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Propofol and bradycardia: causation, frequency and severity

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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 A systematic search for any type of report, published and unpublished, was made to review the evidence that propofol increases the risk of bradycardia, asystole and death from bradycardic events.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

Anaesthetics i.v., propofol. Heart, heart rate. Complications, bradycardia. Complications, asystole. Anaesthesia, audit.

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,[1] smooth induction characteristics, a recovery profile with a low incidence of adverse effects[2] and non-hypnotic therapeutic properties.[3] It was suggested that the excellent haemodynamic state was of particular use in paediatric patients.[4]

During propofol anaesthesia a low heart rate may occur despite decreased arterial pressure.[5,6] 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.[7–9] Severe, refractory and fatal bradycardias in children in the ICU have been observed with long-term propofol sedation.[10–12] The question has been raised of when, if ever, case reports become good enough evidence on which to base practice.[13]

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.[14] The OCR, a trigemino-vagal reflex, may induce severe bradycardia and asystole. Fatal outcome has been described.[15,16]

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

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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), concomitant 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[5 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[5 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 Bradycardic 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)

Ref	Surgery	Prophylactic AC	Other drugs	Bradycardic event (definition of bradycardia)	Comparison	Event rate with propofol	Event rate with control	Odds ratio (95% CI)	NNT (95% CI)
[34]	Adults different	No	Alfentanil	Bradycardia during induction (30/′)	P/alfentanil *vs* thio/suxamethonium	1/31	0/33		
[35]	Micro ENT	Yes	Alfentanil, suxamethonium	Bradycardia during surgery (< 50/′)	P *vs* etomidate	1/15	0/15		
[36]	Minor gynaecology	No	None	Bradycardia during surgery (1 asystole)	P *vs* thio/halothane	2/21	0/22		
[36]	Minor gynaecology	Yes	None	Bradycardia during surgery	P *vs* thio/halothane	0/39	0/38		
[37]	Abdominal	No	Fentanyl, vecuronium	Bradycardia during surgery (< 50/′ for > 5 min)	P±N_2O *vs* thio/isoflurane/N_2O	25/40	9/20		
[38]	Minor gynaecology	No	Fentanyl	Bradycardia during surgery (HR < 50/′): atropine	P *vs* thiopental/isoflurane	6/59	3/59		
[39]	Paed strabismus	Yes	Alfentanil, vecuronium	OCR during surgery (HR < 15%)	P *vs* thio/halothane	11/60	0/30		
[40]	Paed strabismus	Yes	Fentanyl, vecuronium	OCR during surgery (HR < 20%)	P *vs* thio/halothane	15/22	4/22		
[41]	ENT	Yes	Fentanyl, pancuronium	Bradycardia during surgery (definition N/A)	P *vs* thio/isoflurane	0/25	3/25		
[42]	Adults different	No	Fentanyl, atracurium	Bradycardia during surgery (< 45/′): atropine	P *vs* thio/isoflurane	1/25	0/25		
[43]	Gynaecology laps	Yes	Alfentanil, suxamethonium	Bradycardia during surgery (< 50/′): 1x atropine (HR 37/′)	P *vs* P/isoflurane	3/15	0/15		
[44]	Paed strabismus	Yes	Dextromoramide, vecuronium	OCR during surgery (HR < 20%)	P *vs* P/enflurane	9/21	3/21		
[45]	Gynaecology laps	No	Sufentanil, vecuronium	Bradycardia during surgery (definition N/A)	P *vs* thiamylal/enflurane	8/30	9/30		
[46]	Orthopaedic	No	Fentanyl, d-tubocurarine	Complete heart block (HR 30/′) requiring atropine at induction	P *vs* desflurane	0/23	1/46		
[47]	Paed ENT	Yes	Suxamethonium	Bradycardia (definition N/A) or junctional rhythm at induction	P *vs* barbiturates	14/75	2/48		
[48]	Paed strabismus	Yes	Alfentanil, vecuronium	OCR during surgery (HR < 20%)	P *vs* thio/isoflurane	10/20	3/20		
[49]	Laryngoscopy	Yes	Alfentanil, suxamethonium	Bradycardia (N/A) during surgery treated with atropine	P *vs* midazolam/thio and metho	1/20	0/20		
[50]	Paed strabismus	Yes	Morphine, vecuronium	OCR during surgery (HR < 15%)	P *vs* halothane	41/90	10/30		
*[51]	Thoracoabdominal	No	Fentanyl, vecuronium	Bradycardia during surgery (38/′-46/′)	P *vs* thio/halothane	5/20	0/20		
*[52]	Aortic	No	Fentanyl, vecuronium	Bradycardia + hypotension + ST depression	P *vs* etomidate	1/9	0/9		
Bradycardic events: combined studies						154/660	47/548	2.5 (1.8–3.6)	6.8 (5.3–9.3)
Asystole: combined studies						1/660	0/548	2.3 (0.1–37)	660
Sensitivity analysis									
Bradycardic events combined: only OCR						86/213	20/123	3.4 (2–5.6)	4.1 (3–6.7)
Bradycardic events combined: not OCR						68/447	27/425	2.3 (1.5–3.4)	11.3 (7.7–21)

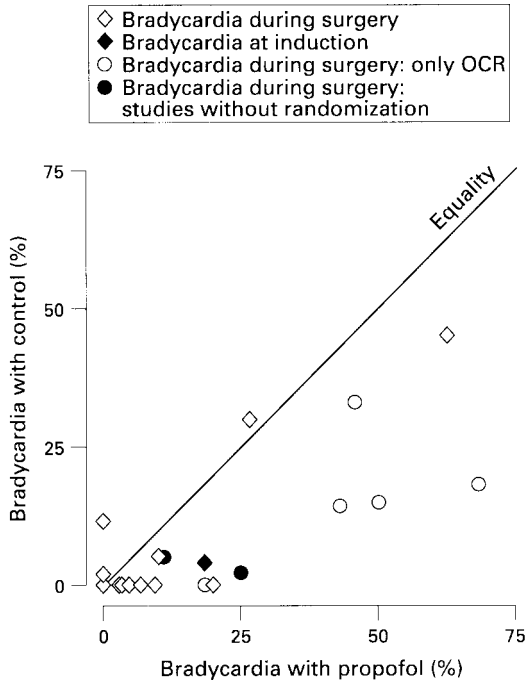

Figure 1 Propofol and bradycardic events. Each symbol represents one study. Numbers indicate percentages of patients with a bradycardic event with propofol or a non-propofol anaesthetic (control). Data from 17 randomized, controlled trials and two controlled trials without randomization.

In five RCT with more than 330 children undergoing strabismus surgery the average incidence of an OCR in controls was 16.2%.[39 40 44 48 50] 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.[56] An early review of the safety and tolerance of propofol based on 27 separate studies with 1459 patients receiving propofol reported one cardiac arrest.[57] A cardiac conduction defect was thought to be a contributory factor to this major complication.[57] No bradycardic events were reported in a post-launch trial involving 879 patients receiving propofol.[58] 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.[59]

The results of a propofol phase IV study were described in two separate analyses.[60 61] One analysis concentrated on any type of adverse event during propofol anaesthesia, as reported by anaesthetists and nurses.[60] 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.[60] 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.[61] In a *post hoc* analysis, bradycardia was significantly associated with beta-blockers, but not with anticholinergics, opioids, neuromuscular blocking agents or heart disease.[61] 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.[61]

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.[7–9 19 62–74] 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.[74] 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,[55] was not dose-dependent[54 75] and was more pronounced in children less than 2 yr of age than in older children[53] but was not different between the ages of 3 and 15 yr.[75] One study without randomization reported a lower incidence of OCR with a higher propofol dosage regimen.[76]

In adults, anticholinergic agents prevented propofol-induced bradycardia but not hypotension.[77–79] Established bradycardia was unresponsive to increasing doses of i.v. atropine.[80] Bradycardia was potentiated by fentanyl,[81 82] but was not increased when lignocaine was given to prevent propofol pain at injection.[83] A tendency to slower heart rates was seen in older patients (65–80 yr) undergoing propofol anaesthesia compared with younger patients (25–40 yr).[84] A dose–response was seen for hypotension but not for bradycardia in elderly patients.[85]

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

Report	A: Potential major harm AR of bradycardia with propofol (per 100 patients)	B: Major harm AR of asystole with propofol (per 10 000 patients)	C: Disaster AR of bradycardia-related death (per 100 000 patients)	A:B Ratio	Ref.
Controlled trials: without OCR	15.2 (68/447)	*15.2 (1/660)*	*N/A*	N/A	[34–38, 41–43, 45–47, 49], *[51], *[52]
Controlled trials: only OCR	40.4 (86/213)			N/A	[39,40,44,48,50]
Controlled trials combined	*23.3 (154/660)*	*15.2 (1/660)*	*N/A*	*154:1*	
Series (phase IV)	4.8 (1178/24 548)	0.8 (2/25 981)	0 (0/25 981) ("rule of 3": at most 12)	623:1	[61,60]
Series (post-launch)	N/A	0 (0/860) ("rule of 3": at most 35)	N/A	N/A	[58]
Series (ophthalmologic surgery)	N/A	11.5 (3/2606)	N/A	N/A	[59]
Small series	3.3 (1/30)	0 (0/30)	N/A	1:0	[56]
Review (27 studies)	N/A	6.9 (1/1459)	N/A	N/A	[57]
Series combined	4.8 (1179/24 578)	*With phase IV: 1.9 (6/30 936)* *Without phase IV: 8.1 (4/4955)*	N/A	*240:1*	

ESTIMATION: ABSOLUTE RISK OF BRADYCARDIC EVENTS WITH PROPOFOL

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 an 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.[25]

ESTIMATION: RATIOS BETWEEN ABSOLUTE RISKS OF DIFFERENT LEVELS OF HARM

In controlled trials one of 154 bradycardic episodes led to an asystole (table 2). Across all case series, including the review of 27 studies, an average of 240 bradycardias led to one asystole. In the phase IV trial alone, 623 bradycardias led to one asystole. Death was not reported in controlled studies or case series, therefore calculation of a ratio between major harm and disaster is not possible.

In observational reports (case reports and spontaneous reports to drug monitoring centres) approximately four bradycardias led to one asystole and one-third of asystoles were fatal (table 3). Asystole after propofol-induced bradycardia was 43 times more likely to be reported in observational reports than in controlled trials.

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

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

Report	A: Potential major harm Bradycardia	B: Major harm Asystole	C: Disaster Death	A:B Ratio	B:C Ratio	Ref
Case reports ($n=23$)	A(1) = 16	B(1) = 7 B(2) = 7	C(1) = 0 C(2) = 1	A(1):B(1) = 2.3 n/a	B(1):C(1) = 0 B(2):C(2) = 7	[9], [19], [63], [72-74] [74]
Spontaneous reports ($n=187$)	A(2) = 95	B(3) = 25 B(4) = 40	C(3) = 9 C(4) = 14	A(2):B(3) = 3.8 n/a	B(3):C(3) = 2.8 B(4):C(4) = 2.9	
Combined A:B	A(1+2) = 111	B(1+3) = 32		*A(1+2):B(1+3) = 3.5*		
Combined B:C		B(1+2+3+4) = 79	C(1+2+3+4) = 24		*B(1+2+3+4):C(1+2+3+4)=3.3*	

tonic–clonic movements,[64] arrhythmia of unknown type,[36] junctional rhythm,[63 64] supraventricular bradycardia,[65] recurrence of asystole,[67 70] and intermittent episodes of heart block.[70]

Treatment of bradycardic events consisted in most cases of i.v. administration of anticholinergics, but also catecholamines,[7 51 52 59] precordial chest thump[65] and external cardiac massage.[36 59 63 72] Resistance to both i.v. atropine[7 51 52 59 65] and isoprenaline[7] was reported. In several reports heart rate normalization occurred after stopping the propofol infusion.[7 51 52 66] Several bradycardic episodes resolved spontaneously. The longest duration of asystole in surviving patients was 45 s.[64]

Several factors, alone or in combination, were coincident with bradycardic complications during propofol anaesthesia and were therefore suspected in the original reports to be jointly responsible for the negative outcome: surgical stimulation,[9 36] lack of surgical stimulation,[63 67] extradural anaesthesia,[51] previous syncope,[7 64 67] preoperative conduction abnormalities,[57 71] fentanyl,[8 63 65] suxamethonium,[35 62 65] atracurium,[8] beta-blocker,[61 70] ornipressin,[8] neostigmine,[70] any factors or drugs potentiating vagal stimulation,[19 68–70 72 73] absence of vagal stimulation,[63] too light anaesthesia,[76] insufficient prophylactic dose of atropine[48 50] and an individual susceptibility to propofol.[63 65] Most authors concluded that a prophylactic anticholinergic may be indicated in the presence of any risk factor if propofol is to be used.

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 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.[86] 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.[87]

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 praised as having the unique advantage of systematically collected information, and was therefore presumed to reflect adequately the incidence of clinically significant adverse events.[60] 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,[60] the incidence of bradycardia was 10 times higher but no cardiac arrests reported in the other.[61] 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.[88]

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[89] 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.[90] 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 mates 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

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.[91] Death caused by bradycardic 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.[7–9 35 39 40 43 44 47 48 50 51] Several reports suggested an inadequate response of propofol-induced bradycardia to atropine.[7 51 52 59 65 80] Especially in children, prevention and treatment of bradycardia with atropine is controversial.[92] In this context, the suggestion that the prophylactic dose of atropine should be increased seems to be inappropriate.[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.[27] In young children cardiac output is more rate-dependent than in adults because of a limited ability to increase myocardial contractility.[93] The frequency of bradycardia during anaesthesia in children increases with both decreasing age and poorer ASA physical status.[94] There is evidence that propofol decreases heart rate more in children less than 2 yr of age compared with older children.[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 man 3 yr old; in four the outcome was fatal.[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.[16 95–96] 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.[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.[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,[17] 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,[61 70] procedures with an increased risk of bradycardia,[87] including squint repair,[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.

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References

1. Deegan RJ. Propofol: a review of the pharmacology and applications of an intravenous anesthetic agent. *American Journal of the Medical Sciences* 1992; **304**: 45–49.
2. Smith I, White PF, Nathanson M, Gouldson R. Propofol. An update on its clinical use. *Anesthesiology* 1994; **81**: 1005–1043.
3. Borgeat A, Wilder-Smith OHG, Suter PM. The non-hypnotic therapeutic applications of propofol. *Anesthesiology* 1994; **80**: 642–656.
4. Morton NS, Johnston G, White M, Marsh BJ. Propofol in paediatric anaesthesia. *Paediatric Anaesthesia* 1992; **2**: 89–97.
5. Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J. Effect of propofol anesthesia on baroreflex activity in humans. *Anesthesia and Analgesia* 1987; **66**: 1115–1120.
6. Claeys MA, Gepts E, Camu F. Heamodynamic changes during anaesthesia induced and maintained with propofol. *British Journal of Anaesthesia* 1988; **60**: 3–9.
7. Thomson SJ, Yate PM. Bradycardia after propofol infusion. *Anaesthesia* 1987; **42**: 430.
8. Marsch SCU, Schaefer H-G. Pronounced bradycardia after application of POR-8 (ornipressin) under total intravenous anaesthesia with propofol. *Acta Anaesthesiologica Scandinavica* 1990; **34**: 514.
9. Bricchi M, Gemma M. Asystolie lors d'une anesthésie avec propofol. *Annales Françaises d'Anesthésie et de Réanimation* 1991; **5**: 492–495.
10. Parke TJ, Stevens JE, Rice ASC, Greenaway CL, Bray RJ, Smith PJ, Waldmann CS, Verghese C. Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. *British Medical Journal* 1992; **305**: 613–616.
11. Barclay K, Williams AJ, Major E. Letter to the Editor. *British Medical Journal* 1992; **305**: 953.
12. Bray RJ. Fatal myocardial failure associated with a propofol infusion in a child. *Anaesthesia* 1995; **50**: 94.
13. Dearlove O, Dobson A. Does propofol cause death in children? *Anaesthesia* 1995; **50**: 916.
14. Tramèr M, Moore A, McQuay H. Prevention of vomiting after paediatric strabismus surgery: a systematic review using the numbers-needed-to-treat method. *British Journal of Anaesthesia* 1995; **75**: 556–561.
15. Fayon M, Gauthier M, Blanc VF, Ahronheim GA, Michaud J. Intraoperative cardiac arrest due to the oculo-cardiac reflex and subsequent death in a child with occult Epstein-Barr virus myocarditis. *Anesthesiology* 1995; **83**: 622–624.
16. Blanc VF, Hardy J-F, Milot J, Jacob J-L. The oculocardiac reflex: a graphic and statistical analysis in infants and children. *Canadian Anaesthetists Society Journal* 1983; **30**: 360–369.
17. Warden JC, Pickford DR. Fatal cardiovascular collapse following propofol induction in high-risk patients and dilemmas in the selection of a short-acting induction agent. *Anaesthesia and Intensive Care* 1995; **23**: 485–487.
18. Munoz R, Goldberg ME, Cantillo J, Subramoni J, Nemiroff MS. Perioperative arrhythmias with a propofol-based anesthetic. *Journal of Clinical Anesthesia* 1991; **3**: 149–152.
19. Ricós P, Trillo L, Crespo MT, Guilera N, Puig MM. Bradicardia y asistolia asociadas a la administración simultánea de propofol y fentanilo en la inducción anestésica. *Revista Espanhola Anestesiología y Reanimación* 1994; **41**: 194–195.
20. L'Abbé K, Detsky AS, O'Rourke K. Meta-analysis in clinical research. *Annals of Internal Medicine* 1987; **107**: 224–233.
21. Gardner MJ, Altman DG, eds. *Statistics with Confidence.* London: British Medical Association, 1989.
22. Cooper H, Hedges LV. *The Handbook of Research Synthesis.* New York: Russel Sage Foundation, 1994.
23. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *The New England Journal of Medicine* 1988; **318**: 1728–1733.
24. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *British Medical Journal* 1995; **310**: 452–454.
25. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. *Journal of the American Medical Association* 1983; **249**: 1743–1745.
26. Colson P, Barlet H, Roquefeuill B, Eledjam J-J. Mechanism of propofol bradycardia. *Anesthesia and Analgesia* 1988; **67**: 906–907.
27. Brüssel T, Theissen JL, Vigfusson G, Lunkenheimer PP, Van Aken H, Lawin P. Hemodynamic and cardiodynamic effects of propofol and etomidate: negative inotropic properties of propofol. *Anesthesia and Analgesia* 1989; **69**: 35–40.
28. Blake DW, Jover B, McGrath BP. Haemodynamic and heart rate reflex responses to propofol in the rabbit. *British Journal of Anaesthesia* 1988; **61**: 194–199.
29. Runciman WB, Mather LE, Selby DG. Cardiovascular effects of propofol and of thiopentone anaesthesia in the sheep. *British Journal of Anaesthesia* 1990; **65**: 353–359.
30. Monk CR, Coates DP, Prys-Roberts C, Turtle MJ, Spelinka K. Haemodynamic effects of a prolonged infusion of propofol as a supplement to nitrous oxide anaesthesia. *British Journal of Anaesthesia* 1987; **59**: 954–960.
31. Samain E, Marty J, Gauzit R, Bouyer I, Coudrec E, Farinotti R. Effects of propofol on baroreflex control of heart rate and on plasma noradrenaline levels. *European Journal of Anaesthesiology* 1989; **6**: 321–326.
32. Deutschman CS, Harris AP, Fleisher LA. Changes in heart rate variability under propofol anesthesia: a possible explanation for propofol-induced bradycardia. *Anesthesia and Analgesia* 1994; **79**: 373–379.
33. Coates DP, Monk CR, Prys-Roberts C, Turtle M. Hemodynamic effects of infusions of the emulsion formulation of propofol during nitrous oxide anesthesia in humans. *Anesthesia and Analgesia* 1987; **66**: 64–70.
34. Beck GN, Masterson GR, Richards J, Bunting P. Comparison of intubation following propofol and alfentanil with intubation following thiopentone and suxamethonium. *Anaesthesia* 1993; **48**: 876–880.

35. De Grood PMRM, Mitsukuri S, Van Egmond J, Rutten JMJ, Crul JF. Comparison of etomidate and propofol for anaesthesia in microlaryngeal surgery. *Anaesthesia* 1987; **42**: 366–372.
36. Henriksson B-A, Carlsson P, Hallén B, Hägerdal M, Lundberg D, Pontén J. Propofol vs thiopentone as anaesthetic agents for short operative procedures. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 63–66.
37. Jensen AG, Granfeldt H, Kalman SH, Nyström P-O, Eintrei C. A comparison of propofol and isoflurane anaesthesia: the need for ephedrine and glycopyrrolate. *European Journal of Anaesthesiology* 1995; **12**: 291–299.
38. Jenstrup M, Wiberg-Jørgensen F, Arnfred I, Clausen LM, Clausen BA, Gabrielsen J, Højsted J, Tegtmeier Raaby J, Skauge L. Propofol versus tiopental som hovemiddel ved korte indgreb. *Ugeskrift for Laeger* 1988; **150**: 2454–2457.
39. Klockgether-Radke A, Junge M, Braun U, Mühlendyck H. Einfluss von Propofol auf das Erbrechen nach Strabismusoperationen bei Kindern. *Anaesthesist* 1995; **44**: 755–760.
40. Larsson S, Asgeirsson B, Magnusson J. Propofol–fentanyl anesthesia compared to thiopental–halothane with special reference to recovery and vomiting after paediatric strabismus surgery. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 182–186.
41. Ledderose H, Rester P, Carlsson P, Peter K. Recovery times and side effects after propofol infusion and after isoflurane during ear surgery with additional infiltration anaesthesia. *Anaesthesia* 1988; **43** (Suppl.): 89–91.
42. Nathan N, Rezzoug A, Dolan P, Bonada G, Feiss P. Propofol en perfusion ou isoflurane en circuit fermé. Etude du coût. *Annales Françaises d'Anesthésie el de Réanimation* 1993; **12**: 571–574.
43. Oikkonen M. Propofol vs isoflurane for gynaecological laparoscopy. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 110–114.
44. Queinnec MC, de Dieuleveult C, Chupin AM, Pinaud M. Propofol en perfusion à débit continu versus enflurane chez l'enfant opéré de strabisme. Comparaison de la qualité de l'anesthésie et du réveil. *Annales Françaises d'Anesthésie et de Réanimation* 1989; **8**: 37–41.
45. Randel GI, Levy L, Kothary SP, Pandit SK. Propofol *versus* thiamylal–enflurane anesthesia for outpatient laparoscopy. *Journal of Clinical Anesthesia* 1992; **4**: 185–189.
46. Rapp SE, Conahan TJ, Pavlin DJ, Levy WJ, Hautman B, Lecky J, Luke J, Nessly ML. Comparison of desflurane with propofol in outpatients undergoing peripheral orthopedic surgery. *Anesthesia and Analgesia* 1992; **75**: 572–529.
47. Saarnivaara L, Hiller A, Oikkonen M. QT interval, heart rate and arterial pressures using propofol, thiopentone or methohexitone for induction of anaesthesia in children. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 419–423.
48. Snellen FT, Vanacker B, Van Aken H. Propofol–nitrous oxide *versus* thiopental sodium isoflurane–nitrous oxide for strabismus surgery in children. *Journal of Clinical Anesthesia* 1993; **5**: 37–41.
49. Sonne NM, Clausen TG, Valentin N, Munksgaard A. Total intravenous anaesthesia for direct laryngoscopy: propofol infusion compared to thiopentone combined with midazolam and methohexitone. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 250–254.
50. Watcha MF, Simeon RM, White PF, Stevens JL. Effect of propofol on the incidence of postoperative vomiting after strabismus surgery in pediatric outpatients. *Anesthesiology* 1991; **75**: 204–209.
51. Coquelin G, Quinot JF, Donnard G, Saissy YM, Chateau J. Anesthésie péridurale en chirurgie thoraco-abdominale. Comparaison propofol-méthohexital pour narcose de complément. *Cahiers d'Anesthesiologie* 1987; **35**: 449–455.
52. Chauvreau C, Fouillard A, Ferrat PL, Michel JM, Lathalize M, Gasquet N, Feiss P. Le propofol dans la chirurgie du carrefour aortique. Comparaison avec l'isoflurane. *Annales Françaises d'Anesthésie el de Réanimation* 1987; **6**: 254–257.
53. Aun CST, Sung RYT, O'Meara ME, Short TG, Oh TE. Cardiovascular effects of i.v. induction in children: comparison between propofol and thiopentone. *British Journal of Anaesthesia* 1993; **70**: 647–653.
54. Short SM, Aun CST. Haemodynamic effects of propofol in children. *Anaesthesia* 1991; **46**: 783–785.
55. Hiller A, Saarnivaara L. Injection pain, cardiovascular changes and recovery following induction of anaesthesia with propofol in combination with alfentanil or lignocaine in children. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 564–568.
56. De Grood PMRM, Ruys AHC, van Egmond J, Booij LHDJ, Crul JF. Propofol ('diprivan') emulsion for total intravenous anaesthesia. *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 65–69.
57. Stark RD, Binks SM, Dutka VN, O'Connor KM, Arnstein MJA, Glen JB. A review of the safety and tolerance of propofol ('Diprivan'). *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 152–156.
58. Sanderson JH, Blades JF. Multicentre study of propofol in day case surgery. *Anaesthesia* 1988; **43** (Suppl): 70–73.
59. Dandoy M, Reynaud S, Lampl E. Quatre cas d'inefficacité cardio-circulatoire pendant une anesthésie: rôle du propofol? *Cahiers d'Anesthésiologie* 1992; **2**: 141–142.
60. McLeskey CH, Walawander CA, Nahrwold ML, Roizen MF, Stanley TH, Thisted RA, White PF, Apfelbaum JL, Grasela TH, Hug CC jr. Adverse events in a multicenter phase IV study of propofol: evaluation by anesthesiologists and postanesthesia care unit nurses. *Anesthesia and Analgesia* 1993; **77** (Suppl): S3–S9.
61. Hug CC jr, McLeskey CH, Nahrwold ML, Roizen MF, Stanley TH, Thisted RA, Walawander CA, White PF, Apfelbaum JL, Grasela TH. Hemodynamic effects of propofol: data from over 25,000 patients. *Anesthesia and Analgesia* 1993; **77** (Suppl): S21–S29.
62. Baraka A. Severe bradycardia following propofol–suxamethonium sequence. *British Journal of Anaesthesia* 1988; **61**: 482–483.
63. Dandoy M, Poisson F, Lampl E. Arrêt cardiocirculatoire lors d'une anesthésie associant propofol et fentanyl. *Annales Françaises d'Anesthésie et de Réanimation* 1990; **9**: 465.
64. Dorrington KL. Asystole with convulsion following a sub-anaesthetic dose of propofol plus fentanyl. *Anaesthesia* 1989; **44**: 658–659.
65. Egan TD, Brock-Utne JG. Asystole after anesthesia induction with a fentanyl, propofol, and succinylcholine sequence. *Anesthesia and Analgesia* 1991; **73**: 818–820.
66. Elhairy A, Séguir JC, Sinda P. Trouble de la conduction auriculo-ventriculaire lors d'une administration continue de propofol. *Cahiers d'Anesthesiologie* 1992; **40**: 417–418.
67. Figueira A, Suarez R, Llorente A, Fernandez MJ, Busto N. Bloqueo cardiaco y asistolia ventricular reversible tras administración de propofol. *Revista Espanola Anestesiologia y Reanimación* l994; **4**: 30l.
68. Guise PA. Asystole following propofol and fentanyl in an anxious patient. *Anaesthesia and Intensive Care* 1991; **19**: 116–18.
69. Ganansia M-F, Francois TP, Ormezzano X, Pinaud ML, Lepage J-Y. Atrioventricual Mobitz I block during propofol anesthesia for laparoscopic tubal ligation. *Anesthesia and Analgesia* 1989; **69**: 524–525.
70. James MFM, Reyneke CJ, Whiffler K. Heart block following propofol: a case report. *British Journal of Anaesthesia* 1989; **62**: 213–215.
71. Lemerle J, Cousin MT. Trouble de la conduction observé lors d'une anesthésie associant propofol et fentanyl. *Cahiers d'Anesthésiologie* 1992; **40**: 49–50.
72. Sutera PT, Smith CE. Asystole during direct laryngoscopy and tracheal intubation. *Journal of Cardiothoracic and Vascular Anesthésia* 1994; **8**: 79–80.
73. Thirion B, Haberer JP. Arrêt circulatoire lors d'une anesthésie par propofol. *Annales Françaises d'Anesthésie et de Reanimation* 1989; **8**: 386–387.
74. Van der Auwera D, Berborgh C, Loef B. Cardiovascular collapse after continuous infusion of propofol in elderly patients. *Acta Anaesthesiologica Belgica* 1990; **41**: 13–16.
75. Manschot HJ, Meursing AEE, Axt P, Byttebier GO, Erdmann W. Propofol requirements for induction of anesthesia in children of different age groups. *Anesthesia and Analgesia* 1992; **75**: 876–879.
76. Dandoy M, Poisson F, Lampl E, Reynaud S, Rondet S, Proust MN, Mallet A, Maurin JP. Anesthésie au propofol lors de la chirurgie du strabisme chez l'enfant. Comparaison de deux protocoles différents d'induction et d'entretien. *Cahiers d'Anesthésiologie* 1990; **38**: 241–245.

77. Skues MA, Richards MJ, Jarvis AP, Prys-Roberts C. Preinduction atropine or glycopyrrolate and hemodynamic changes associated with induction and maintenance of anesthesia with propofol and alfentanil. *Anesthesia and Analgesia* 1989; **69**: 386–390.
78. Sneyd JR, Berry A. Effect of preinduction glycopyrrolate on the hemodynamic responses to anesthesia with propofol. *Anesthesia and Analgesia* 1991; **72**: 831–834.
79. Sneyd JR, Mayall R. The effect of pre-inductipn glycopyrronium on the haemodynamic response of elderly patients to anaesthesia with propofol. *Anaesthesia* 1992; **47**: 620–621.
80. Cross G, Gaylard D, Lim M. Atropine-induced heart rate changes: a comparison between midazolam–fentanyl–propofol–N_2O and midazolam–fentanyl–thiopentone–enflurane–N_2O anaesthesia. *Canadian Journal of Anaesthesia* 1990; **37**: 416–419.
81. Lepage JYM, Pinaud ML, Hélias JH, Juge CM, Cozian AY, Farinotti R, Souron RJ. Left ventricular function during propofol and fentanyl anesthesia in patients with coronary artery disease: assessment with a radionuclide approach. *Anesthesia and Analgesia* 1988; **67**: 949–955.
82. Van Aken H, Meinshausen E, Prien T, Brüssel T, Heinecke A, Lawin P. The influence of fentanyl and tracheal intubation on the hemodynamic effects of anesthesia induction with propofol/N_2O in humans. *Anesthesiology* 1988; **68**: 157–163.
83. Tham CS, Khoo ST. Modulating effects of lignocaine on propofol. *Anaesthesia and Intensive Care* 1995; **23**: 154–157.
84. Scheepstra GL, Booij LHDJ, Rutten CLG, Coehen LGJ. Propofol for induction and maintenance of anaesthesia: comparison between younger and older patients. *British Journal of Anaesthesia* 1989; **62**: 54–60.
85. Peacock JE, Lewis RP, Reilly CS, Nimmo WS. Effect of different rates of infusion of propofol for induction of anaesthesia in elderly patients. *British Journal of Anaesthesia* 1990; **65**: 346–352.
86. Tramèr M, Moore A, McQuay H. Omitting nitrous oxide in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials. *British Journal of Anaesthesia* 1996; **76**: 186–193.
87. Doyle DJ, Mark PWS. Reflex bradycardia during surgery. *Canadian Journal of Anaesthesia* 1990; **37**: 219–222.
88. Roizen MF. Introductory remarks: the phase IV study of propofol. *Anesthesia and Analgesia* 1993; **77**: S1–S2.
89. Jick H. The discovery of drug-induced illness. *New England Journal of Medicine* 1977; **296**: 481–485.
90. Guide for authors (revised Jan 1994). *Anesthesiology* 1994; **80**: 43A–44A.
91. Warden JC, Horan BF. Deaths attributed to anaesthesia in New South Wales, 1984–1990. *Anaesthesia and Intensive Care* 1996; **24**: 66–73.
92. Blanc VF. Atropine and succinylcholine: beliefs and controveries in paediatric anaesthesia. *Canadian Journal of Anaesthesia* 1995; **42**: 1–7.
93. Hatch DJ. Paediatric anaesthesia. In: Nimmo WS, Rowbotham DJ, Smith G, eds. *Anaesthesia, vol.*, 2nd Edn. Oxford: Blackwell, 1994; 912ff.
94. Keenan RL, Shapiro JH, Kane FR, Simpson PM. Bradycardia during anesthesia in infants. *Anesthesiology* 1994; **80**: 976–982.
95. Loewinger J, Friedmann-Neiger I, Cohen M, Levi E. Effects of atracurium and pancuronium on the oculocardiac reflex in children. *Anesthesia and Analgesia* 1991; **73**: 25–28.
96. Braun U, Feise J, Mühlendyck H. Is there a cholinergic and an adrenergic phase of the oculocardiac reflex during strabismus surgery? *Acta Anaesthesiologica Scandinavica* 1993; **37**: 390–395.
97. Reimer EJ, Montgomery CJ, Bevan JC, Merrick PM, Blackstock D, Popovic V. Propofol anaesthesia reduces early postoperative emesis after paediatric strabismus surgery. *Canadian Journal of Anaesthesia* 1993; **40**: 927–933.
98. Weir PM, Munro HM, Reynolds PI, Lewis IH, Wilton NCT. Propofol infusion and the incidence of emesis in pediatric outpatient strabismus surgery. *Anesthesia and Analgesia* 1993; **76**: 760–764.
99. Korttila K. Recovery from propofol: does it really make a difference? *Journal of Clinical Anesthesia* 1993; **5**: 443–446.
100. Dexter F, Tinker JH. Comparisons between desflurane and isoflurane or propofol on time to following commands and time to discharge. A metaanalysis. *Anesthesiology* 1995; **83**: 77–82.
101. Tramèr M, Moore A, McQuay H. Propofol-anaesthesia and postoperative nausea and vomiting: quantitative systematic review of randomised controlled studies. *British Journal of Anaesthesia* 1997; **78**: 247–255.
102. Bazin JE. Utilisation du Diprivan en chirurgie laparascopique. *Annales Françaises d'Anesthésie et de Réanimation* 1994; **13**: 549–553.
103. Mackay P. Fatal cardiovascular collapse following propofol induction in high-risk patients. *Anaesthesia and Intensive Care* 1996; **24**: 125–126.