Ximelagatran/melagatran against conventional anticoagulation: a meta-analysis based on 22,639 patients

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CRD summary
The authors concluded that ximelagatran/melagatran had comparable efficacy to conventional anti-coagulant therapy in the rate of major adverse events and major bleeds, but that it carried a prohibitive risk of hepatic toxicity. The manufacturer has withdrawn ximelagatran/melagatran. This was a generally well-conducted review, but the unknown quality of included trials means that the reliability of the authors' conclusions is unclear.

Authors' objectives
To evaluate the risks and benefits of ximelagatran/melagatran compared to conventional anticoagulant therapy.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials were searched until March 2006, with no language restrictions. Search terms were reported. Relevant reviews and quoted papers were also handsearched for further studies.

Study selection
Randomised controlled trials (RCT) comparing ximelagatran/melagatran with conventional anticoagulant therapy were eligible for inclusion. Included trials were required to measure the incidence of adverse events, major bleeds or the incidence of alanine aminotransferase elevation more than three times above the upper normal limit. Only trials using intention-to-treat analyses were eligible for inclusion.

Included trials were of ximelagatran in doses ranging from 24 mg twice daily to 60 mg twice daily compared to warfarin, enoxaparin or dalteparin in varying doses. In four trials, melagatran in doses ranging from 2 mg to 4 mg twice daily, was administered to the intervention group prior to surgery. Patients in the included trials were either undergoing total knee or hip replacement and were: receiving treatment, from six to 12 days, as prophylaxis for deep vein thrombosis; receiving treatment for deep vein thrombosis, ranging from two weeks to six months; or were receiving treatment, lasting between three and 20 months, for the prevention of thromboembolic stroke after non-valvular atrial fibrillation. The definitions of the endpoints were homogeneous across all trials.

Two reviewers independently selected the studies for review.

Assessment of study quality
The methodological quality of included trials was assessed using the Cochrane Collaboration Criteria, which assesses the risk of selection, performance, attrition and adjudication bias, as either low (A), moderate (B) or high (C). Allocation concealment was judged as either adequate (A), unclear (B), inadequate (C) or not used (D).

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

Data extraction
The number of major adverse events, major bleeds or alanine aminotransferase elevation more than three times the upper limit were extracted for each group and used to calculate odds ratios (OR) with 95% confidence intervals (CI). Where different doses of ximelagatran/melagatran were used in a trial, only data on the highest dose were extracted.

Two reviewers independently extracted the data for the review.

Methods of synthesis
Pooled odd ratios with 95% CI were calculated using random-effect and fixed-effects models. Subgroup analyses were conducted for the different clinical settings and for use of more than three months. Heterogeneity was assessed using the Cochrane Q test and quantified using the I² statistic. Sensitivity analyses were conducted by removing one trial at a time commencing with the lowest quality score. Publication bias was assessed using funnel plots and Egger's test.

**Results of the review**

Thirteen RCTs were included for review (n=22,639). There was some evidence of publication bias for major adverse events but not for major bleeds or hepatic toxicity.

**Major bleeds**: When all studies were combined, there was no significant difference between ximelagatran/melagatran and conventional anticoagulant therapy in the rate of major bleeds, but there was evidence of significant heterogeneity for these outcomes. Ximelagatran/melagatran was associated with significantly lower risk of major bleeds in the treatment of deep vein thrombosis (OR 0.51, 95% CI: 0.27 to 0.98; two RCTs) and in the prevention of atrial fibrillation-related stroke (OR 0.71, 95% CI: 0.55 to 0.92; three RCTs) compared to conventional anticoagulant therapy.

**Major adverse events**: Ximelagatran/melagatran was not associated with any significant difference in the risk of major adverse events compared to conventional anticoagulant therapy. There was no evidence of significant statistical heterogeneity for these outcomes.

**Hepatic toxicity**: When all studies were combined, ximelagatran/melagatran was not associated with a significantly increased risk of hepatic toxicity, but there was evidence of significant statistical heterogeneity. When used in the treatment of deep vein thrombosis (OR 5.16, 95% CI: 3.38 to 7.89; two RCTs) and in the prevention of atrial fibrillation-related stroke (OR 8.31, 95% CI: 5.65 to 12.23; three RCTs), ximelagatran/melagatran was associated with a significantly increased risk of hepatic toxicity. Use of ximelagatran/melagatran for three months or more was associated with a significantly increased risk of hepatic toxicity (OR 6.73, 95% CI: 5.01 to 9.05). There was no evidence of significant statistical heterogeneity for these outcomes.

Sensitivity analyses did not significantly alter the results.

**Authors' conclusions**

Although ximelagatran/melagatran had comparable efficacy to conventional anticoagulant therapy, in terms of major adverse events and major bleeds, it carried a prohibitive risk of hepatic toxicity. The manufacturer has withdrawn ximelagatran/melagatran.

**CRD commentary**

The review addressed a clear question. Inclusion criteria were defined for study design, intervention and outcomes but not for participants. Three relevant databases were searched for papers in any language, minimising the risk of language bias. However, a search did not appear to have been made for unpublished data. Publication bias was assessed and no significant risk of bias was found. Appropriate steps were taken in the data extraction and study selection processes to minimise the risk of reviewer error and bias. The authors reported that a validity assessment was performed, but, the results of the validity assessment were not reported. Consequently, it was not possible to ascertain the quality of included trials and the reliability of the data used. The pooling of results was appropriate. Statistical heterogeneity was assessed and suitable subgroup analyses were carried out. This is a generally well-conducted review but, given the unclear quality of the included trials, the reliability of the authors' conclusions is unclear.

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

**Practice**: The authors stated that there is a need for more safe and effective alternatives to conventional anticoagulant therapy.

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

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