Budesonide once versus twice-daily administration: meta-analysis
Masoli M, Weatherall M, Holt S, Beasley R

CRD summary
This review compared budesonide given once versus twice daily for the treatment of asthma. The authors concluded that once-daily administration had similar efficacy to twice-daily administration for the treatment of mild to moderate asthma. However, the lack of a validity assessment threatens the reliability of the authors’ conclusion.

Authors’ objectives
To determine the efficacy of budesonide administered once daily compared with twice daily for the treatment of asthma.

Searching
MEDLINE (from 1966 to 2003) and EMBASE (from 1980 to 2003) were searched using the terms reported. There was no language restrictions. The reference lists of relevant articles were examined and the manufacturer was contacted for additional studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of at least 4 weeks' duration were eligible for inclusion. Both double-blind and open-labelled studies were eligible, and both were included in the review.

Specific interventions included in the review
Studies that compared equal doses of budesonide given once or twice daily, delivered using the same device, were eligible for inclusion. The total daily dose of budesonide ranged from 200 to 800 microg/day, and was administered using a Turbuhaler in all studies.

Participants included in the review
Studies of adults and children with asthma were eligible for inclusion. Studies in which the participants were dependent on oral corticosteroids, or were involved in regimens of oral corticosteroid reduction, were excluded. Most of the included studies were in patients with mild to moderate asthma, with baseline forced expiratory volume in 1 second (FEV1) values ranging from greater than 60% to greater than 90% of predicted values. The mean age of the participants ranged from 9 to 48 years.

Outcomes assessed in the review
The primary outcomes of interest were FEV1, morning peak expiratory flow (PEF) and withdrawals due to asthma. The secondary outcomes of interest were evening PEF, symptom score and beta-agonist use. However, symptom scores were not assessed.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the eligibility of studies for inclusion.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.
For continuous outcomes, data were extracted to calculate a mean difference between the comparison groups. For binary outcomes, data were extracted on the occurrence of the outcome of interest from each comparison group to calculate an odds ratio (OR). For the outcome of withdrawals due to asthma, 0.5 was added for studies with ‘zero’ values. The data were collected on an intention-to-treat basis.

**Methods of synthesis**

- **How were the studies combined?**
  The results from the individual studies were combined using a meta-analysis (unspecified method). A pooled standardised mean difference (SMD) with 95% confidence intervals (CIs) was calculated for continuous outcomes, while a pooled OR with 95% CIs was calculated for binary outcomes.

- **How were differences between studies investigated?**
  Statistical tests (unspecified) of homogeneity were performed as part of the meta-analysis. Forest plots allowed a visual examination of differences across the included studies.

**Results of the review**

Ten RCTs (n=1,922) were included in the review. Seven were double-blind and three were open-labelled in design.

**FEV1 (3 RCTs).**

Twice-daily budesonide was associated with a slightly favourable FEV1, although this was not statistically significant (SMD 0.09, 95% CI: -0.09, 0.27). No evidence of statistical heterogeneity was found (data not given).

**Morning PEF (8 RCTs; 9 comparisons).**

Twice-daily budesonide was associated with a slightly favourable PEF, although this was not statistically significant (SMD 0.07, 95% CI: -0.04, 0.17). No evidence of statistical heterogeneity was found (data not given).

**Withdrawals due to asthma (9 RCTs; 10 comparisons).**

No significant difference was found between budesonide once and twice daily on withdrawals due to asthma (OR 1, 95% CI: -0.43, 0.43). No evidence of statistical heterogeneity was found (data not given).

**Secondary outcomes.**

No difference was found between budesonide once and twice daily on evening PEF, or on day or night beta-agonist use (results not given).

**Authors’ conclusions**

In patients with mild to moderate asthma, once-daily budesonide has similar efficacy to a twice-daily regimen at doses of up to 800 microg/day.

**CRD commentary**

The review addressed a clear research question with inclusion criteria that were detailed and appeared appropriate. The search used to identify relevant studies was not extensive, and the possibility of publication bias was not investigated. Methods were used to minimise bias when selecting studies for inclusion. However, no details were given on whether methods were used to minimise reviewer bias and error in the data abstraction process. No quality assessment was undertaken, which makes it difficult to comment on the validity of the results.

Adequate details on each included study were presented. Formal tests for homogeneity were undertaken, and these suggested that the decision to combine the studies was appropriate. However, details of the statistical methods used to combine the studies were limited. For example, in the meta-analysis it was unclear whether steps were taken to avoid
counting the same control group twice when two outcome measures from within a study were pooled as if they were from separate studies. In addition, it might have been useful to have performed separate analyses of double-blind and open-labelled studies, and those of children. In summary, the lack of transparency in part of the review process and no validity assessment threaten the reliability of the authors' conclusion.

**Implications of the review for practice and research**

**Practice:** The authors stated that the incorporation of a once-daily approach is likely to have a positive impact on adherence and optimise therapeutic efficacy.

**Research:** The authors did not state any implications for further research.

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