

CLINICAL PRACTICE



Survival from perioperative anaphylaxis in Western Australia 2000–2009

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Editor's key points

- This study aimed to determine the actual perioperative anaphylaxis mortality rate by analysing two West Australian databases (Anaesthetic Mortality Committee database and Anaesthetic Drug Reaction Clinic database).
- They found no deaths related to perioperative anaphylaxis in the decade 2000–2009, despite at least 264 cases of perioperative anaphylaxis with a 95% confidence interval (CI) of 0/264 mortality rate being 0–1.4%.

Background. The mortality from perioperative anaphylaxis has recently been quoted in a range between 3 and 9%. However, it was our impression in Western Australia that we had had no deaths from perioperative anaphylaxis for over a decade. As we have comprehensive processes in place to investigate both perioperative anaphylaxis and anaesthesia-related deaths, we undertook this study to determine our actual perioperative anaphylaxis mortality rate.

Methods. We obtained the number of deaths related to perioperative anaphylaxis for the decade 2000–2009 from the database of the West Australian Anaesthetic Mortality Committee; in Western Australia it is a legal requirement to report all deaths that occur within 48 h of an anaesthetic, and all deaths due to a complication of an anaesthetic. We obtained the number of cases of perioperative anaphylaxis for the same period from the database of the West Australian Anaesthetic Drug Reaction Clinic.

Results. From 2000 to 2009, there were 45 anaesthesia-related deaths in Western Australia, but none of these involved anaphylaxis. Over this period, there were 264 cases classified by the West Australian Anaesthetic Drug Reaction Clinic as anaphylaxis. The 95% confidence interval for the observed 0/264 mortality rate is 0–1.4%. There were about three million anaesthetics administered in Western Australia over the decade, giving a perioperative anaphylaxis rate of ~1:11 000.

Conclusions. Our incidence of perioperative anaphylaxis was within expectations, but our mortality rate was lower than recently quoted figures. It is likely that the current true perioperative anaphylaxis mortality rate is within the range 0–1.4%.

Keywords: anaphylaxis; anaesthetic; complications, death

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The mortality rate from anaphylaxis when it occurs in the perioperative period has recently been quoted in a range between 3 and 9%.^{1–2} However, the true current mortality rate from perioperative anaphylaxis is far less clear. The 3–9% range is often not supported by original source data or relates to data obtained in the 1980s or early 1990s. In many cases, the rate appears to have been extrapolated from other mortality reports.^{3–6} In contrast to these figures, it was our impression in Western Australia that although the incidence of perioperative anaphylaxis appeared to be similar to other reports, there had been no deaths related to perioperative anaphylaxis for over a decade.

In order to calculate the mortality rate for perioperative anaphylaxis it is necessary to identify the number of deaths related to perioperative anaphylaxis and the number of cases of perioperative anaphylaxis in the index period. 'Perioperative' in this context usually refers to the period from the induction of anaesthesia to discharge from anaesthesia

care. As we have comprehensive systems in place in Western Australia for investigating and recording both perioperative anaphylaxis and anaesthesia-related deaths, we undertook this study to determine our actual state-wide mortality rate for perioperative anaphylaxis for the decade 2000–2009.

Methods

The number of deaths due to a suspected anaphylactic reaction occurring between the induction of anaesthesia and 48 h after operation was obtained from the database of the West Australian Anaesthetic Mortality Committee. In Western Australia, it is a legal requirement for anaesthetists or others involved in the care of a patient who dies during or within 48 h of an anaesthetic to report the death to the West Australian Anaesthetic Mortality Committee, irrespective of the presumed cause of death (West Australian Health Act Section 336B.1).⁷ Moreover, if a death occurs after the 48 h

period, but is suspected of being related to a complication of anaesthesia, there is a similar legal requirement to report the death (Section 336B.2).⁷ The role of the Committee is to determine whether there is a possible anaesthetic contributory factor in the death, and where necessary to make recommendations to the West Australian Department of Health in order to improve anaesthetic safety in Western Australia. The Committee has broad representation from anaesthetic and other professional organizations in Western Australia, and input from a general practitioner and a clinical nurse (and when necessary by a surgeon or obstetrician) (Section 340BB.2–4),⁷ and is afforded legal privilege and confidentiality under the Act (Section 336B.7).⁷ Confidentiality is further supported by a provision in the West Australian Health Services (Quality Improvement) Bill 1994.⁸ The Committee assesses anaesthetists' reports and where necessary patients' medical records. All information is de-identified in relation to the anaesthetist involved, the hospital, and the patient. With this mandatory reporting and comprehensive assessment process in place, we anticipated that all deaths associated with perioperative anaphylaxis for the index period would be identified. The Health Act also has provision for publication of de-identified data in scientific journals (Section 340BL),⁷ affording permission to publish relevant findings.

The number of cases of perioperative anaphylaxis was obtained from the West Australian Anaesthetic Drug Reaction Clinic database. This clinic, which provides a state wide service, is based at Sir Charles Gairdner Hospital. All cases of suspected anaphylaxis referred to the clinic for investigation from January 2000 to December 2009 were included. As this is the only specific anaesthetic allergy investigation service in Western Australia, and all anaesthetists are expected to refer patients with suspected anaphylactic reactions for investigation, advice, and follow-up, we expected to identify the vast majority if not all cases of perioperative anaphylaxis over this period. Accessing the database for the purposes of obtaining de-identified data to calculate the perioperative anaphylaxis mortality rate was registered as a Quality Improvement project at Sir Charles Gairdner Hospital.

Anaphylaxis was defined with reference to the position papers of the World Allergy Association,⁹ and the British Society for Allergy and Clinical Immunology,¹⁰ with the aim of being consistent with previous large surveys of anaesthesia-associated anaphylaxis. These surveys were conducted using data collected by the Perioperative Anaphylactoid Reactions Study Group (GERAP) in France, most recently for the periods 1999–2000 and 1997–2004.^{3 11} Perioperative anaphylaxis is defined here as an acute, potentially life-threatening hypersensitivity reaction, involving the release of pre-formed mediators from mast cells or basophils, and occurring after induction of anaesthesia and before discharge from anaesthesia care. These cases were then subdivided on the basis of subsequent investigation (skin-prick, intradermal testing, or demonstration of serum-specific antibodies) into allergic (usually IgE-mediated) or non-allergic anaphylaxis.¹²

The severity of each reaction was graded according to the four-level scale for perioperative anaphylaxis used by Mertes and colleagues^{3 11} when reporting GERAP data. Grade 1 is defined as the presence of generalized cutaneous signs only. Grade 2 requires measurable, but not life-threatening symptoms, including a decrease in arterial pressure by >30%, in association with unexpected tachycardia and cutaneous signs, cough, or difficulty in mechanical ventilation. Grade 3 requires the presence of life-threatening reactions including cardiovascular collapse, severe bronchospasm, or both, while Grade 4 requires circulatory or respiratory insufficiency or cardiac arrest.

From the numerator and denominator obtained the mortality rate was determined, and its 95% CI was calculated.

We obtained the number of anaesthetics administered in Western Australia over the period January 1, 2000 to December 31, 2008 from the West Australian data presented in the last three triennial 'Safety of Anaesthesia in Australia' reports (2000–2002, 2003–2005, and 2006–2008) published by the Australian and New Zealand College of Anaesthetists.^{13–15} We extrapolated the 2009 number from the 2006–2008 data, allowing for an increase proportional to the increase in population in Western Australia from 2008 to 2009 (2.7%).¹⁶

Results

During the decade January 2000 to December 2009 there were 895 deaths reported to the West Australian Anaesthetic Mortality Committee. Forty-five of these were classified by the West Australian Anaesthetic Mortality Committee as anaesthesia-related (Categories 1–3 of the ANZCA Mortality Classification).¹⁵ However, none of the deaths were considered by the Committee to have been either directly or indirectly related to anaphylaxis.

Between January 1, 2000 and December 31, 2009, there were 264 cases investigated by the West Australian Anaesthetic Drug Reaction Clinic that were classified as perioperative anaphylaxis. The median age of the patients was 45 years (range 5–91 years, 69% female). Of these, 175 were confirmed as IgE-mediated, for which hypersensitivity to the trigger was demonstrated with skin testing (median age 45 years, range 5–91 years, 70% female). The remaining 89 had a clinical picture consistent with anaphylaxis (severe sustained hypotension or bronchospasm, and tachycardia or rash), but hypersensitivity could not be demonstrated on skin testing (median age 45 years, range 6–82 years, 67% female). The severities of the 264 reactions are given in Table 1.

There were a further 29 cases of isolated intraoperative bronchospasm, for which it was difficult to distinguish an allergic cause from poorly controlled asthma or other non-allergic cause. There were a further seven cases of isolated hypotension, which had no other features suggestive of an allergic mechanism. There were 23 cases of isolated urticaria and 18 cases of isolated angioedema that presented in the post-anaesthesia care

Table 1 Severity of anaphylactic reactions in Western Australia 2000–2009. Severity grade based on the classification used by Mertes and colleagues.³ CPR, cardiopulmonary resuscitation; ICU, intensive care unit

Severity	IgE mediated (n=175)	Non-IgE mediated (n=89)
Grade 1	25 (14%)	48 (54%)
Grade 2	31 (18%)	21 (24%)
Grade 3	89 (51%)	19 (21%)
Grade 4	30 (17%)	1 (1%)
Surgery abandoned	79 (45%)	19 (21%)
CPR required	20 (11%)	0 (0%)
Postoperative ICU required	83 (47%)	16 (18%)

unit or later. None of these additional 77 cases were classified as anaphylaxis.

As the estimated number of anaesthetics performed for the decade was about three million, the perioperative anaphylaxis rate was ~1:11 000 anaesthetics. The 95% CI for the 0/264 mortality is 0–1.4%.¹⁷

Discussion

These findings confirm our impression of a lower mortality from perioperative anaphylaxis in Western Australia than would be expected from recently quoted figures. We had no deaths related to perioperative anaphylaxis despite at least 264 cases of perioperative anaphylaxis over the decade studied. The 95% CI for this zero mortality rate is 0–1.4%. Even the upper limit of this interval is less than half the lower limit of the range recently quoted (3–9%).^{1,2} Our findings suggest that the previously quoted mortality rates for perioperative anaphylaxis may now be considered an overestimate.

The accuracy of our observed mortality rate depends on the accuracy of both the numerator (number of deaths due to perioperative anaphylaxis in the index period) and the denominator (number of cases of perioperative anaphylaxis in the index period). We are confident that the numerator is correct. None of the deaths reported to the West Australian Anaesthetic Mortality Committee over the study period had a clinical presentation suggestive of anaphylaxis. Moreover, it is unlikely that a death associated with anaphylaxis would not have been reported to the Committee. Anaphylaxis is a rare complication of anaesthesia, and death due to anaphylaxis would attract considerable attention within the anaesthesia community. The cause of such an unexpected death would also come under scrutiny and would typically require an investigation by the State Coroner. Under these circumstances it would be unlikely that the anaesthetist involved would not fulfil his or her legal obligation to report the death. This would pertain even if the death occurred some time later as a result of a complication occurring during the anaphylaxis episode.

Similarly, we are confident that we obtained an accurate denominator (number of cases of perioperative anaphylaxis). All 264 cases met established criteria for an anaphylactic reaction, and all occurred in the perioperative period. While it is possible that some cases of perioperative anaphylaxis were not reported to the West Australian Anaesthetic Drug Reaction Clinic for investigation and follow up, it is unlikely. The follow-up of perioperative anaphylaxis is essential to avoid a repeat occurrence with future anaesthetics, and would be considered a standard of care. However, in the event that some cases of perioperative anaphylaxis were not referred for investigation, the denominator would be larger not smaller, and the upper limit of the 95% CI would be <1.4%.

The observed incidence of perioperative anaphylaxis over the study period (~1:11 000) was within expectations, as the incidence reported from previous studies ranges from ~1:10 000 to ~1:20 000.^{1–3} The relative proportions of both IgE mediated and non-IgE mediated, and the various grades of severity of reactions were also similar to previous reports.³ This latter finding indicates that our low mortality rate was not related to a skewed sample of mostly mild reactions or non-IgE mediated reactions. Sixty-six per cent of the reactions were IgE mediated, and 68% of these were Grade 3–4; many involved abandoning surgery, a cardiac arrest, and postoperative transfer to an intensive care unit. While the severity was less in the non-IgE mediated group as expected, 22% of their reactions were also classified as Grade 3–4.

In an editorial in late 2011, Levy and Castells¹ quoted ‘a mortality rate of 4%’ for perioperative anaphylaxis, citing two previous articles, one by Mertes and colleagues³ in 2003, and the other by Sampson and colleagues⁴ in 2005.⁴ However, the Mertes article, which describes the results of a survey on anaphylactic and anaphylactoid reactions occurring during anaesthesia in France from 1999 to 2000, does not specifically mention a mortality rate.³ The article by Sampson and colleagues includes a comment that the ‘mortality rate is ~4%’, citing the same article from 2003,³ and another publication by Hepner and Castells¹⁸, also from 2003. Hepner and Castells refer to the possibility of cardiovascular collapse and death, but like the publication from Mertes and colleagues, do not specifically mention a mortality rate.

In a review of perioperative anaphylaxis in 2010, Mertes and colleagues² state that the ‘reported expected mortality ranges from 3% to 9%’. They cite an article by Mitsuhashi and colleagues published in 1992, which reported a mortality rate of 4.6%, calculated on the basis of five deaths from 105 case reports in Japanese anesthesiology-related journals between 1952 and 1990.⁶ They also cite an article by Light and colleagues⁵ on the relationship between gender and adverse effects of neuromuscular blocking agents, based on data obtained from yellow card reporting in the UK from 1967 to 2000. This latter study reported a mortality rate of 9% for anaphylactic reactions across the range of neuromuscular blocking agents, with 22% mortality for reactions to

succinylcholine. However, there were only 998 reports over the 33-year period, which would most likely be a small proportion of the total number of anaphylactic reactions that occurred. In any event, both the Mitsuhata and colleagues and Light and colleagues studies include mortality data from the 1960s, 1970s, and 1980s, which may not be representative of more current mortality rates.

Another recent review¹² referred to a French survey of anaesthesia-related mortality published by Lienhart and colleagues¹⁹ in 2006, which reported that 3% of all anaesthesia-related deaths involved anaphylaxis. They also referred to the updated guidelines of the Association of Anaesthetists of Great Britain and Ireland, published in 2009, which stated that 10% of all anaesthesia-related reactions reported to their agency over a 6-year period were fatal.²⁰ However, neither article provided a mortality rate for perioperative anaphylaxis.

Although we are not aware of any recent reports of mortality rates related to perioperative anaphylaxis from other states in Australia, rough estimates can be extrapolated from the triennial 'Safety of Anaesthesia in Australia' reports (2000–2002, 2003–2005, and 2006–2008).^{13–15} Over the three reports, there were 27 deaths in which an adverse drug event (not related to drug selection or dosage) was considered a causal or contributory factor. The reports covered a total of ~20 million anaesthetics. There is no figure for the number of perioperative anaphylactic reactions that occurred over this period, but using the rate we observed in Western Australia (~1:11 000), the estimated number would be ~1800. If all 27 'adverse drug events' were perioperative anaphylaxis, the perioperative anaphylaxis mortality rate would be 27/1800=1.5%. However, not all the 27 adverse drug events were necessarily perioperative anaphylaxis. Other adverse reactions to anaesthetic drugs such as hyperkalemia after succinylcholine, intravascular injection of local anaesthetic, and malignant hyperthermia would also fall into this category. Therefore, the mortality rate for perioperative anaphylaxis would most likely be slightly less. While these estimates should be interpreted with caution, because the exact denominators are not known, they nevertheless support a rate of <1.5%, not the 3–9% range recently quoted.

There is no reason to expect a lower mortality rate from perioperative anaphylaxis in Western Australia in comparison with any other Australian state, or indeed any developed country. It is more likely that the true mortality rate for perioperative anaphylaxis in developed countries is within the 95% CI of our observed rate (0–1.4%). This low rate may be a result of better education on the management of perioperative anaphylaxis, particularly on the importance of early diagnosis and treatment, and the availability of guidelines.^{18 21 22} The use of simulation to improve team management of anaesthesia crises, including anaphylaxis, may also have contributed to reduced mortality.

A reduction in the mortality rate from perioperative anaphylaxis over the last 20–30 years would be consistent

with the overall reduction in anaesthetic mortality from other causes that has occurred over this time. For example, for the 1985–1987 triennium, the anaesthesia-related mortality rate in Australia was ~1:36 000,²³ whereas the rate in the most recent triennial report (2006–2008) was only ~1:55 000.¹⁵ Moreover, the rate for anaesthesia-caused mortality (in which perioperative anaphylaxis would most likely be included) has fallen even further, from ~50% of all anaesthesia-related deaths in the 1985–1987 triennium,²³ to ~15% in the 2006–2008 triennium.¹⁵ A review of anaphylaxis by Fisher²⁴ in 1987 quoted a mortality rate from anaphylaxis of 3–9%. It is unlikely that the rate would not have fallen over the intervening 25 years.

One of the important limitations of this study is the absence of information on long-term serious morbidity related to perioperative anaphylaxis. Unlike mortality, there is no requirement in Western Australia to report serious morbidity. For this reason, we did not include serious morbidity in this study.

In summary, using the comprehensive processes for reporting anaesthetic mortality and investigating perioperative anaphylaxis in Western Australia, we have confirmed that there were no deaths related to perioperative anaphylaxis in the decade 2000–2009, despite at least 264 cases of perioperative anaphylaxis. The 95% CI for this 0/264 mortality rate is 0–1.4%. We feel that the true mortality rate for perioperative anaphylaxis in developed countries is most likely in this range, and that the higher rates recently reported should now be considered an over estimate.

Authors' contributions

N.M.G. obtained the anaesthetic mortality data. P.H.S., R.C.C., and P.R.P. obtained the anaphylactic reactions data. All four authors were involved in the analysis of the data and preparation of the manuscript.

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Declaration of interest

N.M.G. was Chairman of the West Australian Anaesthetic Mortality Committee during the study period. P.H.S., R.C.C., and P.R.P. provide the investigation and advisory services in the West Australian Anaesthetic Drug Reaction Clinic.

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