CRASH
Colorado Review of Anesthesia for Surgicenters And Hospitals
Guiding the future of patient care

Serious Adverse Drug Reactions in Anesthesia

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Anesthesiology
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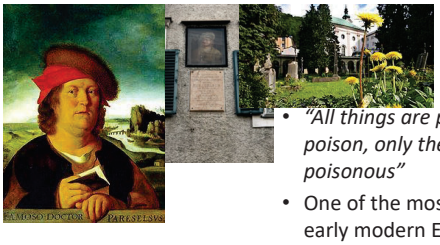
- Anesthesiology – *the art of balancing desirable effects with side effects*
- The specialty has evolved to minimize and manage adverse drug reactions inherent in all anesthetics
  - Respiratory depression
  - Airway obstruction
  - Cardiovascular depression
  - Cardiac arrhythmias
  - Idiosyncratic reactions – malignant hyperthermia, anaphylaxis

Paracelsus, father of toxicology



- *"All things are poison and nothing is without poison, only the dose permits something not to be poisonous"*
- One of the most influential medical scientists in early modern Europe

Paracelsus (Phillippus Aureolus Theophrastus Bombastus von Hohenheim)
Born 1493 in Einsiedeln Switzerland – Died 1541 in Salzburg, Austria at 48 yr old

Renaissance physician, botanist, alchemist, astrologer, and occultist

Adverse drug reactions

- A potentially harmful untoward outcome of therapeutic drug administration
- Major cause of morbidity and mortality worldwide
- Serious ADRs occur in 6-7% of hospitalized patients ($2x10^6$/year), and are fatal in 0.15-0.3% (10^5/year)
- Contribute $billions to healthcare costs

Definition

- World Health Organization: "harmful, unintended reactions to medicines that occur at doses normally used for treatment are called **adverse drug reactions**"
- Assumes that all individuals are "normal" (patients are not)
- Does not consider pathophysiological factors or drug/toxin interactions
- Does not distinguish from predictable side effects

Traditional Classification of ADRs

- Two major types: A and B
  - *Type A*: **frequent, predictable** based on pharmacodynamic and pharmacokinetic properties
    - Dose-dependent (eg hypotension with nifedipine, bleeding with warfarin)
    - Toxicity, side effects, overdose
    - Interactions/indirect
  - *Type B*: **rare, idiosyncratic**/unpredictable
    - Mechanisms often unclear
    - Dose-independent (anaphylaxis)
    - Individual susceptibility (pharmacogenetic, immunologic)

Current Classification of ADRs

- A – Augmented - dose related
- B – Bizarre - drug idiosyncracy, not dose related
- C – Chronic - direct organ damage, dose related and time related
- D – Delayed - time related
- E – End of use - withdrawal
- F – Drug failure

Not included: Medication errors

•Edwards R, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *The Lancet* 2000; 356: 1255-9

Medication errors

- *Preventable event* that can cause or lead to inappropriate medication use or patient harm (National Coordinating Council for Medication Errors Reporting and Prevention)
- Wrong drug, wrong dose, wrong time
- Single most preventable error
- The OR is the "black hole of medication safety"
  - Most drugs are high risk; 10^5 doses/yr average
  - Account for >80% of error reports, 5-fold greater than rest of hospital (Fedorko, 2012)
  - 60% due to incorrect ampoule or labeling

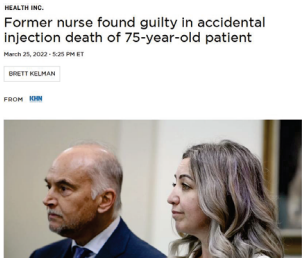
Drug administration errors

- Cause an estimated 7000 deaths/year in the USA
- "Syringe swap" a common error
- At least one medication error/hospital patient/day (http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=11623)
- *Dennis Quaid Recounts Twins' Drug Ordeal: Actor Tells 60 Minutes' Steve Kroft Medical Errors Kill Thousands* (Aug. 24, 2008)
- Occur in 1/133 anesthetics
- Patient safety a major issue with IOM
  - Preventing Medication Errors (2006)

Drug administration errors

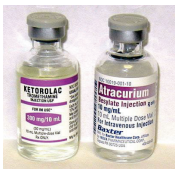
- Verdict against Vanderbilt nurse RaDonda Vaught for death of Charlene Murphey
- Guilty of gross neglect and negligent homicide in wrong drug error: vecuronium for midazolam
- Likely system error
- Unintended consequences of prosecution
- Reduced reporting and less safety

Goes against just culture



Medication errors in anesthesia

- Of 1120 anesthesia medication errors, 15 (1.3%) resulted in severe harm or death
  - Errors are quite common, but severe errors uncommon
  - Most are preventable



Catchpole et al. (2008) Safety in anaesthesia: a study of 12,606 reported incidents from the UK National Reporting and Learning System. Anaesthesia; 63:340–6

Medication errors in anesthesia: ICU

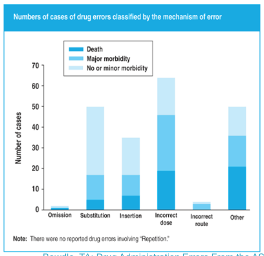
- In an ICU audit, 2428 medication incidents involving 355 different drugs
  - Most common:
    - morphine (207 incidents)
    - gentamicin (190 incidents)
    - norepinephrine (133 incidents)
  - Drugs most commonly associated with patient harm were norepinephrine (55 incidents) and insulin (48 incidents)

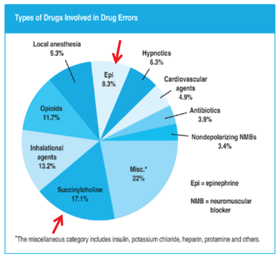
Thomas & Panchagnula (2008) Medication-related patient safety incidents in critical care: a review of reports to the UK National Patient Safety Agency. Anaesthesia; 63:726–33

ASA Closed Claims Review

- 205 drug errors out of 5803 cases (3.5%)
- Many serious
- Succinylcholine and epinephrine stand out

Figure 1

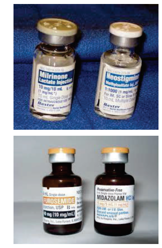




Bowdle, TA: Drug Administration Errors From the ASA Closed Claims Project. *ASA Newsletter* 67(6): 11-13, 2003

Prospective studies on medication errors in anesthesia

	New Zealand	*South Africa*
Number of anesthetics	10 806	30 412
Response rate (%)	72	53
Incidence of error or near miss (%)	0.75	0.36
Adverse outcomes (actual numbers)	3	5
Incorrect dose (%)	32	23
Substitution (%)	27	60
Omission (%)	19	4
Repetition (%)	11	6
Wrong route (actual numbers)	2	7
Error rate	**1/133**	**1/274**



Translates into one error/near miss for every 133 anesthetics in the New Zealand study and one error/near miss for every 274 anesthetics in the South African study (Anaesth Intensive Care 2001; 29:494–500; 2009; 37:93–8)

- WHO (2017) goal to reduce medication errors by 50%

In summary, if the WHO aspirations to reduce medication error are to be met, methods will need refining in the ways we suggest, to compare improvements against previous work and reported incidences.

WHO. *Medication without harm — global patient safety challenge on medication safety*. Geneva: World Health Organization; 2017. Available from: https://apps.who.int/iris/bitstream/handle/10665/255263/WHO-HIS-SDS-2017.6-eng.pdf. [Accessed 30 December 2020]

BJA

British Journal of Anaesthesia, 127 (3): 458–469 (2021)

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Advance Access Publication Date: 6 July 2021
Review Article

QUALITY AND PATIENT SAFETY

An integrative review of method types used in the study of medication error during anaesthesia: implications for estimating incidence

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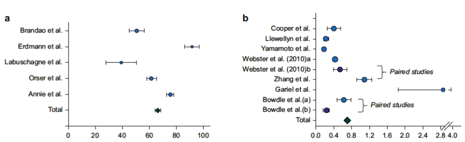
This article is accompanied by an editorial: The evolution of methods to estimate the rate of medication error in anaesthesia by Craig S. Webster, *Br J Anaesth* 2021:127:346–349, doi: 10.1016/j.bja.2021.06.008



Patterns of errors

Editor's key points

- Medication-related adverse events are a frequent cause of patient morbidity and mortality in perioperative care, and must be better understood in order to prevent medication harm.
- Data from a bi-national, multi-centre system focused on perioperative and critical care were analysed, in particular the incidence and characteristics of medication-related adverse events over a 10-yr period.
- Of 7072 incidents analysed, 1970 adverse events were identified, with 31% resulting in patient harm, most frequently in the administration phase.
- Patient harm was more likely in errors involving vasoconstrictor agents, benzodiazepines, and neuromuscular blocking agents.

40% of errors:

- Anticoagulants
- Vasoconstrictors
- Opioids

BJA

British Journal of Anaesthesia, 124 (2): 197–205 (2020)

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Advance Access Publication Date: 25 November 2019
Quality and Patient Safety

QUALITY AND PATIENT SAFETY

Patterns in medication incidents: A 10-yr experience of a cross-national anaesthesia incident reporting system

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Safety bundle: effective in reducing errors

Editor's key points

- Medication errors are a significant concern in anaesthesia patient safety.
- The effects of facilitated reporting and sequential interventions to reduce medication errors were analysed in a single large academic medical centre.
- Using facilitated self-reporting of errors, implementation of a medication safety bundle including smart infusion pumps, and then of a barcode-based medication safety system, was analysed.
- Both interventions resulted in a reduction in facilitated self-reported rates of errors and intercepted errors.
- Further research is needed to clarify the interventions that most effectively prevent anaesthesia medication errors.

Table 1 Relationship between syringe swap, vial swap, and infusion-related errors and various countermeasures

Error type	2002–2003	Countermeasure 2014	Countermeasure 2014–2015
Syringe swap	Syringes prepared by providers from vials, labels made by providers by hand, few prefilled syringes with proper labels	Increased use of prefilled syringes with proper labels (reduction of provider prepared, hand-made labels), coloured syringe plungers or 'flags' for high risk drugs (epinephrine, phenylephrine)	Barcode-based drug safety system with proper labels for all syringes, facility for scanning barcode on syringe label before administration
Vial swap	Few prefilled syringes, high risk vials present in drug trays (epinephrine, phenylephrine)	Increased use of prefilled syringes, removal of high risk vials (epinephrine, phenylephrine)	Barcode-based drug safety system
Infusion related	Infusion pumps without medication menus, infusion concentrations seldom standardised, many infusions prepared by providers instead of pharmacy	Smart infusion pumps, standardised infusion concentrations, pharmacy prepares all drugs for infusion	Smart infusion pumps, standardised infusion concentrations, pharmacy prepares all drugs for infusion

BJA

British Journal of Anaesthesia, 121 (6): 1338–1345 (2018)

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Advance Access Publication Date: 20 October 2018
Quality and Patient Safety

QUALITY AND PATIENT SAFETY

Facilitated self-reported anaesthetic medication errors before and after implementation of a safety bundle and barcode-based safety system

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This article is accompanied by an editorial: Feedback and constraints: rethinking medication safety countermeasures by Grigg & Litman, *Br J Anesth* 2018:121:1188–1190, doi: https://doi.org/10.1016/j.bja.2018.08.003.

NHS recommendations to reduce the risk of drug error in anesthesia

1. Anaesthetists should be **aware** of the risks of drug errors and ensure that checking procedures are in place. Errors often occur in situations of haste, distraction or fatigue.
2. **Lighting** of the operating room environment is critical for safety. In situations of reduced lighting, specific arrangements should be made for checking anesthetic drugs.
3. Drug **storage** arrangements should be consistent in all anesthetic care delivery units.
4. Ampoules should be **read and re-read** before drugs are drawn up into a syringe. Errors are unlikely to be detected once the syringe is prepared.
5. Drugs are **prepared** by the person who will administer them, immediately before use.
6. Syringes should be **labeled** with the name and concentration.
7. Syringes intended for an **emergency** should be stored away from the immediate work area.
8. The international **color-coded syringe labeling** system should be used.
9. Consider using **pre-filling syringes** for emergency drugs that are prepared by the pharmacy unit to assure quality of contents and accurate labeling.
10. **Pharmacists** should regularly visit the operating rooms to ensure safe drug use.
11. When drug manufactures, packaging and formulation changes, **anaesthetists should be alerted** to the change before the drugs are provided in the operating rooms.

http://www.dh.gov.uk/assetRoot/04/07/15/07/04 071507.pdf

Adverse drug reactions

An *injury* caused by medical management rather than the underlying condition of the patient (Institute of Medicine)

A *Augmented* (dose-related)—an abnormal pharmacodynamic response to a drug, for example, sensitivity to an opioid drug resulting in respiratory depression.

B *Bizarre* (idiopathic; non-dose-related)—anaphylactic or anaphylactoid reactions.

C *Chronic* (dose-related and time-related)—due to prolonged exposure to a drug, for example, renal failure secondary to ketorolac.

D *Delayed* (time-related)—teratogenesis seen with thalidomide.

E *End of use* (withdrawal)—suppression of the hypothalamic–pituitary–adrenal axis after prolonged steroid therapy.

F *Failure* (unexpected failure of a therapy)—awareness under general anesthesia.

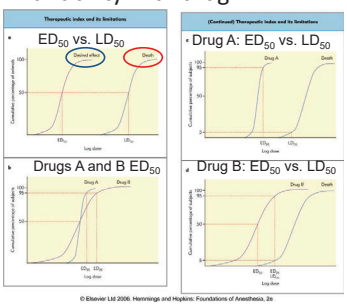
Glavin RJ (2010) Drug errors: consequences, mechanisms, and avoidance. Br J Anaesth;105:76-82

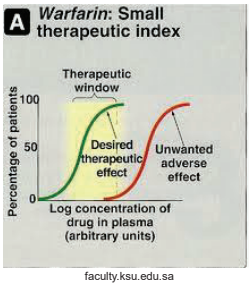
Therapeutic index

- Propensity for predictable ADRs described by therapeutic index:
  - Ratio of LD_{50} (lethal dose in 50%) to ED_{50} (effective dose in 50%)
- Limited by population variability in effects
- *Certain safety factor* is a more clinically useful concept to describe drug intolerance:
  - Toxic dose producing adverse effect vs. effective dose in a specified percentage of the population (depending on severity of unwanted effect)
  - For 1%, TD_1/ED_{99}

Therapeutic index limitations

- Two drugs with same ED_{50} but greater variability with drug B





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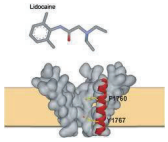
Specific examples

- Drug toxicity
  - Local anesthetics (covered previously)
- Idiosyncratic drug reactions
  - Pharmacogenetics
  - Long QT syndrome
  - Plasma cholinesterase deficiency
  - Malignant hyperthermia
  - Allergic drug reactions (anaphylaxis/anaphylactoid)

A. Augmented: Local anesthetic toxicity

- Able to monitor and treat most common adverse anesthesia drug reactions
  - Hypotension, hypoventilation
- Local anesthetic systemic toxicity (LAST) difficult to treat; prevention is key
- LAs act by blocking voltage-gated Na^+ channels essential for neuronal function
- Multiple off-target effects as well
- Selectivity based on precise delivery
  - UGRA



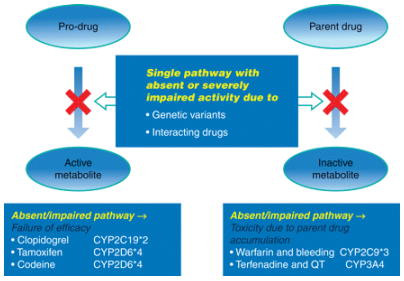
Immediate treatment of LAST

- Stop injecting/Call for help
- ABC: intubate, 100% O_2, IV access
- Control seizures: benzos, *not* propofol
- CPR/alert CPB team
- Consider lipid emulsion rescue therapy
  - 1.5 ml/kg bolus of 20% Intralipid over 1 min infusion of 0.25-0.5 ml/kg/min
  - Can be repeated for persistent CV collapse
  - Supported by anecdotal case reports and laboratory studies only
  - http://www.lipidrescue.org/

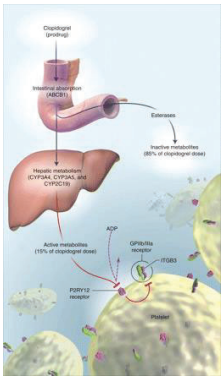
B. Bizarre: Idiosyncratic drug reactions

- Most currently unpredictable
- Identifying genetic risk factors is changing this
- Gene-linked adverse drug reactions (ADRs)
  - Glucose-6-phosphate dehydrogenase polymorphisms with hemolytic anemia
  - Plasma cholinesterase deficiency and prolonged succinylcholine duration
- Polymorphisms in drug-metabolizing enzymes or drug target genes
  - Patients with CYP 2C9*2 and CYP 2C9*3 genetic variations have increased risk of bleeding with warfarin; change in label

Genetically based bioavailability of the active compound

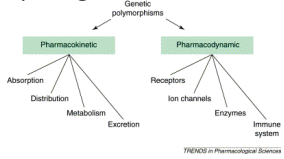


Barash & Akhtar (2010) Coronary stents: factors contributing to perioperative major adverse cardiovascular events. Br J Anaesth;105 Suppl 1:i3-15.



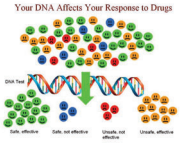
Pharmacogenomics

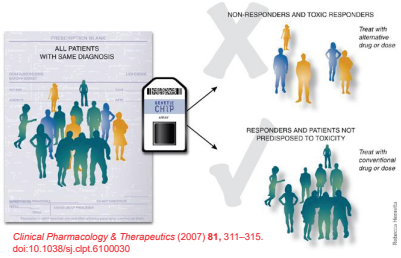
- Genetic contribution to idiosyncratic ADRs appreciated since the 1950s
  - Plasma cholinesterase deficiency, G6PD variants
- Whole genome single nucleotide polymorphism (SNP) profiling might allow unbiased method of determining genetic predisposing factors for ADRs



Pharmacogenomic approach to personalized medicine

- Drug therapy chosen for each patient based on particular genetic profile

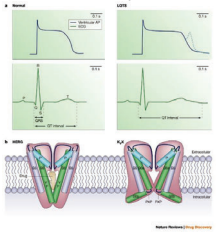


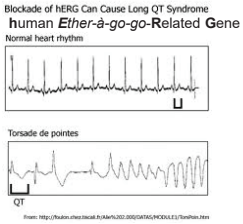


Clinical Pharmacology & Therapeutics (2007) **81**, 311–315. doi:10.1038/sj.clpt.6100030

Drug-induced long QT syndrome

- Common cause for drug withdrawal by manufacturer
  - terfenadine (Seldane)
- Led to controversial black box warning for droperidol
- Polymorphisms in genes associated with congenital LQTS implicated as risk factors (KCNQ1, KCNH2 (HERG))





Drug-induced long QT syndrome

- Frequently related to polypharmacy and drug-drug interactions
  - Pharmacodynamic (antiarhythmic/quinolone)
  - Pharmacokinetic (terfenadine/CYP3 A4 inhibitors)
- At least 1 QTc prolonging drug in >20% patients, 2 in >9%
- Additional risk factors:
  - Electrolytes: hypokalemia, hypomagnesemia
  - Renal failure
  - Age, female (70%)
  - Cardiac: bradycardia, LVH, CHF
  - Genetic LQTS

Plasma cholinesterase deficiency

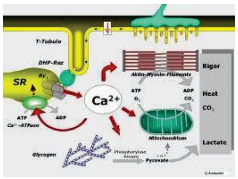
- Genetic variants identified by prolonged response to succinylcholine (scoline apnea)
- Autosomal recessive defect
- Currently detected by phenotyping with inhibitors

Table 10.2 Plasma cholinesterase variants

Name	Base change	Frequency	Enzyme activity (%)	Duration of action of sux
Usual	None	0.98	100	Normal
Atypical	A209T	0.02	30	2 hrs
Silent	G351A	0.0003	Zero	3–4 hrs
Fluoride	C728T	0.003	40	1–2 hrs
H type	G424A	?	10	2–3 hrs
K type	G1615A	0.0013	<1 hr	
J type	A1490T	?	34	1–2 hrs

The names of the variants were given after their characterization by enzyme activity and inhibitor studies. The variants are due to missense mutations in the plasma cholinesterase gene, which lies on chromosome 3. The normal duration of action of succinylcholine (sux) is 4–6 minutes, depending on the dose administered.

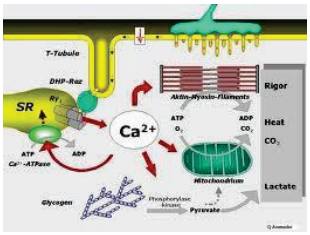
Malignant hyperthermia

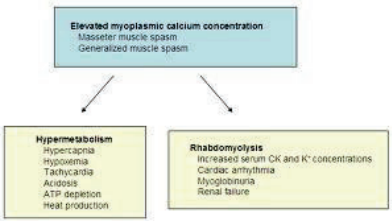


- First reported in 1960
- Autosomal dominant defect in intracellular Ca^{2+} regulation triggered by volatile anesthetics and succinylcholine
- >200 polymorphisms in RYR1 gene for the sarcoplasmic reticulum Ca^{2+} release channel; 29 produce functional defects compatible with MH; present in 70% of cases
- Molecular genetics and possible genetic test are not straightforward
  - Some mutations required in combination, or with other defects in Ca^{2+} regulation

Malignant hyperthermia: Mechanisms

- Unregulated Ca^{2+} release from sarcoplasmic reticulum





Malignant hyperthermia: Clinical signs

- **Early**
  - Increased $ETCO_2$
  - Muscle rigidity/spasm
  - Tachycardia
  - Metabolic and respiratory acidosis
  - Tachypnea
  - Sweating
- **Late**
  - Elevated temperature
  - Myoglobinuria
  - Increased CPK
  - DIC
  - Renal failure
  - Cardiac arrest

MH - Treatment

- Early recognition key/HELP
- Discontinue trigger/use TIVA
- Hyperventilate 100% O_2
- Dantrolene
- ABG, $NaHCO_3$ for acidosis
- Cool to 38-39ºC
- Diuresis
- Hyperkalemia, coagulopathy

http://www.mhaus.org/

2.5 mg/kg at 5-10 min intervals until signs resolve, then 10 mg/kg/day for 24 hours

Glucose, insulin and calcium should be available to treat hyperkalemia, bicarbonate to treat metabolic acidosis and a diuretic to maintain urinary output

http://www.mhaus.org/

Public backlash to MH deaths

Stephanie Kuleba case
18 yo death in elective breast surgery


wastedlives.eu

- "I believe GA should be banned from use in cosmetic surgery facilities" Tom Kuleba
- Sales of dantrolene spiked after this event

Doctors believe that malignant hyperthermia, a genetic disorder which causes an adverse reaction to anesthetics, may be to blame…claiming that Stephanie Kuleba ***received only a fraction of the drug that could have saved her*** from succumbing to malignant hyperthermia.

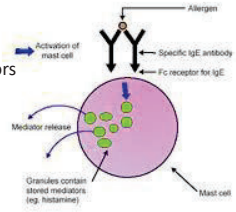
Allergic drug reactions

- Type I (immediate) acute hypersensitivity reactions 1/10-40,000 anesthetics
- ~50% of anaphylactic (IgE-mediated) or anaphylactoid (non-allergic anaphylaxis) reactions in anesthesia occur without prior exposure and are under-reported
- Muscle relaxants, latex, antibiotics (plasma substitutes, blood products, dyes, preservatives; opioids, amide local anesthetics rarely)
- Increased risk in women
- Latex allergy risk factors
  - Healthcare workers, children with urogenital abnormalities or spina bifida
  - Allergies to bananas, avocado, kiwi, chesnut

Hepner & Castells (2003) Anaphylaxis during the perioperative period. Anesth Analg; 97:1381-95

Anaphylaxis

- From the Greek ἀνά **ana**, *against*, and φύλαξις **phylaxis**, *protection*
- Immune mediated
- Acute inflammatory response
- IgE activation on mast cells
  - Degranulation of histamine and other factors
  - Complement activation
- No valid screening test
- Test dose not effective
- Usually immediate but up to 1 hr delay



Hepner & Castells (2003) Anaphylaxis during the perioperative period. Anesth Analg; 97:1381-95

Anaphylaxis - diagnosis and signs

- Vasodilation/hypotension, pulmonary hypertension
- Bronchospasm, airway edema
  - Difficult to treat with asthma or emphysema (air trapping), high mortality
  - Wheezing differential: reactive airways (light anesthesia), pulmonary edema, aspiration, pneumothorax, obstruction
- Itching/urticaria, dizziness, angioedema, sense of doom
- Vascular endothelium permeability increase
  - Edema, hypovolemia, circulatory arrest
- Differential
  - SIRS, cardiac tamponade, venous air embolism, pulmonary embolus

Clinical features in 555 patients (AAGBI)

Feature/Number of patients

- *No pulse 153*
- *Difficult to inflate lungs 140*
- *Flush 107*
- Desaturation 63
- Cough 40
- Rash 25
- ECG abnormality 13
- Urticaria 11
- Subjective 9
- Swelling 7
- No bleeding 2
- Other 19
- **Total 589**

- The commonest presentation is **cardiovascular** with **bronchospasm** and **skin** changes only slightly less common
- Factors which increase severity included asthma, beta blockade and neuraxial anesthesia (all associated with reduced endogenous catecholamine response)

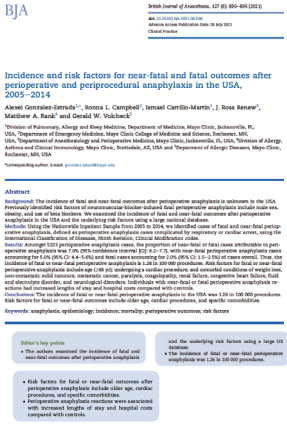
www.aagbi.org

Incidence


BJA

Epidemiology of suspected life-threatening perioperative anaphylaxis: a cross-sectional multicentre study in China

1:11000 similar to NAP6


BJA

Incidence and risk factors for near-fatal and fatal outcomes after perioperative and periprocedural anaphylaxis in the USA, 2005–2014

Perioperative anaphylaxis

Editor's key points

- Diagnosis is critical in suspected cases of perioperative anaphylaxis, but is often challenging under general anaesthesia, and there might be geographical differences in culprit allergens.
- The Japanese Epidemiologic Study for Perioperative Anaphylaxis (JESPA), a nationwide prospective study, assessed the utility of a newly developed tool for identifying patients with a high possibility of anaphylaxis.
- The combination of tryptase and histamine levels, skin tests, basophil activation test results, and the clinical score calculated based on clinical symptoms improved the certainty of anaphylaxis diagnosis.
- The incidence of perioperative anaphylaxis was about 1 in 5000 general anaesthesia cases, with anaphylaxis to rocuronium, sugammadex, and cefazolin the most common.

CLINICAL INVESTIGATION

The Japanese Epidemiologic Study for Perioperative Anaphylaxis, a prospective nationwide study: allergen exposure, epidemiology, and diagnosis of anaphylaxis during general anaesthesia

Tomonori Takazawa[1,*], Tatsuo Horiuchi[2], Kazuhiro Nagumo[2], Yuki Sugiyama[3], Tsubasa Akune[4], Yasuhiro Amano[5], Masataka Fukuda[6], Takashi Haraguchi[2], Chika Ishibashi[7], Eiki Kanemaru[8], Takao Kato[9], Keiichi Katoh[10], Takashi Kawano[11], Tsukasa Kochiyama[6], Michioki Kuri[12], Akihide Kurita[13], Yoshikazu Matsuoka[14], Takahiro Muramatsu[15], Masaki Orihara[1], Yutaka Saito[16], Nobukazu Sato[17], Toshie Shiraishi[18], Kaoru Suzuki[19], Miyuki Takahashi[20], Toshifumi Takahashi[21], Kumiko Tanabe[22], Akihiro Tomioka[23], Yukinari Tomita[24], Tatsuya Tsuji[25], Iwao Watanabe[26], Takashige Yamada[27], Nagahide Yoshida[28], Masao Yamaguchi[29] and Shigeru Saito[2]

Abstract

Background: Diagnosis of perioperative anaphylaxis is often challenging. This study describes the utility of a newly developed tool for identifying patients with a high possibility of anaphylaxis, and aimed to investigate the frequency of anaphylaxis with each drug during the perioperative period in Japan.
Methods: This study included patients with anaphylaxis of Grade 2 or higher severity during general anaesthesia at 42 facilities across Japan in 2019 and 2020. We developed and adopted a unique objective evaluation tool yielding a composite score for diagnosing anaphylaxis, which includes the results of skin tests and basophil activation tests, and clinical scores for perioperative anaphylaxis. The number of cases using each drug and the total number of anaphylaxis cases were investigated to calculate the frequency of anaphylaxis.
Results: General anaesthesia was performed in 218 936 cases, which included 55 patients with suspected perioperative anaphylaxis. The developed composite score diagnosed 43 of them with a high probability of anaphylaxis. The causative agent was identified in 32 cases. Plasma histamine levels showed high diagnostic accuracy for anaphylaxis. The top causative agents were rocuronium (10 cases in 210 852 patients, 0.005%), sugammadex (7 cases in 150 629 patients, 0.005%), and cefazolin (7 cases in 106 005 patients, 0.007%).
Conclusions: We developed a composite tool to diagnose anaphylaxis, and found that the combination of tryptase levels, skin testing, and basophil activation testing results and clinical score improved the certainty of anaphylaxis diagnosis. The incidence of perioperative anaphylaxis in our study was 1 in about 5000 general anaesthesia cases.
Clinical trial registration: UMIN000035350.

Keywords: antibiotics; basophil activation test; histamine; neuromuscular blocking agents; perioperative anaphylaxis; skin test; sugammadex; tryptase

Editor's key points

- Diagnosis of perioperative anaphylaxis is difficult because of its non-specific signs, and treatments vary between cases.
- This prospective study of perioperative anaphylaxis investigated the clinical signs, its severity, therapeutic drugs used, and epinephrine administration to assess trends and variability.
- Cardiovascular signs, usually hypotension, were the most frequent, followed by skin and respiratory signs, and the most frequently used drugs were epinephrine, antihistamines, and corticosteroids.
- Clinical signs and treatments of perioperative anaphylaxis were variable, indicating a need for further development of standardised approaches based on signs and severity.

CLINICAL INVESTIGATION

The Japanese Epidemiologic Study for Perioperative Anaphylaxis, a prospective nationwide study: clinical signs, severity, and therapeutic agents

Yuki Suigiyama[1], Tomonori Takazawa[2,*], Natsuko Watanabe[1], Kiyoko Bito[3], Tetsuhiro Fujiyoshi[4], Shinsuke Hamaguchi[5], Takashi Haraguchi[6], Tatsuo Horiuchi[6], Yoshinori Kamiya[7], Noboru Maruyama[8], Hitoshi Masumo[9], Harumasa Nakazawa[10], Kazuhiro Nagumo[6], Masaki Orihara[2], Jun Sato[11], Kenichi Sekimoto[12], Kenichiro Takahashi[13], Mutsumi Uchiyama[14], Kazunobu Takahashi[15], Masao Yamaguchi[16] and Mikito Kawamata[1]

Abstract

Background: Diagnosis of perioperative anaphylaxis is difficult because of its non-specific and variable signs and symptoms. Therapeutic agents used to treat anaphylaxis and anaesthesiologist responses also vary depending on the case, which might affect outcomes; however, only a few studies have focused on these factors.
Methods: This prospective study of perioperative anaphylaxis, a part of the Japanese Epidemiologic Study for Perioperative Anaphylaxis, investigated the clinical signs, its severity, therapeutic drugs, epinephrine administration, and anaesthesiologist responses in cases of perioperative anaphylaxis to assess trends and variability. Shock index was used to assess severity of cardiovascular collapse.
Results: In 43 patients analysed in this study, cardiovascular signs (88.4%) were the most frequent, followed by skin (81.4%) and respiratory signs (60.5%). The presence of signs increased during the clinical course. The median time from the first signs to diagnosis of anaphylaxis was 10 (5.0–17.8) min. The rates of epinephrine use were 30.2% (unused), 48.8% (i.v.), and 20.9% (i.m.). The median time from diagnosis of anaphylaxis to epinephrine administration was 7 (interquartile range: 1.5–8.0) min. Antihistamines and corticosteroids were each used in 69.8% of cases. The worst shock index was higher in patients who received i.v. epinephrine (2.77 [0.90] mean [standard deviation]) than in both no epinephrine use cases (1.35 [0.41]) and i.m. epinephrine cases (1.89 [0.77] (P<0.001]).
Conclusions: The clinical signs and treatments of perioperative anaphylaxis are variable, and the choice regarding epinephrine administration is based on symptom severity.
Clinical trial registration: UMIN000035350.

Keywords: anaphylaxis; epinephrine; perioperative anaphylaxis; symptoms; treatment

Table 4 Summary of drugs involved in anaphylaxis. The usage rate indicates the number of cases in which the drug was used as a percentage of all cases evaluated. Share shows the usage rate of a particular drug as a percentage of usage of all drugs in the same category. Five cases of anaphylaxis were caused by substances that were not evaluated in the number of use cases, including chlorhexidine in three cases, fibrin sealant in one case, and microcatheter in one case (Supplementary Table S1). CI, confidence interval; N/A, not applicable; NMBA, neuromuscular blocking agent.

Drug	Number of cases	Usage rate (%)	Share (%)	Anaphylaxis (n)	Incidence (%)	95% CI (%) Clopper–Pearson	95% CI (%) Bootstrap
Overall	218 936	N/A	N/A	43	0.020	0.014–0.026	0.014–0.026
Drug group							
NMBAs	214 869	98.1	N/A	10	0.005	0.002–0.009	0.002–0.008
Antibiotics	199 718	91.2	N/A	10	0.005	0.002–0.009	0.002–0.009
NMBA antagonists	152 803	69.8	N/A	7	0.005	0.002–0.009	0.001–0.009
Individual drug							
Rocuronium	210 852	96.3	98.1	10	0.005	0.002–0.009	0.002–0.008
Cefazolin	106 005	48.4	53.1	7	0.007	0.003–0.014	0.002–0.012
Cefmetazole	37 059	16.9	18.6	1	0.003	0.000–0.015	0.000–0.008
Ampicillin–sulbactam	15 596	7.1	7.8	1	0.006	0.000–0.036	0.000–0.019
Ceftriaxone	4120	1.9	2.1	1	0.024	0.001–0.135	0.000–0.073
Sugammadex	150 629	68.8	98.6	7	0.005	0.002–0.010	0.001–0.009

Table 1 Clinical scoring system and signs of perioperative anaphylaxis. The clinical score of each case is the sum of the net scores of all categories.

	Scores	Cases (%)
Cardiovascular signs		**40 (93.0)**
Hypotension	4	4 (9.3)
Severe hypotension	6	32 (74.4)
Cardiac arrest	9	2 (4.7)
Tachycardia	2	21 (48.8)
Respiratory signs		**26 (60.5)**
Bronchospasm	2	21 (48.8)
Severe bronchospasm	4	5 (11.6)
Bronchospasm occurring before airway instrumentation	2	3 (7.0)
Skin signs		35 (81.4)
Angioedema	3	6 (14.0)
Generalised erythema	3	28 (65.1)
Generalised urticaria	4	18 (41.9)
Combinations		**40 (93.0)**
Cardiovascular and respiratory signs	5	5 (11.6)
Cardiovascular and skin signs	5	14 (32.6)
Respiratory and skin signs	5	3 (7.0)
Cardiovascular, respiratory, and skin signs	8	18 (41.9)
Timings (onset of cardiovascular or respiratory features)		
Within 5 min of possible trigger	7	17 (39.5)
Within 15 min of possible trigger	3	20 (46.5)
Within 60 min of possible trigger	2	1 (2.3)
More than 60 min after possible trigger	−1	1 (2.3)

- 43 cases of anaphylaxis out of 218,936 cases prospectively analyzed
- Major culprit antigens were NMBAs and antibiotics
- Cardiovascular signs were most common, followed by skin signs and respiratory signs
- Clinical signs and treatments were variable: standardized approach based on signs and severity is needed

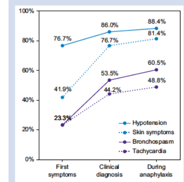
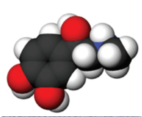


Fig 1. Changes in signs during perioperative anaphylaxis.

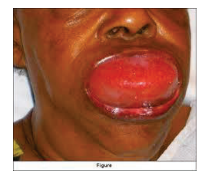
Anaphylaxis-treatment



- Stop suspected agent
- 100% O_2 and secure airway; lie flat
- Treatment of severe cases should include epinephrine; works best when given early
  - 0.5-1 mg IM; 0.05-0.1 mg IV q 1 min titrated to BP
  - Infusion 1-8 mcg/min
  - Norepinephrine 1-32 mcg/min or vasopressin 1-6 U/hr for profound hypotension
- Antihistamines (H1/H2)
- Corticosteroids (0.25 to 1 g hydrocortisone)
- Intravenous fluids (20-50 ml/kg)
- Reduce anesthetic dose

http://anaphylaxisweb.com/

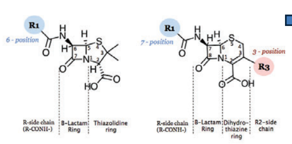
Anaphylaxis-investigation



Figure

- Mast cell tryptase samples
  – immediately after the reaction has been treated
  – 1 h after the reaction
  – 6 h to 24 h after the reaction
- Refer patient allergy testing
- Skin testing can be done immediately

Penicillin allergy delisting



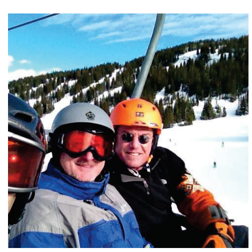
Penicillins   Cephalosporins

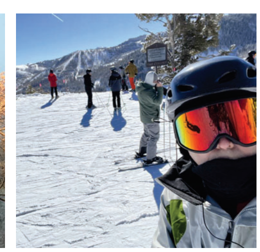
EBM CONSULT

Beta-Lactam Allergy Cross-Reactivity Tips:

Cross-reactive beta-lactams	Penicillin	Amoxicillin	Ampicillin	Cephalexin	Cefazolin	Cefuroxime	Cefoxitin	Ceftriaxone	Cefotaxime	Cefepime	Ceftazidime
Penicillin		X	X	X			X				
Amoxicillin	X		X	X							
Ampicillin	X	X		X							
Cephalexin	X	X	X								
Cefazolin											
Cefuroxime							X	X	X		
Cefoxitin	X					X					
Ceftriaxone						X			X	X	X
Cefotaxime						X		X			X
Cefepime								X			
Ceftazidime								X	X		

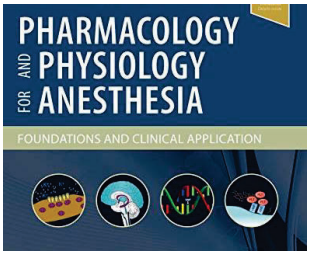
*X indicates antibiotics with similar side chains that may exhibit cross-reactive allergic reactions. Utilize antibiotics that do not share cross-reactivity due to similar side chains.





Thank you!
Questions?

Questions?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