Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis
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CRD summary
This review concluded that occurrence of glucocorticoid-related adverse events depended largely on the disease in the study population. The overall rate of adverse events was 150 per 100 patient-years. Statistical heterogeneity was not assessed, which made it difficult to assess whether an appropriate approach was used to pool the results. Given these methodological concerns, the conclusions may be not reliable.

Authors’ objectives
To assess the adverse events of low to medium dose oral glucocorticoids in patients with chronic inflammatory diseases.

Searching
MEDLINE, EMBASE and CINAHL were searched for full published studies up to Feb 2008. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) and follow-up studies that evaluated adverse events of low to medium dose oral glucocorticoids were eligible for inclusion. Studies needed to have more than one month follow-up duration and be of adult patients with chronic inflammatory diseases. Eligible chronic inflammatory diseases were rheumatoid arthritis, systemic lupus erythematosus, polymyalgia rheumatica, chronic obstructive pulmonary disease, asthma and inflammatory bowel diseases. Eligible dose of glucocorticoids had to be 30mg or less prednisolone equivalent (except for the first month when a high dose of ≤60mg was allowed in one trial). Studies that included patients who previously used glucocorticoids for more than three months or who used glucocorticoids within three months before study onset were excluded. Only studies that reported dichotomous adverse event outcomes were included.

Most of the included studies were RCTs. Follow-up durations of included studies varied from short (one to six months) to long follow-up (greater than six months). Included patients had different types of chronic inflammatory diseases (rheumatoid arthritis, polymyalgia rheumatica and inflammatory bowel disease). Included patients had either low-dose glucocorticoids (≤7.5mg prednisolone equivalent) or medium-dose glucocorticoids (7.5-30mg prednisolone equivalent).

Two reviewers independently assessed studies for inclusion. Any disagreement was resolved by consensus.

Assessment of study quality
Study quality was assessed using the criteria: standardised adverse event scoring protocol; predefined adverse events; and description of missing data. Maximum study quality score was 3.

Two reviewers independently performed the validity assessment. Any disagreement was resolved by consensus.

Data extraction
Data were extracted on rates of adverse events and number of patient-years to enable the calculation of adverse events per 100 patient-years.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
The studies were combined in a meta-analysis. Pooled adverse events per 100 patient-years, with 95% confidence
intervals (CIs), were calculated. Subgroup analyses were conducted on study quality, types of diseases, different doses of glucocorticoids (low-dose versus medium-dose) and different follow-up durations (short versus long follow-up).

**Results of the review**

Twenty-eight studies (n=2,382) were included in the meta-analyses. Mean study quality was 2.2. Fourteen studies had a short follow-up and fourteen studies had a long follow-up. When all studies were pooled, risk of glucocorticoid-related adverse events was 150 per 100 patient-years (95% CI 132 to 169).

In patients with rheumatoid arthritis (14 studies, n=796), risk of glucocorticoid-related adverse events was 43 per 100 patient-years (95% CI 30 to 55).

In patients with polymyalgia rheumatica (four studies, n=167), risk of glucocorticoid-related adverse events was 80 per 100 patient-years (95% CI 15 to 146).

In patients with inflammatory bowel disease (10 studies, n=1,419), risk of glucocorticoid-related adverse events was 555 per 100 patient-years (95% CI 391 to 718).

The most frequently reported adverse events were psychological and behavioural adverse events (such as minor mood disturbances). Gastrointestinal adverse events (such as dyspepsia and dysphagia) were also commonly reported. Higher rates of adverse events were reported in high-quality studies with a short follow-up, particularly in studies of patients with inflammatory bowel disease. Subgroup analysis of low and medium doses did not show dose dependency for any adverse event.

**Authors’ conclusions**

Occurrence of oral glucocorticoid-related adverse events largely depended on the disease in the study population. The overall rate of adverse events was 150 per 100 patient-years. Adverse events varied from 43 per 100 patient-years in rheumatoid arthritis and 80 per 100 patient-years in polymyalgia rheumatica to 555 per 100 patient-years in inflammatory bowel disease.

**CRD commentary**

The inclusion criteria were clear. Relevant sources were searched. Efforts were made to find published studies, but not unpublished studies and this introduced potential for publication bias. The authors did not state whether language restrictions were applied in the search, which made it difficult to assess the risk of language bias. Steps were taken to minimise bias by having more than one reviewer undertake study selection and validity assessment; it was unclear whether the process of data extraction was performed in duplicate. Given that most of the included studies were RCTs, the criteria used for quality assessment in these studies appeared to be limited and use of summary scores can obscure useful information for quality assessment. Statistical heterogeneity was not assessed, which made it difficult to assess whether an appropriate approach was used to pool the results. There was a lack of details in methods and reporting. Given the limitations outlined above, the authors’ conclusions may be not reliable.

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

**Practice:** The authors stated that adherence to recently published recommendations on the use of long-term glucocorticoid in rheumatic diseases would most likely help reduce the occurrence of glucocorticoid-related adverse events in any chronic inflammatory disease.

**Research:** The authors stated that more rigorous research was required to evaluate safety of long-term glucocorticoid use in chronic inflammatory diseases. Future studies with patient involvement were required to develop a core set of adverse event assessment tools for glucocorticoid-related adverse events.

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