26 Perioperative cardiac arrest and anaesthetic drug choice and dosing

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Key findings

- In the Activity Survey, anaesthetists reported 5 drug errors per 10,000 non-obstetric cases (95% CI 2.8-8.7) and 9.4 (95% CI 3.2 – 27.7) per 10,000 obstetric cases.
- Drug choice and/or dosing was judged to have contributed to a substantial proportion of perioperative cardiac arrest cases.
- Issues around choice or dosing of anaesthetic drugs were more common in older and frail patients, and those with higher ASA grades or acute illness.
- In 12 cases of perioperative cardiac arrest, the panel considered that ketamine should have been used in place of propofol or other agents for induction of unstable patients.
- Use of vasopressors around induction may have prevented some arrests.
- A failure to tailor total intravenous anaesthesia (TIVA) and/or remifentanil to the individual patient was judged to have contributed to a number of cardiac arrests around induction.
- The administration of an epidural test dose contributed to several cardiac arrests, in most cases due to apparent unrecognised intrathecal placement.
- Drug errors continue to occur and some may have been prevented through a systems approach.

What we already know

Drug-related incidents were responsible for 20% of legal claims against anaesthetists between 2008 and 2018, with 31% having a severe or fatal outcome (Oglesby 2022); 79% of cases attracted damages, with the overall cost coming second only to cases of cardiac arrest. Drug errors were associated with 26% of claims involving cardiac arrest, with specific issues including unflushed cannulae, wrong drug or incorrect drug concentration (Oglesby 2022).

Guidelines for the safe practice of TIVA recommend the use of target-controlled infusion (TCI) for propofol maintenance and tailoring initial target concentrations to the characteristics of the patient, co-administered drugs and the clinical situation. In the frail and unwell, a low initial target concentration of propofol with small incremental increases should be used to minimise cardiovascular disturbance (Nimmo 2018).

Propofol is the most widely used induction agent in UK anaesthetic practice, accounting for 90% of single-agent general anaesthetic inductions compared with 0.7% for ketamine in 2016 (Marinho 2018). However, propofol may not be the ideal choice for unstable or unwell patients, despite familiarity with its use, and dose reduction alone may not be sufficient to maintain adequate cardiac output (Sikorski 2014). Ketamine has been shown to maintain haemodynamic stability in the emergency surgery setting and is recommended as a rational choice for rapid sequence induction in haemodynamically compromised patients because of its more favourable pharmacological properties (Morris 2009; Marland 2013; Sikorski 2014). Little work has prospectively compared propofol and ketamine in this context (Morris 2009); however, retrospective studies have shown that ketamine use is favoured in patients who are shocked, supporting its superior haemodynamic profile (Breindahl 2021).

Guidance from the National Institute for Health and Care Excellence on intrapartum care (NICE 2022) provides recommendations on establishing epidural analgesia in labour (Chapter 34 Obstetrics) but wider guidance on the use of epidural analgesia in other clinical contexts, such as for laparotomy, is lacking.

What we found

Activity Survey

Data from the Activity Survey reveal an increased use of TIVA in routine UK anaesthetic practice from 8% of general anaesthetics in 2013 (Pandit 2014, Sury 2014) to 26% in 2022. Drug errors were reported in 12 non-obstetric cases (estimated incidence of 5 per 10,000 cases, 95% CI 2.8–8.7 per 10,000) and 3 obstetric cases (estimated incidence 9.4, 3.2–27.7 per 10,000).

Case reports

A total of 288 (32.7%) cases of perioperative cardiac arrest reported to NAP7 were identified for this chapter, meeting one or more of the following criteria:

- comments by the review panel included reference to drug choice, dosing, TIVA and/or remifentanil
- case reporter selected 'drug dosing contributed to cardiac arrest' when reporting
- on review the panel-attributed cause of cardiac arrest was 'drug error'.

Total intravenous anaesthesia and/or remifentanil

There were 49 cases (5.6% of all cases) in which the review panel specifically mentioned TIVA and/or remifentanil in their comments. Pre-arrest care was rated 'good' in only 16% of these cases, with 57% having elements of poor care; notably, lower ratings of care than in the overall dataset. On panel review, anaesthesia care was thought to be a key cause of cardiac arrest in 37 of 49 (75.5%) cases and patient factors in 40 of 49 (81.6%), most commonly in combination (25 of 49, 51%). Patient outcomes after these events were slightly better than after other arrests, with 41 (84%) surviving the initial event (vs 75%) and 27 (64%) of those with hospital outcome data surviving to discharge (vs 52%).

In reports of this type, cardiac arrest commonly followed induction of anaesthesia using TIVA and/or remifentanil in older, frail or unwell patients undergoing non-elective surgery. Greater age, higher ASA grade and frailty were overrepresented compared with the Activity Survey (Figure 26.1). Sepsis, major haemorrhage and trauma were often present. Three-quarters of these cases included remifentanil (alongside propofol bolus induction, propofol TIVA or as sedation), which typically provoked bradycardia and/or respiratory depression. Cases of cardiac arrest using TIVA with propofol alone typically presented as sudden circulatory collapse on or after induction. The panel considered that several instances of bradycardia and/or hypotension were predictable, given the patient factors and/or clinical context, but often no preventative action was taken (see vignettes).

An older patient graded ASA 2 on pre-existing beta blocker treatment was undergoing an expedited orthopaedic procedure. Induction with propofol and remifentanil TIVA resulted in profound hypotension and cardiac arrest. The case reporter and reviewers judged the initial target concentration of propofol chosen was too high for the patient, resulting in an excessive initial bolus dose.

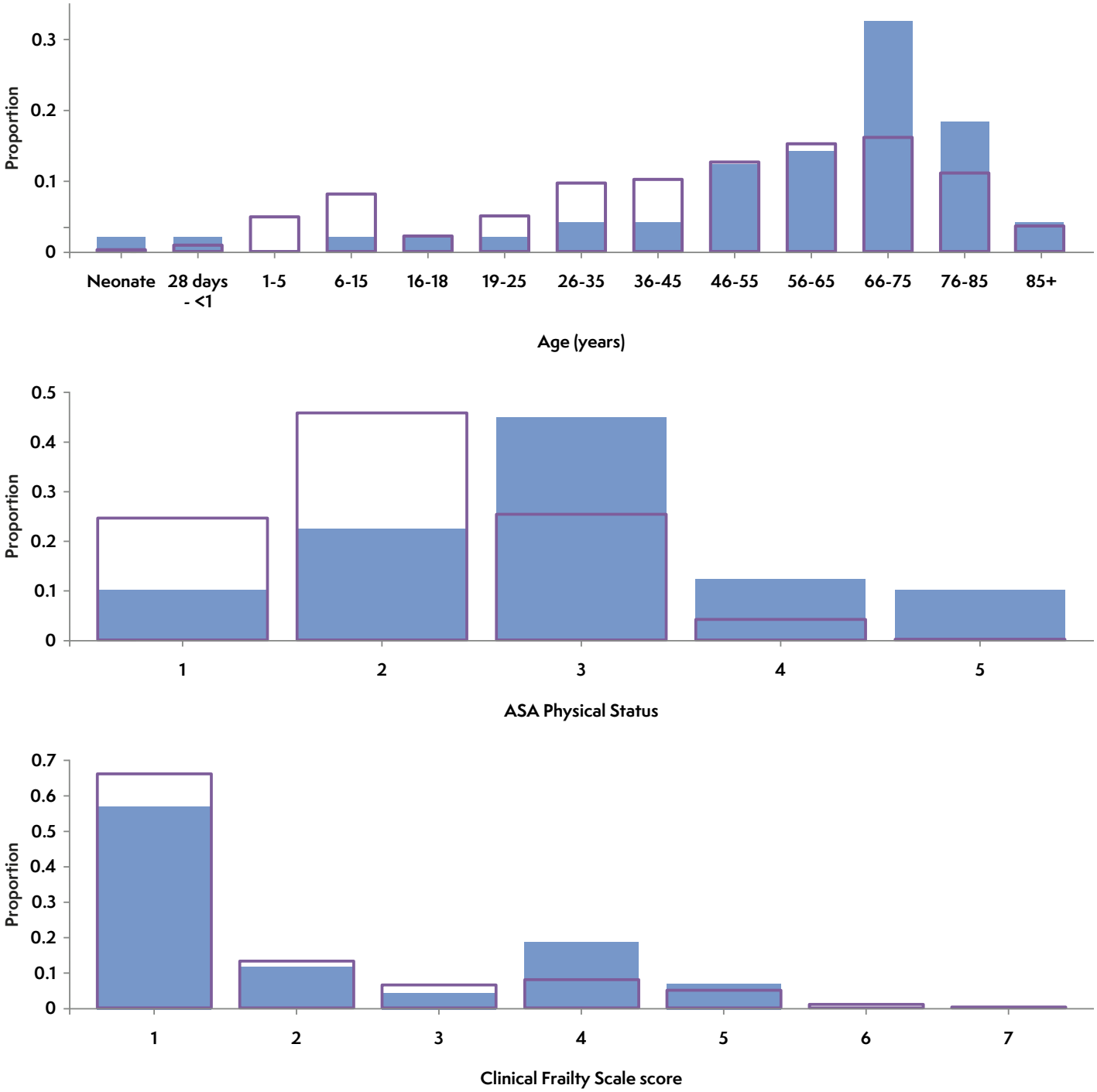
A healthy middle-aged patient graded ASA 1 with a slow heart rate at rest presented for a day case procedure. The patient became increasingly bradycardic after anaesthetic induction with propofol, remifentanil infusion and midazolam. Glycopyrrolate and atropine were ineffective and the patient required cardiopulmonary resuscitation and titrated adrenaline.

A previously healthy middle-aged patient with polytrauma required a long-bone fixation. Induction with propofol and remifentanil TIVA was rapidly followed by circulatory collapse and a pulseless electrical activity cardiac arrest. The case reporters and panel reviewers judged that the patient had been inadequately resuscitated and that physiological compensation hypovolaemia had not been recognised.

There were cases in which the combination of TIVA with other techniques was thought to be the cause of cardiac arrest; for example, following central neuraxial blockade or converting to TIVA after gas induction without reducing initial target concentrations accordingly. Intermittent boluses or manual infusions (eg ml/hour) rather than TCI, because of a lack of equipment or operator choice, and a lone anaesthetist delivering sedation alongside awake fibreoptic intubation were possible contributory factors in other cases of cardiac arrest.

A middle-aged patient graded ASA 3 with severe obesity and difficult intravenous access underwent elective joint replacement under spinal anaesthesia, which was reported as being technically challenging. No target-controlled infusion pumps were available, so the patient was given propofol sedation as an initial manual bolus followed by a mg/kg/hour infusion. During the case, the patient's oxygen saturation decreased and they had a respiratory arrest with bradycardia progressing to asystolic cardiac arrest.

Figure 26.1 Patient characteristics in TIVA/remifentanil cases compared with Activity Survey denominator data (solid blue bars represent cases, purple lines Activity Survey). A bar extending above the line indicates overrepresentation of that feature and a line above the bar underrepresentation of that feature.



Issues of drug dose and choice

There were a further 108 cases in which the panel review commented on the drug choices, the dose or an actual drug error (see below). Considering these cases with the TIVA/remifentanil cases above, elements of poor care before cardiac arrest were present in 57% and again patient factors of higher age, ASA and clinical frailty scale (CFS) score were overrepresented compared with the Activity Survey. Anaesthesia was considered to be a key cause of arrest in 113 (72%) of these cases, most commonly in combination with patient factors (67, 43%).

Similar to the propofol TIVA cases above, the use of propofol as the prime induction agent was judged to be contributory to or causal in a number of cardiac arrests. It was the view of the NAP7 reviewers that, in 12 cases, propofol was not the best induction agent and ketamine would probably have been more appropriate. This was particularly true in unwell or unstable patients; for example, in the context of bleeding or sepsis (see vignette). There were, however, also cases of cardiac arrest after induction with ketamine. The addition of midazolam was also thought to have been contributory to some cases of induction-related arrest.

A middle-aged patient graded ASA 4 required emergency laparotomy for a perforated viscous. The patient had signs of septic shock and required supplementary oxygen before surgery; risk assessment identified a risk of mortality greater than 10%. On induction of anaesthesia with propofol, the patient became hypotensive and had a cardiac arrest despite dose adjustment and metaraminol administration. The case reporter reflected that propofol may have caused circulatory decompensation and ketamine may have been preferred.

A further observation by the review panel was that some cases might have benefited from prophylactic vasopressor at or soon after the time of induction, given the inevitable drop in systemic vascular resistance associated with even modest doses of induction agents. This is allied to the issue of arterial line use, discussed in Chapters 28 Older frailer patients and 31 Monitoring. However, there were again cases in which cardiac arrest occurred despite the appropriate use of vasopressors to counteract the effect of induction.

Other recurrent issues judged potentially contributory to cardiac arrests included excess opioid use other than remifentanil (eight cases) and the administration of magnesium boluses (three cases).

At the end of anaesthesia, there were multiple cases of arrhythmia after administration of reversal agents. Both tachy- (two cases) and bradyarrhythmia (one case) were seen after administration of glycopyrrolate/neostigmine, with a further case of bradycardia when neostigmine was given without an anticholinergic. There was one case of complete heart block after sugammadex administration but the patient had also received ondansetron and had a preoperative ECG showing bradycardic atrial fibrillation with left bundle branch block.

Drug error

Drug error was rated as the primary cause of cardiac arrest in 16 (2%) cases and a secondary cause in a further 12 (1.5%) cases.

- Absolute or relative excess dose:

  A total of 13 of 26 (50%) were cases in which the panel judged that dosing was excessive enough to warrant being labelled as an error. Most of these related to propofol (n = 7) and remifentanil (n = 3), as described above. Other issues included an excessive dose of adrenaline used to treat a bradycardia (with no prior atropine/glycopyrrolate), an opioid overdose and a case where a patient received an inadvertent excessive bolus of induction drugs due to a blood pressure cuff being inflated.

- Regional anaesthesia/analgesia (excess dose and/or wrong route):

  Two drug errors were cases in which the initial bolus of local anaesthetic via an epidural catheter contributed to cardiac arrest due to apparent unrecognised intrathecal placement. There were a further two cases reported to NAP7 in which an epidural bolus dose probably contributed to cardiac arrest, although they were not marked as 'drug errors' by the review panel. One was again probably due to unrecognised intrathecal placement and, in the remaining case, the resulting sympathetic neuraxial block exacerbated existing septic shock. A further three cases of drug error were reports in which the dose of drug chosen for spinal anaesthesia was judged by the panel to be excessive in the context of frailty and these are discussed in Chapter 28 Older frailer patients.

An older patient graded ASA 4 who had a significant cardiac history was taken to theatre for an emergency laparotomy. The patient had signs of severe septic shock with tachycardia and hypotension before anaesthesia and a risk assessment indicated a mortality risk greater than 10%. An initial epidural bolus was given around the time of induction of anaesthesia and cardiac arrest occurred soon after.

- Wrong drug:

  There were three cases in which the wrong drug was given because of 'slips' or 'lapses' (unintended actions due to failure of attention or memory; Cranshaw 2009). Two were emergency situations and included human factors: one due to similarity in the appearance of the ampoules of different drugs, the other reported as being due to a communication issue between members of the anaesthetic team. A third was the result of residual drug being inadvertently flushed from a cannula. A further three cases of erroneous drug administration could be classified as 'mistakes' (errors of judgment or decision making in the application of knowledge or rules; Cranshaw 2009). Two were judged to be inappropriate use of boluses of magnesium to treat perioperative arrhythmias and the third related to the administration of neostigmine without any anticholinergic agent as described above.

- Drug omission:

  The remaining four cases judged to be drug errors were due to drug omission. Two were the result of interrupted vasopressor infusions, one a failure to deliver volatile anaesthetic resulting in an under-anaesthetised patient and finally a case in which a steroid-dependent patient did not receive their regular steroid mediation or perioperative supplementation. There was an additional case in which hypotension was probably compounded by the omission of regular steroids, although this was not judged as a drug error by the panel.

Discussion

Drug choice and/or dose used was judged to have contributed to a substantial proportion of cases reported to NAP7. These cases highlight the challenge of anaesthetising high-risk patients such as older patients, those with frailty, with high ASA grades or acute illness such as hypovolaemia (bleeding/other) or sepsis. Cardiac arrest might have been avoided with different management, such as more aggressive resuscitation before induction of anaesthesia, the use of invasive blood pressure monitoring (and prompt response to any changes), the use of vasopressors during induction, and the use of induction agents associated with less haemodynamic instability.

There are three major limitations to our analysis of these cases. The first is that, for most cases, we did not have details of drug doses. We relied on narrative from the reporter or conclusions from collateral data in the report. Second, there is a risk of hindsight and outcome bias, which is a constant risk with a retrospective review of cases with adverse outcomes, and perhaps particularly so when such review is undertaken without direct access to those involved. Notwithstanding these limitations, and the awareness of the panel of such biases, it was our clear judgement (and often also of the case reporter) that drug dosing, choice and occasionally frank error contributed to many cases of cardiac arrest reported to NAP7. A third consideration is that the NAPs do not get to see cases which have gone 'well' – the many cases where cardiac arrest might have been expected but did not occur due to good drug decisions in choice, dose, co-administration – that prevented it. Thus, our finding of a proportion of cases in which drugs contributed to cardiac arrest is not a criticism of the profession or an indication that 'anaesthetists make bad decisions' – we have only examined one side of the coin – it is an attempt merely to report honestly the data that we have reviewed.

Propofol has the benefit of being very widely used with most anaesthetists experienced and confident in its use. However, when given in high doses and/or as a rapid bolus it is associated with significant haemodynamic instability. In unstable patients, ketamine may be a better option but judicious dosing and the use of vasopressors may still be required (Morris 2009; Marland 2013; Sikorski 2014). Cases of cardiac arrest in conjunction with propofol TIVA highlight several issues that are addressed in existing guidelines on the safe practice of TIVA. These include the use of TCI instead of bolus or manual infusion (eg ml/hour) and in frailer and high-risk patients, starting induction with TIVA with a lower initial target concentration followed by incremental increases, rather than a large initial bolus dose (Nimmo 2019). It is also recommended that all anaesthetists should be trained and competent in the delivery of TIVA. TIVA should be used with caution in conjunction with other anaesthetics (eg spinal or after gas induction), choosing lower initial targets and titrating upwards slowly, with careful haemodynamic monitoring and early recourse to vasopressors when indicated. An appreciation is also required of the underlying pharmacokinetic model when using TIVA, as 'bolus doses' may vary widely between models (eg the induction bolus for a 70-year-old, 70-kg, 175-cm male with an initial target concentration of 4 4 µg/ml ranges from 20 mg (Schneider, plasma target) to 150 mg (Eleveld, effect site target; Luk 2022). Models that administer a lower initial dose may well be more suitable for high-risk or unstable patients. Similarly, early recourse to vasopressors should be a central component of anaesthetic induction of the critically ill, remembering that simply underdosing anaesthetic agent has its own problems, as this risks accidental awareness (Pandit 2014).

Similar to propofol, when using remifentanil the use of TCI should be considered rather than manual infusion, as this will provide a smoother pharmacokinetic loading. Prophylactic measures to counteract bradycardia should be considered when higher-dose remifentanil is administered, and anaesthetists should be aware that some patients are likely to be particularly susceptible to respiratory depression.

Human factors played a significant role in cases of drug error reported to NAP7 (as they have in previous NAPs; Pandit 2014). Recent guidelines highlight that design of ampoules and packaging should incorporate human factors principles to reduce the risk of mis-selection (Kelly 2023) and that 'teams that work together should train together' (Ockenden 2022, Kelly 2023). Reporting of drug errors locally and nationally (eg to the

Medicines and Healthcare products Regulatory Agency via the Yellow Card system, and the Safe Anaesthesia Liaison Group), review of events including near-misses in morbidity and mortality meetings and close attention to national alerts is recommended.

Four cases were specifically related to epidural test dose administration (ie establishing epidural analgesia), three due to apparent intrathecal catheter placement. The message should be to treat every dose as a test dose. Boluses should be given incrementally and the highest dose used for analgesia should not have adverse effects if inadvertently injected intrathecally. In patients who are acutely unstable due to other pathology (eg sepsis), extreme caution should be taken as the effects of an epidural test dose (even if correctly sited) are likely to be exaggerated.

Additional issues that arose from cases judged to involve drug errors include a need to avoid rapid boluses of magnesium in unstable patients and the fact that anaesthetists need to be aware of patients' critical medications, particularly corticosteroids, the omission of which may result in haemodynamic issues under anaesthesia. Additional supplementation may also be required as per guidance from the Association of Anaesthetists and others (Woodcock 2020).

We also received reports of three cases of arrhythmia resulting in cardiac arrest after neostigmine/glycopyrrolate reversal was given. One was a bradyarrhythmia and two were tachyarrhythmias. There are isolated case reports of arrhythmias after administration of these agents suggesting these are rare but recognised potential adverse effects (Nkemngu 2018, Jovanović 2022). There was also one report of complete heart block after sugammadex but it was unclear whether the sugammadex contributed in the context of a baseline abnormal ECG and recent ondansetron administration. A Cochrane systematic review of randomised controlled trials comparing sugammadex with neostigmine did find reduced risk of bradycardia and fewer adverse events in patients receiving sugammadex but no difference in the risk of serious adverse events (Hristovska 2017).

Overall, drug choice and dosing contributed to a notable proportion of cases of perioperative cardiac arrest reported to NAP7. However, our analysis is subject to the limitations discussed above and is unable to fully reflect the impact of these issues in anaesthetic practice as a whole owing to the sample of cases available to us.

Recommendations

National

- In keeping with others (Kelly 2022), we recommend that design of drug ampoules and packaging should aim to optimise readability to reduce the risk of mis-selection and that these factors should form part of decision making in drug procurement.

Institutional

- Hospital guidelines should recognise the following high-risk cardiovascular settings:
  - hypovolaemic and cardiovascularly unstable patents
  - the frailer and older patient
  - patients presenting for vascular surgery
  - patients with bradycardia and those undergoing surgery with vagal stimuli.

  In these cases, there should be consideration of the choice, dose and speed of administration of induction drugs.
- Each hospital should aim to have sufficient dedicated TIVA (TCI) pumps available such that equipment shortage is not a limitation to delivery of safe TIVA.
- Cases of drug error, including near-miss incidents, should be discussed in morbidity and mortality meetings.
- Storage and availability of medications should be optimised to reduce the risk of mis-selection.

Individual

- Individual practice should recognise the following high-risk cardiovascular settings:
  - hypovolaemic and cardiovascularly unstable patents
  - the frailer and older patient
  - patients presenting for vascular surgery
  - patients with bradycardia and those undergoing surgery with vagal stimuli.

Induction technique may require modification, such as using ketamine instead of propofol, or by co-administering vasopressor medication to counteract hypotension. High-dose or rapidly-administered propofol, in combination with remifentanil, should be avoided. Similar considerations apply to the modification of doses of intrathecal drugs.

- Anaesthetists should make appropriate adjustments to initial TIVA target concentrations in unstable, frail or older patients, and in cases where TIVA is started after other techniques (eg neuraxial blockade or gas induction).
- All anaesthetists delivering TIVA or intravenous sedation should ensure they have knowledge of the model(s) to be used and have been specifically trained to do so effectively and safely.
- Anaesthetists should be aware of the risk of bradycardia when using remifentanil and should monitor carefully to detect it, considering prophylactic measures in high-risk patients.
- Anaesthetists should report drug errors, including near-miss incidents, through appropriate local and national channels.
- Anaesthetists should treat every epidural dose as a potential test dose and choose an appropriate volume and concentration of local anaesthetic.

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