Sildenafil for pulmonary hypertension: need for evidence generation

Shafiq N, Reddy S, Pandhi P, Manoj R, Talwar K K, Malhotra S

CRD summary
This review concluded that sildenafil produced significant improvement in functional and clinical parameters of pulmonary hypertension compared to placebo, but showed no differences compared to bosentan. This review was carried out robustly, but the small number of primary trials make the results difficult to interpret. The authors’ conclusions reflect the evidence presented, but appear strong given the limited data available.

Authors' objectives
To compare the efficacy and adverse effects of sildenafil compared to placebo, prostacyclin analogues and bosentan for the management of pulmonary hypertension.

Searching
Two reviewers independently identified trials through a computerised bibliographic search of MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials until June 2007. Search terms were reported. References of retrieved articles were reviewed, additional searches of key journals were undertaken and conference abstracts were sought.

Study selection
Randomised, double-blind placebo-controlled trials of sildenafil in patients with primary or secondary pulmonary hypertension were eligible for inclusion. Trials were required to compare sildenafil with placebo, prostacyclin analogues or endothelin receptor antagonists in head-to-head comparisons. Trials in which sildenafil was given as an add-on therapy were also included. Trials with a follow up time of less than one week were excluded.

Outcomes included change from baseline in the following: six minutes walk test; mean pulmonary artery pressure; mean right atrial pressure; Borg dyspnea score; mean cardiac index; pulmonary vascular resistance. Improvement in functional class and clinical worsening were also investigated.

Follow up time in the included trials ranged from two to 16 weeks.

Assessment of study quality
The quality of each trial was assessed using the following criteria; randomisation, baseline comparability, blinding, withdrawals and intention to treat analysis.

The authors did not state how the validity assessment was performed.

Data extraction
Numbers of events in each group were used to derive odds ratios and 95% confidence intervals for dichotomous outcomes. Continuous variables were reported as means (standard deviations). If data were not reported in the required format, study authors were contacted.

Two reviewers independently extracted data from each study and data were compiled by a third reviewer.

Methods of synthesis
For dichotomous outcomes, the pooled odds ratios and corresponding 95% confidence intervals were calculated; for continuous outcomes, weighted mean differences and corresponding 95% confidence intervals were calculated. Where significant heterogeneity was present, a random-effects model was used; otherwise a fixed-effect model was used. Statistical heterogeneity was assessed using a chi-squared test. Publication bias was assessed using funnel plots.
Results of the review

Five randomised controlled trials (RCTs) were included in the review (n=190 participants). Three RCTs were cross-over design, while the other two were parallel group trials.

Sildenafil versus placebo: Patients in the sildenafil group showed significantly greater improvements in the six minutes walk test (weighted mean difference 68.90 metres, 95% confidence interval (CI): 31.14 to 106.65; three RCTs); mean pulmonary artery pressure (weighted mean difference -13.04 mmHg, 95% CI: -25.94 to -0.15; three RCTs); mean cardiac index (weighted mean difference 0.39 l/min/m², 95% CI: 0.24 to 0.54; one RCT); mean Borg dyspnea score (weighted mean difference -1.23, 95% CI: -1.36 to -1.10; two RCTs); mean pulmonary vascular resistance (weighted mean difference -171 dyn.sec.cm⁻⁵, 95% CI: -300 to -30.90; one RCT) and improvement in functional class (odd ratio 6.48, 95% CI: 2.74 to 15.33; two RCTs). There were no significant differences between groups for mean right atrial pressure or number of patients with clinical worsening.

In the comparison of sildenafil with placebo for improvements in the six minutes walk test, publication bias could not be ruled out and 11 studies would be required to reverse the direction of study results according to Rosenthal's File Drawer Method.

Sildenafil versus bosentan: There were no significant differences between groups for the six minutes walk test, mean cardiac index or mean Borg dyspnea score.

Authors' conclusions

Sildenafil was shown to produce a significant improvement in functional and clinical parameters of pulmonary hypertension compared to placebo, but showed no difference when compared to bosentan. Adequately powered randomised controlled trials of sildenafil compared to placebo and to other treatments approved for use in pulmonary hypertension are needed.

CRD commentary

This review addressed a clear question supported by appropriate inclusion criteria. Relevant databases were searched, although it was unclear whether language restrictions were applied. Efforts were made to retrieve unpublished data. Suitable methods were used throughout the review process to minimise the risks of reviewer error and bias. Although validity was assessed, the table describing the details of assessment was missing a key, which would no doubt add significant value.

Heterogeneity was reported in the forest plots, but was not discussed. Significant heterogeneity for the main outcomes may mean the the decision to pool studies in meta-analyses was not appropriate.

In terms of methodology, this review was carried out robustly, but the small number of primary trials and small trial sizes make the results difficult to interpret. The authors’ conclusions are based on the evidence presented, but appear a little strong given the limited data available for evaluation.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that adequately powered trials, using active controls and longer duration follow up with comparisons of various end-points, adverse effect profiles and haemodynamic studies for various treatment options, are needed. The authors also stated that trials assessing effects of combination regimens on different outcomes are required.

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