-analyses were done using a fixed-effects model. In both adults and children, standard PMDIs did not differ from any of the other 10 handheld inhaler devices (Turbohaler, Diskhaler, hydrofluoroalkane PMDI, Rotahaler, Spiros, Easyhaler, multidose-powder inhaler, Clickhaler, Gentlehaler, and Autohaler) for FEV_1, forced vital capacity, peak expiratory flow rate, area under the curve for FEV_1, blood pressure, symptoms, bronchial hyperreactivity, systemic bioavailability, inhaled steroid requirement, serum potassium level, or use of additional relief brochodilators. However, regular use of the hydrofluoralkane PMDI containing salbutamol was associated with reduced requirement for short courses of oral corticosteroids (relative risk 0.67, 95% CI 0.49 to 0.91).

CONCLUSION

In patients with stable asthma, the standard chlorofluorocarbon-containing pressurized metered-dose inhaler (PMDI) is as effective as other handheld inhalers, including chlorofluorocarbon-free PMDIs, for delivering β_2-agonist bronchodilators.

Source of funding: NHS Research and Development Health Technology Assessment Programme.

For correspondence: Dr. J. Wright, Bradford Hospitals NHS Trust, Bradford, England, UK. E-mail john.wright@bradfordhospitals.nhs.uk.■

COMMENTARY *(continued from page 110)*

The amount of aerosol delivered to the lungs is determined by aerosol particle size, velocity, and inspiratory flow rate. In the hydrofluoroalkane PMDIs, the drug is reformulated as a solution. This approach increases the fine-particle fraction, which results in increased drug delivery to the lung and decreased oropharyngeal deposition. Hydrofluoroalkane PMDIs are portable, convenient, and contain no chlorofluorocarbon propellants.

DPI systems are a portable, propellant-free, breath-actuated alternative to PMDIs that help overcome breath-to-hand coordination difficulties. Many have dose counters that allow patients and physicians to monitor treatment. However, in outpatient settings, delivery that requires loading may be inconvenient and may result in decreased adherence to therapy. The efficiency of drug delivery with DPIs also varies according to a patient's inspiratory flow rate.

With all handheld delivery systems, drug delivery and efficacy are affected by such patient factors as coordination, inspiratory flow rate, and technique. As clinicians, our primary goal is to enhance compliance with therapy for optimal drug delivery while keeping overall costs low. To maximize treatment success, the choice of a delivery system must take into account patient preference, ability, lifestyle, and disease severity. Cost-effectiveness will be maximized with a delivery device that is tailored to a patient's needs and abilities because reduced adherence may result from lack of perceived efficacy.

These 2 reviews provide evidence that in an ideal setting, PMDIs can be as effective as newer technologies developed to overcome pitfalls in patient technique and compliance.

Amy R. Blanchard, MD
Medical College of Georgia
Augusta, Georgia, USA

Joseph A. Golish, MD
Cleveland Clinic Foundation
Cleveland, Ohio, USA

Reference

1. **McFadden ER Jr.** Improper patient techniques with metered dose inhalers: clinical consequences and solutions to misuse. J Allergy Clin Immunol. 1995;96:278-83.

