Authors' objectives
To review the evidence that propofol increases the risk of bradycardia, asystole and death from bradycardic events.

Searching
MEDLINE (1984 to December 1995) was searched with the terms 'propofol', 'adverse effects', 'bradycardia', 'asystole' and 'death'. The search had no restriction on the language of publication. Reference lists from published reports and review articles on propofol and the authors' in-house bibliography on propofol were handsearched. Thirty-eight national centres participating in the WHO drug monitoring scheme were contacted by letter, and the manufacturer of propofol was also contacted to provide relevant information.

Study selection
Study designs of evaluations included in the review
All reports of bradycardic events during propofol anaesthesia were included.

Specific interventions included in the review
Propofol, either with or without prophylactic anticholinergics. Additional drugs used in the treatment arms of controlled studies include alfentanil, suxamethonium, fentanyl, vecuronium, pancuronium, atracurium, dextromoramide, d-tubocurarine, nitrous oxide and morphine. Drugs used in the control arm included different dose of propofol, thiopentone, suxamethonium, etomidate, halothane, isoflurane, nitrous oxide, thiopental, enflurane, thianylal, desflurane, barbiturates, midazolam, methoexitone and etomidate.

Participants included in the review
Adults or children undergoing surgery with propofol anaesthesia were included.

Outcomes assessed in the review
The lowering of heart rate, oculocardiac reflex and first or second degree AV blocks, as defined in the original reports, were considered as potential major harm. Asystole, cardiac arrest, absence of QRS complexes, electromechanical dissociation, and third degree AV block, as described in the original report, were classified as major harm. Death after any bradycardic event was classified as disaster.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
No validity assessment was undertaken, although the results were presented according to study design. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
Information on type of reports, patient characteristics, surgery, propofol regimen, concomitant drugs, anaesthetics in controls, definition, number and treatment of bradycardic events and outcome was taken from each report. Dichotomous data on bradycardic complications in propofol and control groups were extracted from controlled trials. The method by which data extraction was undertaken is not reported.

Methods of synthesis
How were the studies combined?
Quantitative and qualitative analyses of data with different strengths of evidence were performed.

The L’Abbe plot of bradycardic event rates with propofol compared with those of controls was used as a graphical means of exploring the risk of propofol and the homogeneity of the data set. Odds ratio (OR) estimates were calculated with 95% confidence intervals (CI) using a fixed-effect model. Number-needed-to-harm (NNH) and 95% CI were calculated in the same way as number-needed-to-treat (see Other Publications of Related interest no.1 and no.2). Odds ratio and NNH were calculated separately for individual reports and by combining single propofol or control arms. It was assumed that propofol without nitrous oxide had the same risk of bradycardia as propofol with nitrous oxide; these arms were combined for analysis. The 'rule of three' was used in large series to estimate the implications of zero numerators (see Other Publications of Related Interest no.3).

How were differences between studies investigated?
The results were discussed according to the strength of evidence. The homogeneity of the data set was explored using L’Abbe plot.

Results of the review
Sixty-five published reports (randomised controlled trials, non-randomised controlled trials, review of clinical studies, case series, case reports) and unpublished data from 12 drug monitoring centres were included.

In controlled clinical trials, propofol significantly increased the risk of bradycardia compared with other anaesthetics (number-needed-to-harm 11.3; 95% CI 7.7, 21). In paediatric strabismus surgery the number-needed-to-harm was 4.1 (95% CI 3, 6.7). The risk of bradycardia-related death during propofol anaesthesia was estimated to be 1.4 in 100,000.

Authors' conclusions
Propofol carries a finite risk for bradycardia with potential for major harm.

CRD commentary
A well-documented review incorporating both published and unpublished reports. Further information regarding the assessment of the relevance and validity of included studies could have enhanced the review.

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