Propofol and bradycardia: causation, frequency and severity

M. R. TRAMÈR, R. A. MOORE AND H. J. McQUAY

Summary
As part of the development of a model for the study of adverse events, we have investigated the risk of bradycardia with propofol. A systematic search for any type of report, published and unpublished, was made to review the evidence that propofol increases the risk of bradycardia, asystole and death from bradycardic events. Quantitative and qualitative analyses of data with different strengths of evidence were performed. Sixty-five published and 187 spontaneous reports to drug monitoring centres described with different strength of evidence a biological basis for propofol-induced bradycardia, 1444 bradycardias, 86 asystoles and 24 deaths. In controlled clinical trials, propofol significantly increased the risk of bradycardia compared with other anaesthetics (number-needed-to-harm 11.3 (95% confidence interval 7.7–21)). In paediatric strabismus surgery the number-needed-to-harm was 4.1 (3–6.7). One of 660 patients undergoing propofol anaesthesia had an asystole. The risk of bradycardia-related death during propofol anaesthesia was estimated to be 1.4 in 100 000. Data from the phase IV study of propofol did not agree with data from controlled studies. Propofol carries a finite risk for bradycardia with potential for major harm. Study of adverse events should be made with systematically searched data and, in contrast with study of efficacy, not restricted to randomized, controlled trials. (Br. J. Anaesth. 1997; 78: 642–651).

Key words

Propofol has been available since the early 1980s. It has gained widespread popularity because it is thought to have specific advantages compared with other anaesthetics, such as favourable kinetics, smooth induction characteristics, a recovery profile with a low incidence of adverse effects and non-hypnotic therapeutic properties. It was suggested that the excellent haemodynamic state was of particular use in paediatric patients.

During propofol anaesthesia a low heart rate may occur despite decreased arterial pressure. Absence of reflex tachycardia may be considered beneficial because it is not associated with an increase in myocardial oxygen consumption.

However, observational reports on profound bradycardia and asystole with the use of propofol in healthy adult patients, despite prophylactic anticholinergics, have been published repeatedly. Severe, refractory and fatal bradycardias in children in the ICU have been observed with long-term propofol sedation. The question has been raised of when, if ever, case reports become good enough evidence on which to base practice.

There is now strong evidence from a meta-analysis of all relevant randomized controlled trials (RCT) that propofol anaesthesia, compared with other anaesthetics, increases substantially the incidence of the oculocardiac reflex (OCR) in paediatric strabismus surgery despite the use of prophylactic anticholinergics. The OCR, a trigemino-vagal reflex, may induce severe bradycardia and asystole. Fatal outcome has been described.

These data from both observational reports and RCT suggest with different strengths of evidence, and hence different powers of causation and estimation of frequency, a clinically relevant relationship between propofol and bradycardia or asystole.

Methods
A systematic search was made for any type of report (any or no study architecture) of bradycardic events during propofol anaesthesia. MEDLINE (KnowledgeServer) was searched (1984 to December 95), not restricted to the English language, with the terms propofol, adverse effects (sub-heading), bradycardia, asystole and death, and combinations of these words. Reference lists from published reports and review articles on propofol, and the authors’ in-house bibliography on propofol were hand searched. Thirty-eight national centres participating in the WHO drug monitoring scheme were contacted by letter and asked for detailed information on spontaneous reports (yellow card scheme) on propofol and bradycardic events. The manufacturer of propofol was contacted to provide relevant data. Abstracts from scientific meetings, reports of propofol sedation in the ICU, reports of death not definitely related to bradycardic events (cardiovascular collapse without obvious relationship to bradycardia)

MARTIN TRAMER, MD, ANDREW MOORE, DSC, HENRY MCQUAY, DM, Pain Research, Nuffield Department of Anaesthetics, The Churchill, Oxford Radcliffe Hospital, Headington, Oxford OX3 7JL. Accepted for publication: February 18, 1997.

Correspondence to M. T.
or asystole, for instance 17) or of arrhythmias other than bradycardia 18 were not considered.

All types of reports were sought which supported a biological basis for propofol-induced bradycardia, reported absence or presence of bradycardic events with propofol anaesthesia or studied additional information on propofol-related bradycardia (prevention, therapy, risk factors, dose–response, pharmacological interactions).

Based on observational reports 9, 19 there was a prior hypothesis that there is a potential continuum with propofol-induced bradycardia. This implies that bradycardia, which is usually perceived as minor harm, is actually potential major harm because of the possibility of its progressing to actual major harm, asystole and possibly to a disaster. Therefore, lowering of heart rate, OCR, 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 III degree AV block, as described in the original reports, were classified as major harm. Death after any bradycardic event was classified as disaster. Need for treatment (anticholinergics, catecholamines, external chest massage), comitant symptoms (convulsion, for instance), and spontaneous resolution, duration, recurrence or grading of events (severe bradycardia, for instance) did not alter this classification.

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 L’Abbé plot 20 of bradycardic event rates with propofol compared with bradycardic event rates with controls was used as a graphical means of exploring the risk of propofol and the homogeneity of the data set. A scatter predominantly lying between the line of equality and the propofol axis suggested an increased risk with propofol and homogeneity. Odds ratio (OR) estimates were calculated with 95% confidence intervals (CI) using a fixed effect model. 21 If any cell of a sample was zero, then 0.5 was added to all cell sizes for that sample. 22 A lower limit of the 95% CI of the OR > 1 indicated a statistically significant increased risk with propofol. Number-needed-to-harm (NNH) and 95% CI were calculated in the same way as number-needed-to-treat. 23, 24 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” 25 was used in large series to estimate the implication of zero numerators. Calculations were performed using Excel v 5.0 on a Power Macintosh 7100/66.

Results

Sixty-five published reports (1985–1995) were considered. Types of reports were randomized, controlled trials, controlled trials without randomization, a review of clinical studies, several case series and published case reports. Additional unpublished data came from 12 drug monitoring centres. Information from the manufacturer of propofol did not add to these data. No cohort or case-control study was found.

Biological Basis

Uncontrolled experiments in dogs with pharmacological autonomic denervation led to the conclusion that propofol may have a direct effect on sinus activity. 26 In an RCT in dogs, propofol decreased arterial pressure but failed to induce reflex tachycardia. 27 However, in rabbits 28 propofol increased heart rate, and in sheep 29 both heart rate and arterial pressure were increased with propofol. These findings were considered to be unexpected, contrasting with the response in human 28 and eventually were considered species-specific. 29

Haemodynamic effects of propofol induction and maintenance were tested in several small clinical series 6, 30–32 and one RCT. 33 Heart rate was stable or even decreased despite a significant decrease in arterial pressure. 6, 30, 33 Both baroreflex resetting 31 and a particular autonomic milieu predisposing to a parasympathetic response to noxious stimulation during propofol anaesthesia 32 were suggested as principal mechanisms of this relative bradycardia.

Bradycardic Events with Propofol in Controlled Trials

Seventeen relevant controlled trials were randomized. 34–50 In two further trials no method of randomization was mentioned. 51, 52 Data from these 19 controlled clinical trials were pooled for analysis. In more than 1200 patients, propofol was compared with other regimens for induction or maintenance of anaesthesia, or both, and bradycardic events were reported as dichotomous outcomes (table 1). Children and adults, mainly ASA I or II, were studied in a variety of surgical settings. In five of 11 paediatric RCT the lower age limit was 6 months to 2 yr, 40, 48, 50, 53, 54 and in another three, age limits were not mentioned. 44, 47, 55 In one RCT, 37 five patients had heart disease and were classified as ASA III. Prophylactic anticholinergics were given in 11 studies. The event rate scatter suggested an increased risk of bradycardia with propofol and a homogeneous pattern in these trials (fig. 1). Across all controlled trials the risk with propofol, compared with other anaesthetics, was significantly increased; the combined NNH for one bradycardic episode was approximately 7 (table 1).

In an RCT a bradycardia ended in an asystole in a young woman undergoing a minor gynaecological procedure with propofol. 36 The patient was resuscitated successfully after external chest massage for 30 s and i.v. atropine. Her postoperative electrocardiogram showed a pre-excitation syndrome. The NNH point estimate for an asystole with propofol compared with another anaesthetic across all controlled studies was 660 (table 1).
Table 1  
Bradyocardic events with propofol. Data from 17 randomized controlled trials and two controlled trials without randomization* (laps=laparoscopy, Paed=paediatric, AC=anticholinergics, n=beats per minute, HR=heart rate, N/A=not available, OCR=oculocardiac reflex, P=propofol, thio=thiopentone, metho=methohexitone)  

<table>
<thead>
<tr>
<th>Ref</th>
<th>Surgery</th>
<th>Prophylactic AC</th>
<th>Other drugs</th>
<th>Bradyocardic event (definition of bradycardia)</th>
<th>Comparison</th>
<th>Event rate with propofol</th>
<th>Event rate with control</th>
<th>Odds ratio (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[34]</td>
<td>Adults different</td>
<td>No</td>
<td>Allentanil</td>
<td>Bradycardia during induction (30/s)</td>
<td>P/allentanil vs thio/suxamethonium</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
<td>0/3</td>
</tr>
<tr>
<td>[35]</td>
<td>Micro ENT</td>
<td>Yes</td>
<td>Allentanil, suxamethonium</td>
<td>Bradycardia during surgery (&lt;50/s)</td>
<td>P vs etomidate</td>
<td>1/15</td>
<td>0/15</td>
<td>1/15</td>
<td>0/15</td>
</tr>
<tr>
<td>[36]</td>
<td>Minor gynaecology</td>
<td>No</td>
<td>None</td>
<td>Bradycardia during surgery (1 asystole)</td>
<td>P vs thio/halothane</td>
<td>2/21</td>
<td>0/22</td>
<td>2/21</td>
<td>0/22</td>
</tr>
<tr>
<td>[37]</td>
<td>Abdominal</td>
<td>Yes</td>
<td>None</td>
<td>Bradycardia during surgery (&lt;50/s) for &gt;5 min</td>
<td>P vs thio/halothane</td>
<td>0/39</td>
<td>0/38</td>
<td>0/39</td>
<td>0/38</td>
</tr>
<tr>
<td>[39]</td>
<td>Paed strabismus</td>
<td>Yes</td>
<td>Allentanil, vecuronium</td>
<td>OCR during surgery (HR &lt;15%)</td>
<td>P vs thio/halothane</td>
<td>11/60</td>
<td>0/30</td>
<td>11/60</td>
<td>0/30</td>
</tr>
<tr>
<td>[40]</td>
<td>Paed strabismus</td>
<td>Yes</td>
<td>Fentanyl, vecuronium</td>
<td>OCR during surgery (HR &lt;20%)</td>
<td>P vs thio/halothane</td>
<td>15/22</td>
<td>4/22</td>
<td>15/22</td>
<td>4/22</td>
</tr>
<tr>
<td>[41]</td>
<td>ENT</td>
<td>Yes</td>
<td>Fentanyl, pancuronium</td>
<td>Bradycardia during surgery (definition N/A)</td>
<td>P vs thio/isoflurane</td>
<td>0/25</td>
<td>3/25</td>
<td>0/25</td>
<td>3/25</td>
</tr>
<tr>
<td>[42]</td>
<td>Adults different</td>
<td>No</td>
<td>Fentanyl, atracurium</td>
<td>Bradycardia during surgery (&lt;45/s): atropine</td>
<td>P vs thio/isoflurane</td>
<td>1/25</td>
<td>0/25</td>
<td>1/25</td>
<td>0/25</td>
</tr>
<tr>
<td>[43]</td>
<td>Gynaecology laps</td>
<td>Yes</td>
<td>Allentanil, suxamethonium</td>
<td>Bradycardia during surgery (50/s): 1x atropine (HR 37/s)</td>
<td>P vs propofol</td>
<td>3/15</td>
<td>0/15</td>
<td>3/15</td>
<td>0/15</td>
</tr>
<tr>
<td>[45]</td>
<td>Gynaecology laps</td>
<td>Yes</td>
<td>Sufentanil, vecuronium</td>
<td>Bradycardia during surgery (definition N/A)</td>
<td>P vs thiama/fluurane</td>
<td>8/30</td>
<td>9/30</td>
<td>8/30</td>
<td>9/30</td>
</tr>
<tr>
<td>[46]</td>
<td>Orthopaedic</td>
<td>No</td>
<td>Fentanyl, d-tubocurarine</td>
<td>Complete heart block (HR 30/s) requiring atropine at induction</td>
<td>P vs desflurane</td>
<td>0/23</td>
<td>1/46</td>
<td>0/23</td>
<td>1/46</td>
</tr>
<tr>
<td>[47]</td>
<td>Paed ENT</td>
<td>Yes</td>
<td>Suxamethonium</td>
<td>Bradycardia (definition N/A) or junctional rhythm at induction</td>
<td>P vs barbiturates</td>
<td>14/75</td>
<td>2/48</td>
<td>14/75</td>
<td>2/48</td>
</tr>
<tr>
<td>[48]</td>
<td>Paed strabismus</td>
<td>Yes</td>
<td>Allentanil, vecuronium</td>
<td>OCR during surgery (HR &lt;20%)</td>
<td>P vs thio/isoflurane</td>
<td>10/20</td>
<td>3/20</td>
<td>10/20</td>
<td>3/20</td>
</tr>
<tr>
<td>[49]</td>
<td>Laryngoscopy</td>
<td>Yes</td>
<td>Allentanil, suxamethonium</td>
<td>Bradycardia (N/A) during surgery</td>
<td>P vs midazolam/thio and metho</td>
<td>1/20</td>
<td>0/20</td>
<td>1/20</td>
<td>0/20</td>
</tr>
<tr>
<td>[50]</td>
<td>Paed strabismus</td>
<td>Yes</td>
<td>Morphine, vecuronium</td>
<td>OCR during surgery (HR &lt;15%)</td>
<td>P vs halothane</td>
<td>41/90</td>
<td>1/30</td>
<td>41/90</td>
<td>1/30</td>
</tr>
<tr>
<td></td>
<td>*[51] Thoracoabdominal</td>
<td>No</td>
<td>Fentanyl, vecuronium</td>
<td>Bradycardia during surgery (58°~46°) treated with atropine</td>
<td>P vs thio/halothane</td>
<td>5/20</td>
<td>0/20</td>
<td>5/20</td>
<td>0/20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*[52] Aortic</td>
<td>No</td>
<td>Fentanyl, vecuronium</td>
<td>Bradycardia + hypotension + ST depression</td>
<td>P vs etomidate</td>
<td>1/9</td>
<td>0/9</td>
<td>1/9</td>
<td>0/9</td>
</tr>
</tbody>
</table>

Bradycardic events: combined studies
Asystole: combined studies
Sensitivity analysis
Bradycardic events combined: only OCR
Bradycardic events combined: not OCR
In five RCT with more than 330 children undergoing strabismus surgery the average incidence of an OCR in controls was 16.2%. In these studies the combined NNH for an OCR with propofol was 4, despite prophylactic anticholinergics (table 1). In all other controlled trials (12 RCT and two controlled trials without randomization) the average incidence for bradycardia in controls was 6.4%, and the NNH to produce a bradycardia with propofol was approximately 11 (table 1).

**BRADYCARDIC EVENTS WITH PROPOFOL IN CASE SERIES**

In a small series, one of 30 patients needed atropine to treat bradycardia. An early review of the safety and tolerance of propofol based on 27 separate studies with 1459 patients receiving propofol reported one cardiac arrest. A cardiac conduction defect was thought to be a contributory factor to this major complication. No bradycardic events were reported in a post-launch trial involving 879 patients receiving propofol. In more than 2600 children and adults undergoing a standard propofol anaesthetic, two III degree AV blocks and one bradycardia progressing into an asystole were described in three healthy adults.

The results of a propofol phase IV study were described in two separate analyses. One analysis concentrated on any type of adverse event during propofol anaesthesia, as reported by anaesthetists and nurses. Without definitions, this article documented intraoperative bradycardia in 102 (0.4%), severe bradycardia in four and cardiac arrest in two of 25 981 patients, respectively. The second analysis of the same data concentrated specifically on the haemodynamic effects of propofol anaesthesia and reported a 2% incidence of bradycardia (heart rate lower than 50 beat min$^{-1}$) at induction and an additional 2.8% during maintenance. In a post hoc analysis, bradycardia was significantly associated with beta-blockers, but not with anticholinergics, opioids, neuromuscular blocking agents or heart disease. Hug and colleagues concluded that even in the hands of inexperienced anaesthetists propofol had a low incidence of untoward haemodynamic changes and that these changes were predictable.

**BRADYCARDIC EVENTS WITH PROPOFOL IN PUBLISHED CASE REPORTS**

Seventeen published case reports from 10 countries described, in 25 adults, 13 bradycardias, three heart blocks, 13 asystoles, one electromechanical dissociation and one death. Seven bradycardias progressed to asystole. In an elderly patient with atrial flutter, electromechanical dissociation without preceding bradycardia had a fatal outcome; post-mortem examination excluded acute myocardial ischaemia. Case reports were published between 1987 and 1994 without any chronological clustering.

**BRADYCARDIC EVENTS WITH PROPOFOL IN SPONTANEOUS REPORTS TO DRUG MONITORING CENTRES**

Twelve of 38 national drug monitoring centres responded to our inquiry. In three countries (Croatia, New Zealand, Thailand) no bradycardic events were reported. The other nine countries reported 95 bradycardias, 65 asystoles and 23 bradycardia-related deaths during propofol anaesthesia: Australia (six reports), Belgium (six), Canada (four), Denmark (five), Eire (11), Norway (five), Sweden (two), Switzerland (one) and UK (147). Twenty-five bradycardias progressed to asystole; nine of these were fatal. Death was documented in another 14 patients after asystole.

**ADDITIONAL DATA**

In RCT in children, the reduction in heart rate with propofol was more pronounced when alfentanil was also given, was not dose-dependent and was not different between the ages of 3 and 15 yr. One study without randomization reported a lower incidence of OCR with a higher propofol dosage regimen.

In adults, anticholinergic agents prevented propofol-induced bradycardia but not hypotension. Established bradycardia was unresponsive to increasing doses of i.v. atropine. Bradycardia was potentiated by fentanyl but was not increased when lignocaine was given to prevent propofol pain at injection. A tendency to slower heart rates was seen in older patients (65–80 yr) undergoing propofol anaesthesia compared with younger patients (25–40 yr). A dose–response was seen for hypotension but not for bradycardia in elderly patients.
The likelihood of bradycardic events with propofol depended on the type of report (table 2). In 19 controlled trials the average incidence of bradycardia with propofol was 23.3% in 660 patients (15.2% when OCR was excluded). In case series the incidence of bradycardia with propofol was 4.8% (1179 bradycardic events in 24578 patients).

In controlled trials one of 660 propofol patients developed an asystole, corresponding to an incidence of 15 asystoles in 10 000 patients (table 2). In uncontrolled series, six asystoles were described in 30 936 patients receiving propofol, corresponding to a n incidence of 1.9 asystoles in 10 000 treated patients (8.1 in 10 000 when the phase IV study was excluded).

The post-launch study did not report asystole and the phase IV trial did not report death; one can then be 95% confident that an asystole with propofol anaesthesia does not happen more often than 35 times in 10 000 patients, and that not more than 12 deaths caused by bradycardia happen in 100 000 propofol anaesthetics.

Table 2  Propofol and bradycardic events. Absolute risk (AR) and ratio in 19 controlled trials (17 RCT, two trials without randomization*), four case series and one review of 27 studies

<table>
<thead>
<tr>
<th>Report</th>
<th>A: Potential major harm Bradycardia (per 100 patients)</th>
<th>B: Major harm Asystole (per 10 000 patients)</th>
<th>C: Disaster AR of bradycardia-related death (per 100 000 patients)</th>
<th>A:B Ratio</th>
<th>B:C Ratio</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled trials:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>without OCR</td>
<td>15.2 (68/447)</td>
<td>15.2 (1/660)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>[34–38, 41–43, 45–47, 49], *[51], *[52]</td>
</tr>
<tr>
<td>Controlled trials:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>only OCR</td>
<td>40.4 (86/213)</td>
<td></td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td>[39,40,44,48,50]</td>
</tr>
<tr>
<td>Controlled trials combined</td>
<td>23.3 (154/660)</td>
<td>15.2 (1/660)</td>
<td>N/A</td>
<td>154:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Series (phase IV)</td>
<td>4.8 (1178/24 548)</td>
<td>0.8 (2/25 981)</td>
<td>0 (0/25 981)</td>
<td>623:1</td>
<td></td>
<td>[61,60]</td>
</tr>
<tr>
<td>Series (phase IV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>post-launch</td>
<td>N/A</td>
<td>0 (0/860)</td>
<td>(“rule of 3”: at most 35)</td>
<td>N/A</td>
<td>N/A</td>
<td>[58]</td>
</tr>
<tr>
<td>Small series</td>
<td>3.3 (1/30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[59]</td>
</tr>
<tr>
<td>Review (27 studies)</td>
<td>N/A</td>
<td>6.9 (1/1459)</td>
<td>N/A</td>
<td></td>
<td>N/A</td>
<td>[56]</td>
</tr>
<tr>
<td>(n = 187)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined A:B</td>
<td>A(1+2) = 111</td>
<td>B(1+2) = 32</td>
<td>C(1+2) = 32</td>
<td>A(1+2):B(1+2) = 3.5</td>
<td>B(1+2):C(1+2) = 2.9</td>
<td>[9], [19], [63], [72-74]</td>
</tr>
<tr>
<td>Combined B:C</td>
<td>B(1+2+3+4) = 79</td>
<td></td>
<td>C(1+2+3+4) = 24</td>
<td></td>
<td></td>
<td>[74]</td>
</tr>
</tbody>
</table>

Table 3  Propofol and bradycardic events: ratios in observations (published case reports and spontaneous reports to drug monitoring centers)

<table>
<thead>
<tr>
<th>Report</th>
<th>A: Potential major harm Bradycardia</th>
<th>B: Major harm Asystole</th>
<th>C: Disaster Death</th>
<th>A:B Ratio</th>
<th>B:C Ratio</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case reports (n = 23)</td>
<td>A(1) = 16</td>
<td>B(1) = 7</td>
<td>C(1) = 0</td>
<td>A(1):B(1) = 2.3</td>
<td>B(1):C(1) = 0</td>
<td>[9], [19], [63], [72-74]</td>
</tr>
<tr>
<td>Spontaneous reports (n = 187)</td>
<td>A(2) = 95</td>
<td>B(3) = 25</td>
<td>C(3) = 9</td>
<td>A(2):B(3) = 3.8</td>
<td>B(3):C(3) = 2.8</td>
<td>[74]</td>
</tr>
<tr>
<td>Combined A:B</td>
<td>A(1+2) = 111</td>
<td>B(1+2+3+4) = 79</td>
<td>C(1+2+3+4) = 24</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

QUALITATIVE ANALYSIS OF PUBLISHED REPORTS

Bradycardic complications occurred after induction, during or at the end of propofol anaesthesia. An abrupt, unpredictable decrease, or a progressive slowing of the heart rate, and sudden cardiac arrests were reported. Associated complications involved
bradycardia caused by the OCR was even more pronounced; one of four children treated with propofol will have a bradycardic episode which would not have happened with another anaesthetic. In these latter studies the average incidence of bradycardia in controls was twice as high as in non-ophthalmological settings. This sensitivity analysis was another example of the clinically important relationship between the risk of an outcome without intervention and the number of patients needed to be treated with the intervention in order to produce such an outcome. Although there is no way of assessing the risk for an individual patient, these results may influence clinicians’ choice of interventions for particular groups of patients. These data strongly suggest that propofol is very likely to increase the incidence of bradycardic events compared with other anaesthetic regimens in any clinical setting with an increased risk of bradycardia.

Third, the post-marketing surveillance study of propofol, although including almost 26,000 patients, did not contribute importantly to this analysis. This large but uncontrolled study was raised as having the unique advantage of systematically collected information, and was therefore presumed to reflect adequately the incidence of clinically significant adverse events. However, the two published analyses of this trial did not agree. While a very low incidence of bradycardia (0.4%) but two cardiac arrests were reported in one, the incidence of bradycardia was 10 times higher but no cardiac arrests reported in the other. These differences challenge the reliability of these reports. Compared with controlled studies bradycardia was 3–4 times and asystole 19 times less likely to be reported in this case series, and four times as many bradycardias were necessary to produce one asystole (table 2). Only after combination with data from other series did absolute risk and ratios come closer to data from controlled trials. Drawbacks of phase IV studies have been pointed out previously.

Fourth, in this analysis we used both published case reports and spontaneous reports to drug monitoring centres not only for description of a new or very rare adverse event but to estimate the frequency of disaster. The majority of uncontrolled observations on adverse events are examples of the most dramatic though rare clinical scenarios imaginable. Indeed, published case reports are expected to draw attention to important clinical situations, unusual clinical phenomena and complications.

Therefore, in such reports ratios between different levels of harm are obvious overestimations of the clinical reality. But these reports are often the only source, which makes it possible to establish a ratio between major harm and disaster. Observations enabled a link between all three levels of harm to be made.

There is strong evidence that bradycardia is more likely to happen with propofol than with other anaesthetics. The question then is how serious is propofol-induced bradycardia? One response is to interpret it as minor harm, trivial and of no clinical importance. Such a response may not be correct. The prior hypothesis that propofol-induced bradycardic events may be an example of a continuum was supported.

Discussion

We have described a new approach to adverse event reporting. The focus was on one particular complication with one particular drug.

The three main results of this study are of both methodological and clinical importance: first, a systematic approach to adverse event reporting, taking into account all types of reports with data of different strengths of evidence and both quantitative and qualitative analysis of the extracted data is possible; second, the additional risk of bradycardic events with propofol anaesthesia is finite, compared with other anaesthetic regimens; third, bradycardia with propofol is potential major harm.

Information on propofol anaesthesia and bradycardic events came from different sources. First, the biological basis for propofol-induced bradycardia was supported by several experimental animal and human studies. A plausible physiopathological mechanism explaining the occurrence of an adverse event during or after exposure to the treatment in question supports a causal association between adverse event and treatment.

Second, combined analysis of controlled trials showed a statistically significant difference between propofol and other anaesthetics. In non-ophthalmological settings the additional risk of bradycardia with propofol was approximately 9% (number-needed-to-harm 11.3) compared with other anaesthetics. In these studies the average risk of a bradycardic event in controls was less than 7%. In paediatric strabismus surgery where all children received prophylactic anticholinergics, the ability of propofol to produce a
consistently by data from all types of study. This implies that bradycardia during propofol anaesthesia cannot be discounted as minor harm but should be classified as potential major harm. Therefore, major harm and consequential disaster cannot be ignored and their likelihood has to be estimated. There is strong evidence from controlled trials that the incidence of asystole may be of the order of 15 in 10 000 patients receiving propofol anaesthesia. Uncontrolled series gave estimates with less strong evidence; the numbers were 0.8, 6.9, 11.5 and at most 35 asystoles per 10 000 patients, respectively. These numbers are difficult to interpret because of the lack of a comparator. The number-needed-to-harm calculation is more powerful because it enables comparison of the treatment in question with a control, in this case with another anaesthetic. Based on controlled studies, one of 660 patients undergoing propofol anaesthesia may have an asystole caused by propofol, who would not have had such a major complication in the same clinical setting with a different anaesthetic.

The next question is, what is the likelihood that propofol-induced asystole leads to death? Asystole was not always fatal. Several spontaneous restorations of sinus rhythm were described, but on some occasions treatment included catecholamines and external chest massage. Propofol-related bradycardia and asystole may indeed be of minor clinical importance if occurring in healthy subjects and adequately managed. Different potential quantitative scenarios may be described. Death occurred only in observational reports. Ratios suggested that in the worst situation one-third of propofol-induced bradycardias may lead to an asystole, and that one-third of all asystoles may be fatal. In a worst-possible scenario with the most disastrous constellation of risk factors, these ratios from observational reports, together with a 15% absolute risk for bradycardia from controlled trials (strabismus surgery excluded), would translate into an incidence of 128 deaths in 10 000 propofol anaesthetics. However, the ratio between bradycardia and asystole in observational reports seemed to be a 43-fold overestimation compared with controlled trials. The most likely true ratio between propofol-induced asystole and death may then equal the observation-based ratio times this overestimation factor (i.e. 3.3 times 43 or one death after 112 asystoles). This corrected asystole–death ratio together with the absolute risk for asystole in controlled trials (one in 660 propofol anaesthetics) translates into 1.4 bradycardia-related deaths per 100 000 propofol anaesthetics. This number is in agreement with the rule-of-three estimation from the phase IV trial (at most 12 deaths in 100 000). This number is also in agreement with the estimate that one death attributable to any type of anaesthetic occurred in 20 000 operations in New South Wales between 1984 and 1990.\textsuperscript{91} Death caused by bradycardia complications during propofol anaesthesia would then constitute approximately one-fifth of all anaesthesia-related deaths.

What clinical lessons can be drawn from this analysis? According to the manufacturer's data sheet, propofol should be given by those trained in anaesthesia or, where appropriate, doctors trained in the care of patients in intensive care. Severe bradycardia and asystole as possible complications of propofol are mentioned and the manufacturer suggests the prophylactic use of anticholinergics in patients at particular risk for bradycardia, and advises against the use of propofol for induction of anaesthesia in children less than 3 yr of age. These statements are supported by this study. Some comments may, however, be appropriate.

First, despite prophylactic anticholinergics the risk of bradycardia with propofol may still be considerable.\textsuperscript{7, 9, 35, 39, 40, 43, 44, 47, 48, 50} Several reports suggested an inadequate response of propofol-induced bradycardia to atropine.\textsuperscript{71, 52, 59, 65} Especially in children, prevention and treatment of bradycardia with atropine is controversial.\textsuperscript{92} In this context, the suggestion that the prophylactic dose of atropine should be increased seems to be inappropriate.\textsuperscript{48, 50}

Second, a stable heart rate accompanied by a decrease in cardiac output and systemic vascular resistance may result in inadequate peripheral perfusion pressure and oxygen delivery.\textsuperscript{47} In young children cardiac output is more rate-dependent than in adults because of a limited ability to increase myocardial contractility.\textsuperscript{93} The frequency of bradycardia during anaesthesia in children increases with both decreasing age and poorer ASA physical status.\textsuperscript{94} There is evidence that propofol decreases heart rate more in children less than 2 yr of age compared with older children.\textsuperscript{53} The pragmatic question is then, what happens to a young child who is very ill and who receives a long-term propofol infusion? Five of seven seriously ill ICU children who developed refractory bradyarrhythmia after prolonged propofol sedation were between 4 weeks and less than 3 yr old; in four the outcome was fatal.\textsuperscript{10–12}

Third, physicians’ perception of frequency and severity of harm together with their skills to treat major complications and to prevent a disaster may have an important impact on judging the risk/benefit of treatments. For instance, bradycardia caused by OCR has been recognized as an important intraoperative complication of strabismus surgery.\textsuperscript{16, 92–96} However, two of seven published RCT comparing propofol with another anaesthetic in paediatric strabismus surgery did not report any information on the presence or absence of the OCR.\textsuperscript{97, 98} The other five studies reported a much higher incidence of the OCR with propofol than with other anaesthetics (despite prophylactic anticholinergics), but none questioned the indication for propofol in this setting.\textsuperscript{39, 40, 44, 48, 50} Also, estimate of the asystole–death ratio of propofol may be perceived as being extremely low and therefore of no importance. However, this ratio describes only deaths caused by bradycardia-related complications during propofol anaesthesia. Inclusion of other possibly propofol-related deaths, such as cardiovascular collapse,\textsuperscript{37} would have given a less favourable estimate. Most bradycardias and asystoles seem to have been adequately managed by anaesthetists, including resuscitation measurements such as i.v. catecholamines and external chest compression. The same quantity and severity of potential
major and major harm in hands of physicians not used to such resuscitation techniques would probably have given different results.

Finally, the first contraindication to any drug is lack of indication.92 Propofol anaesthesia is by no means a treatment without alternatives. It would therefore be helpful to identify both the subgroups most likely to profit from the beneficial characteristics of propofol and the subgroups at particular risk of complications. For instance, faster recovery and decreased incidence of postoperative nausea and vomiting after propofol anaesthesia are unlikely to be of clinical relevance in every setting.99-101 Results from the sensitivity analysis, together with data from different reports, suggest that the indications for propofol should at least be questioned in the presence of conduction abnormalities,36 57 71 74 heart rate lowering medications such as beta-blockers,51 70 procedures with an increased risk of bradycardia,87 including squatting,14 and laparoscopies,32 43 69 102 and in very sick, old or young patients.10-12 17 53 74 84 103

This article has described an approach to adverse events which showed a biological progression. The example used was propofol bradycardia, asystole and death. It would be misleading to use this hazard out of context. Clearly there are many other hazards in anaesthesia which need to be considered; not all are as well documented. This model may be useful to allow us to be more precise about the other hazards.

Acknowledgements
M.T. holds an Overseas Research Student Award. The review was funded by Pain Research Funds. We are grateful to the Drug Monitoring Centres who responded to our enquiry.

References


100. Dexter F, Tinker JH. Comparisons between desflurane and isoflurane or propofol on time to following commands and time to discharge. A metaanalysis. *Anaesthesiology* 1995; 83: 77–82.