Anaesthesia 2021, 76, 238–250 doi:10.1111/anae.15270

Guidelines

The use of intravenous lidocaine for postoperative pain and recovery: international consensus statement on efficacy and safety

I. Foo,[1] **A. J. R. Macfarlane,**[2] **D. Srivastava,**[3] **A. Bhaskar,**[4] **H. Barker,**[5] **R. Knaggs,**[6] **N. Eipe**[7] and **A. F. Smith**[8]

1 Consultant, Department of Anaesthesia, Western General Infirmary, Edinburgh, UK
2 Consultant, Department of Anaesthesia, Glasgow Royal Infirmary, Glasgow, UK
3 Consultant, Department of Anaesthesia, Raigmore Hospital, Inverness, UK
4 Consultant, Department of Anaesthesia, Imperial College Healthcare NHS Trust, London, UK
5 Lead Nurse, Ashford and St Peter's Hospitals NHS Foundation Trust, Chertsey, UK
6 Associate Professor, School of Pharmacy, University of Nottingham, Nottingham, UK
7 Staff Anesthesiologist, Ottowa Hospital, Ottowa, ON, Canada
8 Consultant, Department of Anaesthesia, Royal Lancaster Infirmary, Lancaster, UK

Summary

Intravenous lidocaine is used widely for its effect on postoperative pain and recovery but it can be, and has been, fatal when used inappropriately and incorrectly. The risk-benefit ratio of i.v. lidocaine varies with type of surgery and with patient factors such as comorbidity (including pre-existing chronic pain). This consensus statement aims to address three questions. First, does i.v. lidocaine effectively reduce postoperative pain and facilitate recovery? Second, is i.v. lidocaine safe? Third, does the fact that i.v. lidocaine is not licensed for this indication affect its use? We suggest that i.v. lidocaine should be regarded as a 'high-risk' medicine. Individual anaesthetists may feel that, in selected patients, i.v. lidocaine may be beneficial as part of a multimodal perioperative pain management strategy. This approach should be approved by hospital medication governance systems, and the individual clinical decision should be made with properly informed consent from the patient concerned. If i.v. lidocaine is used, we recommend an initial dose of no more than 1.5 $mg.kg^{-1}$, calculated using the patient's ideal body weight and given as an infusion over 10 min. Thereafter, an infusion of no more than 1.5 $mg.kg^{-1}.h^{-1}$ for no longer than 24 h is recommended, subject to review and re-assessment. Intravenous lidocaine should not be used at the same time as, or within the period of action of, other local anaesthetic interventions. This includes not starting i.v. lidocaine within 4 h after any nerve block, and not performing any nerve block until 4 h after discontinuing an i.v. lidocaine infusion.

Correspondence to: A. Smith
Email: andrew.smith@mbht.nhs.uk
Accepted: 14 September 2020
Keywords: efficacy; idocaine; pain; safety
This article is accompanied by an editorial by Pandit et al. Anaesthesia 2021; **76**: 156–60
Twitter: @ajrmacfarlane; @naveeneipe

Recommendations

1 The use of intravenous (i.v.) lidocaine for acute pain should be ratified and approved by the local hospital and medication governance committee, or equivalent.
2 Whenever possible, consent should be obtained from patients if i.v. lidocaine is to be used, and a full appraisal of the possible benefits and risks in each case undertaken.
3 Ideal body weight should be used for dose calculation. Intravenous lidocaine should not be used in patients weighing < 40 kg. For any patient, no more than 120 $mg.h^{-1}$ should be infused.
4 Intravenous lidocaine should not be used at the same time as, or within the period of action of, other local anaesthetic interventions, particularly local anaesthetic nerve blocks.
5 A loading dose of no more than 1.5 $mg.kg^{-1}$, given as an infusion over 10 min, is recommended. Thereafter, an infusion of no more than 1.5 $mg.kg^{-1}.h^{-1}$, for no longer than 24 h, is recommended, subject to review and re-assessment. This should be delivered from a suitable infusion device through a separate, dedicated cannula. There should be a separate lidocaine monitoring chart.
6 Outside the operating theatre/recovery room, patients receiving i.v. lidocaine should ideally be managed in a monitored bedspace in a high dependency unit (level 2 care). Particular vigilance is needed in patients with existing comorbidity.
7 Clinicians should remember the possibility of toxicity even though there may be other explanations for a given clinical presentation. Lipid emulsion 20% should be readily available wherever i.v. lidocaine is used, and staff should know where it is kept.

What other consensus statements are available on this topic?

Although i.v. lidocaine is used widely in the management of postoperative pain and recovery in many regions of the world, no consensus statements on its use have been published.

Why was this statement developed?

This statement was developed after an incident in an English hospital where a patient died after being given i.v. lidocaine postoperatively.

How does this statement differ from existing guidelines?

This is the first consensus statement. It aims to provide practical recommendations on the safe use of i.v. lidocaine for postoperative pain and recovery.

Introduction

Lidocaine (originally Xylocaine®, and previously lignocaine) was developed in the first half of the twentieth century and approved for use in humans by the US Food and Drug Administration in 1948 [1,2]. By 1958, intravenous (i.v) lidocaine infusions were being used to provide postoperative analgesia in clinical practice [3]. The postoperative analgesic and antihyperalgesic effects of i.v. lidocaine were confirmed in later studies [4,5].

Currently, i.v. lidocaine is used as a peri-operative analgesic across a wide number of areas, including the operating theatre, recovery room, intensive care unit (ICU) and surgical ward [6]. In a recent survey in Scotland, 12 out of the 16 responding hospitals were either already using i.v. lidocaine infusions for acute pain, or were planning to use them in the near future [7]. Lidocaine has anti-nociceptive, anti-hyperalgesic and anti-inflammatory actions and it is presumably these actions, rather than a direct local anaesthetic effect, which explain the apparent prolonged effect hours after an infusion has been completed [6,8–10].

Given the short- [11] and long-term [12] undesirable effects of opioids, multimodal analgesic strategies are a key component of postoperative pain management. However, concerns have always existed about the narrow therapeutic window and toxicity of lidocaine, both when given i.v. or as part of a regional anaesthetic technique [13–15]. Lidocaine has a multimodal mechanism of action. In therapeutic concentrations during i.v. infusion, it blocks muscarinic (M1, M3) and N-methyl-D-aspartate (NMDA) receptors. At higher and near-toxic concentrations, many receptor types are affected including: Nav1.8/1.7; purinoceptor 7 (P2X7); toll-like receptor 4 (TLR4); 5-hydroxytryptamine-3 (5HT-3); nicotinic cholinergic receptors; voltage-gated calcium channels (VGCC); transient receptor potential ankyrin 1 (TRPA1); and acid-sensing ion channel (ASIC) [8]. It is unsurprising, therefore, that the therapeutic index for i.v. lidocaine is low, with central nervous system toxicity starting at plasma levels only slightly higher than therapeutic levels. The correlation of plasma levels with signs and symptoms of toxicity is not linear [16], as systemic toxicity reflects the unpredictable interaction between patient factors and the pharmacokinetic and pharmacodynamics properties of the drug [15]. This situation is compounded by the fact that data on the systemic toxicity of i.v. lidocaine are seldom collected in clinical trials [17].

Methodology of consensus statement

Recently, the death of a patient who had received an i.v. infusion of lidocaine was reported to the Safe Anaesthesia

Liaison group (SALG) of the Royal College of Anaesthetists. This has been reported subsequently in the media [18]. It is clear that the use of i.v. lidocaine is widespread [7]. While informal experience gathered will tend to make the use of i.v. lidocaine safer [19], there is nevertheless a need for a complementary formal safety guideline. A multidisciplinary group of experts and representatives of relevant professional organisations was assembled to work on the guideline. The aim of the working party was to analyse the index safety incident, review and interpret the available published literature on effectiveness and safety, and provide recommendations for safe use of i.v. lidocaine in peri-operative practice. The guideline was not intended to apply to the use of i.v. lidocaine in the management of chronic pain, either in outpatient or inpatient settings.

In assessing the research and other intelligence, we sought to address three main questions. First, is i.v. lidocaine effective in the treatment of postoperative pain? Second, is it safe? Third, how does the fact that lidocaine is not licensed affect how its use can be recommended?

Is intravenous lidocaine effective in the treatment of postoperative pain?

Many randomised controlled trials have been conducted in the last 15 years investigating the effect of i.v. lidocaine on pain and postoperative recovery, with a number of systematic reviews and meta-analyses having subsequently been performed [17, 20–26]. The largest and most recent of these included patients undergoing any type of surgery (4525 patients in 68 trials) [17]. These large numbers, however, disguise the fact that for many outcomes the volume of available data is much smaller, and hence less robust. Most reviews focus on lidocaine's analgesic effects, whether measured as pain intensity or as analgesic consumption, but some also examine other aspects of postoperative recovery, including opioid-related adverse effects such as postoperative ileus, incidence of nausea and vomiting, and duration of stay in hospital.

However, just as individual trials vary greatly in lidocaine dose, infusion rate, duration of infusion, outcomes chosen and management of patients in the 'control' group, there is heterogeneity among the meta-analyses with respect to a number of important features. These include: the range of surgical specialties and operations incorporated; the primary outcome measure; the assessment of methodological quality (risk of bias) of included trials; the degree to which they take account, or make use of, this quality assessment in their conduct of the review; the detail of the scrutiny of the included studies in general; the interpretation and presentation of the review findings; and the extent to which their reflective discussion deals with methodological, rather than clinical issues.

To illustrate this point, we present a detailed analysis of the available data for one outcome, postoperative pain scores at 24 h in patients who have undergone abdominal surgery, in the online Supporting Information (Appendix S1). The main points are summarised below.

The first four systematic reviews [20–23], published between 2008 and 2012, drew on the same pool of primary trials of lidocaine in abdominal surgery [27–42].

A further systematic review and meta-analysis by Ventham et al. (including an author of this safety guideline, IF) was published in 2015 [25] and included six further studies [43–48]. The authors found a similar mean difference (95%CI) in postoperative pain scores to previous reviews (-0.42 (-0.79 to -0.04)), but were the first team to point out the limited clinical significance of their findings, stating in the discussion of their work that "*in almost all measured outcomes, the difference in pain score was less than the 1.3 point reduction deemed clinically significant*" [49].

The varying degrees of methodological scepticism and expertise in the authors' work is illustrated by the various approaches to the assessment of methodological quality of primary studies, which included the Jadad score [50] (also known as the 'Oxford score'), a modification of the Jadad score [51] or the risk of bias tool used in Cochrane systematic reviews [52–54]. Sun et al. [23] used a further modification of the Oxford scale [55,56], Chang et al. [24] did not cite a method, and Ventham et al. [25] used yet another modification of the Jadad score [57]. Numerical scoring systems for study quality assessment have fallen out of favour, as evidenced by the review by Vigneault et al. [22] where the Jadad scale generally provided a more optimistic view of study quality than the Cochrane tool. Twelve out of the 29 studies (46%) were judged at low risk of bias by the Cochrane tool compared with 23 (79%), which achieved a Jadad score of ≥ 3, the usual cut-off point for 'high' quality. This is echoed by other studies comparing numerical scores with the Cochrane tool [58]; the Cochrane group actively discourage the use of numerical scoring systems, as they have a strong emphasis on reporting rather than conduct, and may not cover one of the most important potential biases in randomised trials, namely allocation concealment. In addition, not all review authors used the information on study quality to restrict their analysis to less biased studies or perform sensitivity analyses excluding lower-quality studies.

The trend of greater understanding and scepticism continues in the Cochrane systematic reviews conducted by

Weibel et al. (first published in 2015 [26] and updated in 2018 [17]). Pain scores were the primary outcome, drawing on previous methodological work suggesting that postoperative analgesic consumption is a less reliable method of measuring analgesic efficacy as the distribution of consumption is often highly skewed [59,60] and there are opportunities for error in conversion when quantities such as 'morphine equivalents' are calculated. In the first review the authors used both the Cochrane risk of bias tool to assess methodological quality [61] and the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) system to appraise the quality of evidence on the basis of the extent to which one can be confident that the estimate of effect reflects the item assessed [62].

The 2018 update [17] incorporated 23 new trials, taking the total number of studies to 68. Out of these, 22 examined open abdominal surgery and 20 laparoscopic surgery, including (in addition to a new study in the 2015 version [63]), a further seven trials [64–70] measuring pain at 24 h. The authors also noted that a number of studies reported small variances, and added the novel methodological feature of 95% prediction intervals. These provide an index of dispersion (based on the SD) that suggests how widely the mean effects vary across populations; reporting a prediction interval in addition to the summary estimate and CI illustrate what range of true mean effects might be expected in future settings, and is also helpful in the clinical interpretation of heterogeneity. Weibel et al [17] suggested that i.v. lidocaine reduced pain scores 0–4 h after surgery, with a standardised mean difference (SMD (95%CI)) of -0.50 (-.72 to -0.28) (29 studies, 1656 patients). This equated to a reduction of between 0.37 cm and 2.48 cm on a visual analogue scale (VAS). There was no evidence of a clinically relevant effect on pain scores at 24 h or 48 h, with the authors noting that the standardised mean difference of -0.14 in average pain score would be equivalent to a mean pain reduction in the order of 0.48 cm to 0.10 cm on a 10-cm VAS (depending on the variance of the study). Further, the 95% prediction intervals "*crossed the line of identity, and the range of true mean effects mostly remained in areas of clinical non-relevance*" [17]. However, the patients in the control groups in many of the primary studies had free access to other analgesics; this can lead to smaller differences in pain scores between groups, and makes benefit harder to demonstrate.

A primary outcome of pain score is perhaps, therefore, the wrong outcome to focus upon. Overall postoperative opioid consumption was reduced, with the mean difference (95%CI) being -4.52 (-6.25 to -2.79) mg morphine equivalents (40 studies, 2201 patients) although the range of true mean effects included areas of clinical non-relevance. The incidence of ileus did appear to be reduced, however, with a risk ratio (RR) (95%CI) 0.37 (0.15–0.87) (four studies, 273 participants). For the time to first bowel movement, the mean difference (95%CI) was reduced by 7.92 (12.71–3.13) h (12 studies, 684 participants). The risk of postoperative nausea was also reduced, with a risk ratio (95%CI) of 0.78 (0.67–0.91) (35 studies, 1903 participants). The quality of evidence was very low for most of these outcomes, however, and ultimately the authors concluded it was uncertain if "*i.v. lidocaine, when compared to placebo or no treatment, has a beneficial impact on pain scores in the early postoperative phase, and on gastrointestinal recovery, postoperative nausea, and opioid consumption*".

The systematic reviews drew on a limited pool of small primary studies, and even taken together, the data are rather sparse [71,72]. They are similar, though, where they reflect the primary trials that they include, as patients who might be expected to be at greater risk of postoperative pain (those already taking analgesics or experiencing long-term pain) were not included. Where the meta-analyses differ is more in the authors' understanding of, and scepticism towards, the conduct of the primary trials [64]. These findings demonstrate that the risk-benefit decision to use i.v. lidocaine needs to reflect the type of surgery and the patient's condition.

Is lidocaine safe?

There are a number of ways of evaluating the safety of i.v. lidocaine. These include: attempts to establish relationships between plasma lidocaine concentrations and toxicity; the infusion regimens used; occurrence of symptoms and signs of toxicity; the documentation of adverse events within clinical studies; and analyses of specific serious problems.

Plasma lidocaine concentrations and toxicity

Early studies investigating lidocaine toxicity infused i.v. lidocaine at a rate of 30 $mg.kg^{-1}.h^{-1}$; this is about 10–20 times higher than modern day regimens, which are typically 12 $mg.kg^{-1}.h^{-1}$ [73]. Adverse events appeared rapidly. Further evidence that speed of infusion was important came from Bromage et al. [74] while Gianelly et al. suggested in a small study of 29 patients, that blood levels associated with serious toxicity were about 9–10 $\mu g.ml^{-1}$ and to avoid toxic effects (central nervous system depression, convulsions and hypotension), the dose should be kept < 3 $mg.kg^{-1}.h^{-1}$ [75].

Sawyer et al. studied continuous infusions of lidocaine in patients with cardiac arrhythmias [76]. In 26 patients an appropriate bolus dose (0.5–4 $mg.kg^{-1}$) was followed by an infusion varying between 1 $mg.min^{-1}$ and 4 $mg.min^{-1}$, as

determined by the patients' physicians, rather than a fixed dosage regimen. This resulted in a range of lidocaine plasma concentrations from 1.65 $\mu g.ml^{-1}$ to 11.33 $\mu g.ml^{-1}$ [76]. Lidocaine clearance values were highly variable. Some of these early studies used lidocaine doses that were not based on patient weight, included small numbers of patients, and had a poorer understanding of the factors affecting clinical toxicity; however, these studies do provide some pointers to the relationship between plasma concentration and toxicity.

Apart from the dose and speed of i.v. lidocaine as determinants of lidocaine toxicity, duration of infusion is also important. Rowland et al. studied disposition kinetics of lidocaine in normal subjects [77]. The half-life of lidocaine was shown to be approximately 100 min following either a bolus or an infusion lasting < 12 h. For infusion durations> 12 h, lidocaine showed non-linear or time-dependent pharmacokinetics. LeLorier et al. examined this further by studying the pharmacokinetics of lidocaine after prolonged i.v. infusions (> 24 h) in patients with uncomplicated myocardial infarction [78]. Twelve patients with no evidence of renal, hepatic or heart failure were given a bolus of 1 $mg.kg^{-1}$ of lidocaine followed by an infusion of 1.2 $mg.kg^{-1}.h^{-1}$. Using pharmacokinetic modelling, the mean half-life of the elimination phase was found to be 3.22 h after 24 h, in contrast to the 100 min when infused for less than 12 h. This suggested that lidocaine pharmacokinetics were linear and predictable only up to 12 h, leading to recommendations that after 24 h, the rate of lidocaine infusion be reduced to approximately 50% even in patients without cardiac and hepatic failure. This inconsistency between observations and recommendation is in the original paper.

Within the peri-operative clinical setting, McCarthy et al. reported plasma lidocaine concentrations from seven of their included studies [27,30,31,33,79–81] in their systematic review [20]. Concentrations were measured after bolus injection and at different time intervals during and after infusion. Toxic concentrations (defined as > 5 $\mu g.ml^{-1}$) were not reached in any study following lidocaine infusion, with the exception of one asymptomatic patient presenting with a peak value of 5.8 $\mu g.ml^{-1}$ measured 5 min after lidocaine bolus [30]. Mean plasma lidocaine concentrations ranged from 0.58 $\mu g.ml^{-1}$ to 5 $\mu g.ml^{-1}$. The highest plasma lidocaine concentration at 24 h was 4.6 $\mu g.ml^{-1}$ after infusion of 1.33 $mg.kg^{-1}.h^{-1}$ for 24 h [31]. Plasma concentrations ranged between 2 $\mu g.ml^{-1}$ and 5 $\mu g.ml^{-1}$ when infused for 48 h at a rate of 30 $\mu g.kg^{-1}.min^{-1}$ [77]. In the study by Cassuto et al.[27] where lidocaine was given as a 100 mg bolus followed by infusion of 2 $mg.min^{-1}$ for 24 h postoperatively, whole blood lidocaine concentrations averaged 1.52 $\mu g.ml^{-1}$ 8 h after the start of infusion and 1.75 $\mu g.ml^{-1}$ after 20 h. Table 1 lists studies which: measured plasma lidocaine concentrations after a bolus dose of 1.5 $mg.kg^{-1}$ (our recommended dose); where a fixed infusion rate was used; and where the results were reported as mean (SD). Figure 1 displays the spread of plasma concentrations obtained at three infusion rates.

Patient factors predisposing to toxicity

The relationship between dose and plasma lidocaine concentrations is not completely clear-cut [16, 74, 82]. Such differences may be explained by understanding the pharmacokinetics of lidocaine in different patient populations [83]. In heart failure, volume of distribution and plasma clearance are significantly reduced. Lidocaine clearance correlates with cardiac index, as this influences hepatic blood flow and therefore lidocaine clearance. Lidocaine is metabolised to mono-ethylglycinexylidide and glycinexylidide by hepatic enzymes. Mono-ethylglycinexylidide has similar pro-convulsant and anti-arrhythmic properties to lidocaine itself but is rapidly converted to glycinexylidide by the liver, which is in turn excreted by the kidney [87]]. Thus patients with hepatic or renal impairment are more susceptible to developing lidocaine toxicity [88]. Plasma clearance is reduced in liver failure, whereas in renal failure patients have a similar clearance to normal subjects; however, authors have speculated that the metabolites might accumulate during prolonged infusion. Several other factors may influence lidocaine toxicity including acid-base status (acidaemia increases the dissociation of lidocaine from plasma proteins) and hypoxaemia [89]. Hypoalbuminaemia and other conditions where plasma proteins are depleted increase the amount of free drug in the plasma and hence make toxicity more likely. Drugs which reduce lidocaine metabolism (e.g. beta-blockers) and clearance (e.g. amiodarone) may enhance lidocaine toxicity, especially with prolonged infusions. Inducers and inhibitors of the hepatic enzyme cytochrome P450 can also have an effect. However, studies in the last 15 years have not specifically reported any adverse effects related to drug interactions as far as we are aware. Low body weight can result in a reduction in skeletal muscle mass (which normally acts as a storage reservoir for local anaesthetic) and may be associated with an increased frequency of adverse reactions [90]. However, patients with high body mass index (BMI) may also have inadvertently higher plasma concentrations [16, 91]; this may be because actual, rather than ideal, body weight is used for dose calculation. This notion is supported by Dale

Table 1 Plasma lidocaine concentrations from 11 studies where samples were taken peri-operatively during lidocaine infusions at three different rates after a bolus of 1.5 $mg.kg^{-1}$. Values are number or mean (SD).

Study	Type of surgery	n	Infusion rate; $mg.kg.h^{-1}$	Sampling time after bolus; h	Plasma concentration; $\mu g.ml^{-1}$
Koppert et al. [5]	Major abdominal surgery	20	1.5	2–4	1.9 (3.1)
Dewinter et al. [65]	Laparoscopic sterilisation	40	1.5	> 2	2.5 (1.1)
Weinberg et al. [69]	Open radical prostatectomy	36	1.5	2–4	1.4 (0.5)
Martin et al. [79]	Total hip arthroplasty	28	1.5	> 2	2.1 (0.4)
El-Tahan et al. [83]	Caesarean section	45	1.5	1	2.1 (0.4)
Grigoras et al. [84]	Breast surgery	17	1.5	2	1.1 (0.4)
Kaba et al. [31]	Laparoscopic colectomy	15	2	2.8	2.4 (0.6)
Striebel et al. [81]	Tonsillectomy	20	2	3	2.0 (0.6)
Birch et al. [82]	Abdominal hysterectomy	9	2	2	2.1 (0.3)
Lee et al. [85]	Off-pump cardiac surgery	15	2	4.65	2.0 (1.2)
Bryson et al. [38]	Abdominal hysterectomy	40	3	1	2.6 (0.6)

et al., who showed that patients' actual plasma concentrations were 20% higher than predicted when actual body weight was used [91]. Some studies have weight exclusions, for example, < 45 kg and > 100 kg [44], which may have reduced the risk of adverse events. Two further safety measures are to have an upper infusion rate limit (e.g. 120 $mg.h^{-1}$) irrespective of body weight calculations and to use ideal body weight rather than actual body weight in lidocaine infusion calculations.

Adverse events in clinical studies and analysis of serious adverse events

Fifty of the 68 studies included in the most recent Cochrane review gave information on adverse events [17]. In 23 of these studies, no significant events were reported, while in the remaining 27, only minor adverse effects such as drowsiness, light-headedness, peri-oral numbness, tinnitus and bradycardia were described. A recently reported large series showed minor adverse events in 37 (6.8%) of the 544 patients in whom i.v. lidocaine had been used [92]. These included: six patients complaining of somnolence and metallic taste; five patients with dizziness; four patients with agitation; and three patients each reporting nausea, peri-oral numbness, tinnitus and tremor. As already discussed, there are many factors which influence plasma lidocaine concentration and clinical evidence of toxicity, but catastrophic events are usually due to human error in dosing, infusion programming or infusion of the wrong drug [9]. These factors were in evidence in the report of an incident in a UK hospital where a patient died during an infusion of i.v. lidocaine. Here, a number of contributing factors were identified [81, 86]. The patient had undergone several abdominal operations in the preceding 18 months, and appeared to have had pain that was difficult to control postoperatively. Both pre-existing systemic factors [93, 94] and communication difficulties [95, 96] appear to have played their part in this unfortunate death.

In summary, although there appears to be some correlation between symptoms and plasma lidocaine concentrations, this is not fully reliable. Diagrammatic representation of the relationship between symptoms and plasma lidocaine concentration, as seen in textbooks [97] (Fig. 2) act as a general guide only. From a safety perspective, peak plasma concentrations and clinical evidence of toxicity are related not only to the total dose given (which in itself needs to be adjusted for the patient's weight and co-morbidities) but also to the speed and duration of infusion. Again, the risk-benefit decision to use i.v. lidocaine needs to reflect the type of surgery and the patient's condition.

'Off-label' use

Drug manufacturers must secure a marketing authorisation (often termed product licence) from the relevant national authority or agency [98]. Despite this, a substantial proportion of all prescriptions in many specialties (particularly paediatrics and palliative care) are written for licensed drugs given for unlicensed indications or administration by a route not stated in the marketing authorisation, which is termed 'off-label use'. Anaesthesia is no exception [99] and there are numerous examples of off-label use including additives or adjuvants in neuraxial or perineural anaesthesia [100].

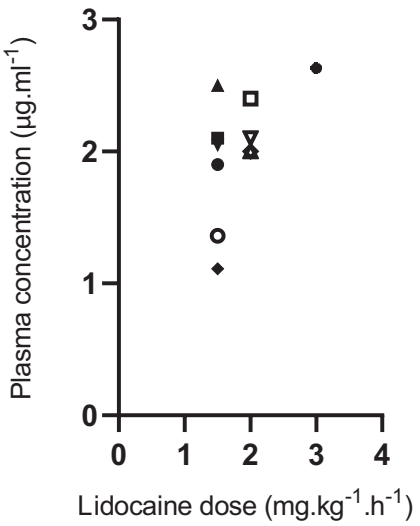

Figure 1 Mean plasma lidocaine concentrations achieved by three lidocaine infusion rates. Studies using 1.5mg.kg^{-1}.h^{-1}: •Koppert et al. [5]; ▲ Dewinter et al. [65]; ◯ Weinberg et al. [69]; ■ Martin et al. [79]; ▼ El-Tahan et al. [83]; and ♦ Grigoras et al. [84]. Studies using 2mg.kg^{-1}.h^{-1}: □ Kaba et al. [31]; △ Striebel et al. [81]; ◇ Birch et al. [82]; and ▽ Lee et al. [85]. Study using 3mg.kg^{-1}.h^{-1}: ● Bryson et al. [38].

While it is usual to prescribe licensed medicines in accordance with the terms of their licence, prescribing outside the license of a medicine is legally permitted. However, the responsibility for the consequences of prescribing lies with the prescriber when medicines are used off-label. When prescribing a medicine off-label, the prescriber must be satisfied there is sufficient safety and efficacy evidence, understand the effects and adverse effects of the medicine, and take responsibility for prescribing and overseeing the patient's care, monitoring and follow-up [101].

Prescribers should provide sufficient information to patients about the expected benefits and potential risks in order for them to make an informed decision. It is not possible to rely on the information provided by the manufacturer as this only relates to licensed indications. Given recent legal cases in the UK, there is a requirement "*to take reasonable care to ensure that a patient is aware of any material risks involved in any recommended treatment, and of any reasonable alternative or variant treatments*" [102].

By prescribing 'off-label' prescribers have a duty to take reasonable care and act in a way consistent with the practice of a responsible body of their peers of similar professional standing. In the UK, the Department of Health has issued provided guidance for the prescribers of unlicensed medicines [103] and some hospitals and other organisations have specific policies and patient information. In the context of i.v. lidocaine infusions, the prescriber needs to assess each patient individually in order to satisfy themselves that the drug is necessary for medical reasons, and there must be discussion about the benefit and risk with the patient so that they are able to provide informed consent.

Detailed recommendations for practice

1 **The use of i.v. lidocaine for acute pain should be ratified and approved by the local hospital and medication governance committee or equivalent**. Its use should be supported by a local standard operating procedure, which should include: dosing advice; required monitoring; recognition of adverse effects; and treatment of toxicity. An example of a standard operating procedure is available in the online Supporting Information (Appendix S2).

2 **Before i.v. lidocaine is started there should be a proper assessment of pain using appropriate methods**. If a patient already has pain, this should be by standard methods [104]. When the option of i.v. lidocaine is discussed with the patient pre-operatively, an appraisal of the patient's risk of experiencing severe pain should be made. This may take into account the extent of the surgical procedure and patient-specific factors such as pre-existing chronic pain or opioid use. Intravenous lidocaine should be started only by, or on the advice of, a consultant anaesthetist/intensivist experienced in the use of i.v. lidocaine infusions both within and outside the operating theatre. There must be confidence that the team running the infusion are competent to do so and are aware of the local guideline.

3 **Clinicians should carefully consider the relative contraindications to the use of i.v. lidocaine**. These include: cardiac disease; patients with electrolyte disorders; patients with seizure disorders, renal or hepatic impairment, pregnancy/breastfeeding; and neurological disorders.

4 **Where possible, explicit consent should be obtained from patients if i.v. lidocaine is to be used**. Given the limited clinical benefit in most patients, the risks and possible advantages should be clearly explained to patients. This should follow standard guidance for the use of medicine for unlicensed indications [9]. Departments of anaesthesia may wish to provide written patient information materials to support the process of informed consent, if time permits. Patients should be informed about what to

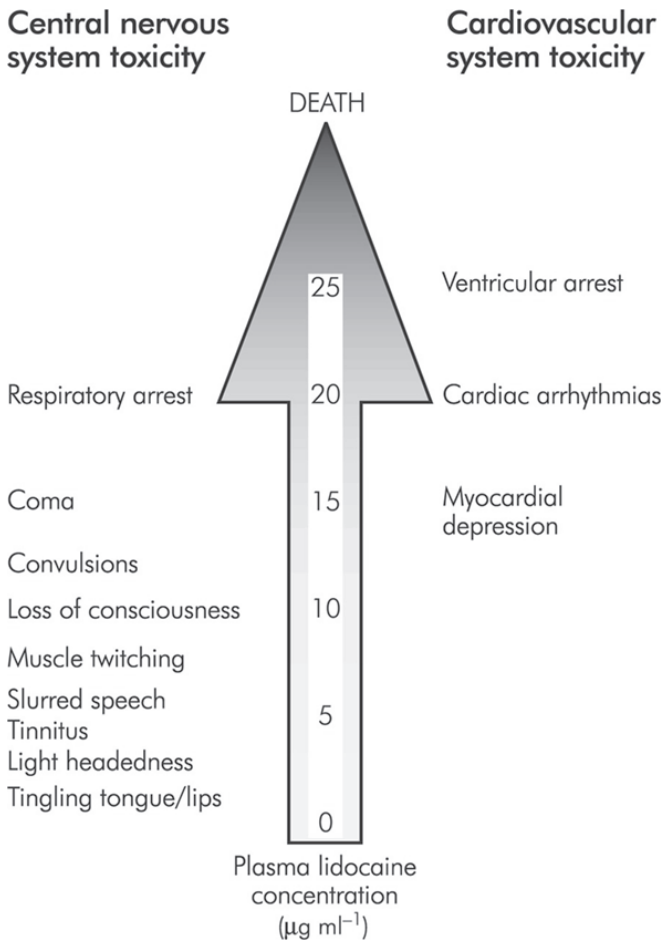

Figure 2 Typical diagram relating plasma lidocaine concentration to toxic effects. Reproduced, with permission, from Lin et al. [97].

expect and report (if appropriate); this should include not only symptoms of local anaesthetic toxicity [7], but also commonly experienced feelings such as euphoria and facial flushing. Anaesthetists should consider obtaining provisional consent if there is the possibility that i.v. lidocaine might be used.

5 **Ideal body weight should be used for dose calculation**. This can be calculated using the simple formula: ideal body weight = (height in cm - 100) for men; and (height in cm - 105) for women. Ideal and actual body weight are similar if the BMI is < 30 $kg.m^{-2}$.

6 **Intravenous lidocaine should not be used in patients weighing < 40 kg. For any patient, no more than 120 $mg.h^{-1}$ should be infused.**

7 **Intravenous lidocaine should not be used at the same time as, or within the period of action of other local anaesthetic interventions**. The following recommendations are based on a consensus among the working group:

- Intravenous lidocaine should not be started within 4 h of any nerve or fascial plane block, or infiltration of laparoscopic port sites.
- No nerve or fascial plane blocks should be performed until 4 h after completion of an i.v. lidocaine infusion.
- Boluses of local anaesthetic must not be given into wound catheters or epidural catheters until 4 h after completion of an i.v. lidocaine infusion.
- Infusions (without boluses) through wound or epidural catheters may be started 30 min after an infusion of i.v. lidocaine has been stopped.
- Topical 5% lidocaine medicated plasters should be removed before starting an i.v. lidocaine infusion.

- Single-shot spinal blockade does not pose a problem given the small dose of local anaesthetic used; intrathecal opioids can be used in conjunction with i.v. lidocaine.
- Concurrent administration of ketamine is acceptable and has often been tried in patients whose pain is difficult to manage, before lidocaine is considered.

8 **A loading dose of i.v. lidocaine of no more than 1.5 mg.kg^{-1}, given as an infusion over 10 min is recommended**. Too rapid an infusion is more likely to cause toxicity [74]. The initial dose should be given with an anaesthetist present; usually the infusion will be started in the operating theatre, often soon after induction, where the patient will be closely monitored. We recommend continuous ECG and pulse oximetry and regular non-invasive blood pressure (every 5 minutes during initial infusion and for the first 15 minutes thereafter). The initial infusion should be completed before skin incision, if possible.

9 **After an initial loading dose, an infusion of i.v. lidocaine at 1.5 mg.kg^{-1}.h^{-1} is recommended, subject to review and re-assessment**. There is no evidence supporting one dose over another for the initial dose or subsequent infusion but these doses have the practical advantage of being numerically the same. Such a dose usually results in plasma concentrations < 5 μg.ml^{-1} [9]. Altering the infusion rate, for instance in the recovery room or thereafter, should be a decision taken by a consultant anaesthetist or intensivist. Frequent changes of infusion rate are to be discouraged.

10 **A suitable infusion device should be used**. Pumps should be dedicated, labelled, lockable and tamperproof, and adjustable so that both a fixed rate and fixed upper rate limit can be set. Anti-siphon and anti-reflux mechanisms should be in place. Commercially prepared syringes and/or bags of lidocaine are available and may reduce the risk of errors in concentration. In any case, a standard concentration and/or formulation should be used throughout the hospital, and specified in the standard operating procedure.

11 **The lidocaine infusion should be delivered through a separate, dedicated cannula**. There should be a minimum flow of sodium chloride 0.9% at 10 ml.h^{-1}, from a dedicated separate fluid bag, to flush in the lidocaine and help reduce tracking (redness) up the vein. This line must have a one-way valve so that lidocaine cannot track retrogradely into simultaneous infusions. The infusion line should be labelled with an ISO-standard grey 'lidocaine' label. There should be a separate lidocaine monitoring chart.

12 **The duration of infusion of i.v. lidocaine should not generally exceed 24 h**. In practice, 24 h is often sufficient as postoperative pain will decrease with time and other analgesics can still be given. Most patients do not benefit from prolonged infusion, though some (for instance, those with chronic pain) might. If the infusion is to be extended after 24 h, this decision should be made by a consultant anaesthetist or intensivist and/or the acute pain team and be within the scope of the relevant hospital guidelines. The infusion rate should also be reduced to 50%.

13 **Outside the operating theatre/recovery room, patients receiving i.v. lidocaine infusions should ideally be managed in a monitored bedspace such as a high dependency unit (level 2 care)**. Observations should be made every 15 min for the first hour, then hourly as a minimum thereafter (increased as necessary). Nurses should be trained in the signs of toxicity; an example of educational material for this purpose is available in the online Supporting Information (Appendix S3). ECG monitoring should be continued in the high dependency area, although it should be noted that cardiovascular signs and ECG changes are late manifestations of lidocaine toxicity. Neurological symptoms and signs are the earliest and include peri-oral tingling, tinnitus, light-headedness and restlessness. Particular vigilance is needed in patients with existing comorbidity. The hospital acute pain team should be involved in monitoring and follow-up.

14 **Lipid emulsion 20% should be readily available wherever i.v. lidocaine is used, and staff should know where it is kept**. This treatment [105] should be used according to the Association of Anaesthetists' management guideline [106].

15 **Clinicians should remember the possibility of toxicity even though there may be other explanations for a given clinical presentation**. In the event of an adverse incident in a patient receiving an i.v. lidocaine infusion: preserve the pump with its settings and memory intact in order to enable investigation; and take blood for later analysis of lidocaine levels in both ethylenediaminetetra-acetic acid (EDTA) tubes and lithium heparin tubes, as the local requirements for assays vary.

In summary, i.v. lidocaine appears to offer some benefits to people undergoing surgery but these must be

balanced against the possible risks. The nature and likelihood of specific risks and benefits is likely to vary across different types of patient and different surgical operations. Careful use of i.v. lidocaine can minimise the risks.

Acknowledgements

AS is Senior Editor for *Anaesthesia* and also co-ordinating editor for the Cochrane Anaesthesia Review Group, which produced the Cochrane systematic review of effectiveness. AM has received an honorarium from Heron therapeutics. The UK division of the European Society of Regional Anaesthesia (RA-UK) "*endorse these safety guidelines for use in circumstances where a clinician feels i.v. lidocaine may be helpful despite the limited evidence of benefit*". The Faculty of Pain Medicine (FPM) sent the following statement: "*The FPM cautiously welcomes the safety statement on i.v. lidocaine. The FPM cannot fully endorse this treatment and aspects of surrounding practice until there is more robust evidence about efficacy and safety for perioperative pain relief and more research surrounding best practice. It is recognised that i.v. lidocaine is widely used for its effect on postoperative pain and recovery but it can be, and has been, fatal when used inappropriately and incorrectly. Intravenous lidocaine is to be regarded as a 'high risk' medicine*." No other external funding or competing interests declared.

References

1. Gordh T. Xylocaine, a new local analgesic. *Anaesthesia* 1949; **4**: 4–9.
2. US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=006488 (accessed 14/04/20).
3. de Clive-Lowe SG, Desmond J, North J. Intravenous lignocaine anaesthesia. *Anaesthesia* 1958; **13**: 138–46.
4. Bartlett EE, Hutserani O. Xylocaine for the relief of postoperative pain. *Anesthesia and Analgesia* 1961; **40**: 296–304.
5. Koppert W, Zeck S, Sittl R, Likar R, Knoll R, Schmelz M. Low-dose lidocaine suppresses experimentally induced hyperalgesia in humans. *Anesthesiology* 1998; **89**: 1345–53.
6. Dunn LK, Duriex ME. Perioperative use of intravenous lidocaine. *Anesthesiology* 2017; **126**: 729–37.
7. Meaney ED, Reid L, Srivastava D. A survey on the use of intravenous lidocaine infusion for acute pain in Scottish Hospitals. *British Journal of Pain* 2020; **2**: 98–103.
8. Hermanns H, Hollmann MW, Stevens MF, et al. Molecular mechanisms of action of systemic lidocaine in acute and chronic pain: a narrative review. *British Journal of Anaesthesia* 2019; **123**: 335–49.
9. Eipe N, Gupta S, Penning J. Intravenous lidocaine for acute pain: an evidence-based clinical update. *British Journal of Anaesthesia Education* 2016; **16**: 292–8.
10. Barreveld A, Witte J, Chahal H, Durieux ME, Strichartz G. Preventive analgesia by local anesthetics: the reduction of postoperative pain by peripheral nerve blocks and intravenous drugs. *Anesthesia and Analgesia* 2013; **116**: 1141–61.
11. Frauenknecht J, Kirkham KR, Jacot-Guillarmod A, Albrecht E. Analgesic impact of intra-operative opioids vs. opioid-free anaesthesia: a systematic review and meta-analysis. *Anaesthesia* 2019; **74**: 651–62.
12. Stevens J, Trimboli A, Samios P, et al. A sustainable method to reduce postoperative oxycodone discharge prescribing in a metropolitan tertiary referral hospital. *Anaesthesia* 2019; **74**: 292–9.
13. Hunter AR. The toxicity of xylocaine. *British Journal of Anaesthesia* 1951; **23**: 153–61.
14. Bennett EDL. A personal account of lignocaine overdosage. *British Journal of Anaesthesia* 1957; **29**: 81–3.
15. Christie LE, Picard J, Weinberg GL. Local anaesthetic systemic toxicity. *British Journal of Anaesthesia Education* 2015; **15**: 136–42.
16. Greenwood E, Nimmo S, Paterson H, et al. Intravenous lidocaine infusion as a component of multimodal analgesia for colorectal surgery—measurement of plasma levels. *Perioperative Medicine* 2019; **8**: 1. https://doi.org/10.1186/s13741-019-0112-4.
17. Weibel S, Jelting Y, Pace NL, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. *Cochrane Database of Systematic Reviews* 2018; (6): CD009642. https://doi.org/10.1002/14651858.CD009642.pub3.
18. Warburton D.Mum dies after two heart attacks when hospital gave her unlicensed drugs. *The Mirror*. 14 December 2019. https://www.mirror.co.uk/news/uk-news/mum-dies-after-two-heart-21100201 (accessed 14/04/2020).
19. Smith AF. In search of excellence in anaesthesiology. *Anesthesiology* 2009; **110**: 4–5.
20. Marret E, Rolin M, Beaussier M, Bonnet F. Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. *British Journal of Surgery* 2008; **95**: 1331–8.
21. McCarthy GC, Megalla SA, Habib AS. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. *Drugs* 2010; **70**: 1149–63.
22. Vigneault L, Turgeon AF, Côté D, et al. Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. *Canadian Journal of Anaesthesia* 2011; **58**: 22–37.
23. Sun Y, Li T, Wang N, Yun Y, Gan TJ. Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials. *Diseases of the Colon and Rectum* 2012; **55**: 1183–94.
24. Chang YC, Liu CL, Liu TP, Yang PS, Chen MJ, Cheng AP. Effect of perioperative intravenous lidocaine infusion on acute and chronic pain after breast surgery: a meta-analysis of randomized controlled trials. *Pain Practice* 2017; **17**: 336–43.
25. Ventham NT, Kennedy ED, Brady RR, et al. Efficacy of intravenous lidocaine for postoperative analgesia following laparoscopic surgery: a meta-analysis. *World Journal of Surgery* 2015; **39**: 2220–34.
26. Kranke P, Jokinen J, Pace NL, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. *Cochrane Database of Systematic Reviews* 2015; (7): CD009642. https://doi.org/10.1002/14651858.CD009642.pub2.
27. Cassuto J, Wallin G, Hogstrom S, Faxen A, Rimback G. Inhibition of postoperative pain by continuous low-dose intravenous infusion of lidocaine. *Anesthesia and Analgesia* 1985; **64**: 971–4.
28. Groudine SB, Fisher HA, Kaufman RP Jr, et al. Intravenous lidocaine speeds the return of bowel function, decreases postoperative pain, and shortens hospital stay in patients undergoing radical retropubic prostatectomy. *Anesthesia and Analgesia* 1998; **86**: 235–9.

29. Kuo CP, Jao SW, Chen KM, et al. Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. *British Journal of Anaesthesia* 2006; **97**: 640–6.
30. Herroeder S, Pecher S, Schonherr ME, et al. Systemic lidocaine shortens length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. *Annals of Surgery* 2007; **246**: 192–200.
31. Kaba A, Laurent SR, Detroz BJ, et al. Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. *Anesthesiology* 2007; **106**: 11–8.
32. Wu CT, Borel CO, Lee MS, et al. The interaction effect of perioperative cotreatment with dextromethorphan and intravenous lidocaine on pain relief and recovery of bowel function after laparoscopic cholecystectomy. *Anesthesia and Analgesia* 2005; **100**: 448–53.
33. Koppert W, Weigand M, Neumann F, et al. Perioperative intravenous lidocaine has preventive effects on postoperative pain and morphine consumption after major abdominal surgery. *Anesthesia and Analgesia* 2004; **98**: 1050–5.
34. Harvey KP, Adair JD, Isho M, Robinson R. Can intravenous lidocaine decrease postsurgical ileus and shorten hospital stay in elective bowel surgery? A pilot study and literature review. *American Journal of Surgery* 2009; **198**: 231–6.
35. Yardeni IZ, Beilin B, Mayburd E, Levinson Y, Bessler H. The effect of perioperative intravenous lidocaine on postoperative pain and immune function. *Anesthesia and Analgesia* 2009; **109**: 1464–9.
36. Lauwick S, Kim DJ, Mistraletti G, Carli F. Functional walking capacity as an outcome measure of laparoscopic prostatectomy: the effect of lidocaine infusion. *British Journal of Anaesthesia* 2009; **103**: 213–9.
37. Lauwick S, Kim DJ, Michelagnoli G, et al. Intraoperative infusion of lidocaine reduces postoperative fentanyl requirements in patients undergoing laparoscopic cholecystectomy. *Canadian Journal of Anaesthesia* 2008; **55**: 754–60.
38. Bryson GL, Charapov I, Krolczyk G, Taljaard M, Reid D. Intravenous lidocaine does not reduce length of hospital stay following abdominal hysterectomy. *Canadian Journal of Anaesthesia* 2010; **57**: 759–66.
39. Swenson BR, Gottschalk A, Wells LT, et al. Intravenous lidocaine is as effective as epidural bupivacaine in reducing ileus duration, hospital stay, and pain after open colon resection: a randomized clinical trial. *Regional Anesthesia and Pain Medicine* 2010; **35**: 370–6.
40. Cepeda MS, Delgado M, Ponce M, Cruz CA, Carr DB. Equivalent outcomes during postoperative patient-controlled intravenous analgesia with lidocaine plus morphine versus morphine alone. *Anesthesia and Analgesia* 1996; **83**: 102–6.
41. Chia YY, Tan PH, Wang KY, Liu K. Lignocaine plus morphine in bolus patient-controlled intravenous analgesia lacks post-operative morphine-sparing effect. *European Journal of Anaesthesiology* 1998; **15**: 664–8.
42. Saadawy IM, Kaki AM, Abd El Latif AA, Abd-Elmaksoud AM, Tolba OM. Lidocaine vs. magnesium: effect on analgesia after a laparoscopic cholecystectomy. *Acta Anaesthesiologica Scandinavica* 2010; **54**: 549–56.
43. Wuethrich PY, Romero J, Burkhard FC, Curatolo M. No benefit from perioperative intravenous lidocaine in laparoscopic renal surgery: a randomised, placebo-controlled study. *European Journal of Anaesthesiology* 2012; **29**: 537–43.
44. Kim TH, Kang H, Hong JH, et al. Intraperitoneal and intravenous lidocaine for effective pain relief after laparoscopic appendectomy: a prospective, randomized, double-blind, placebo-controlled study. *Surgical Endoscopy* 2011; **25**: 3183–90.
45. Kim TH, Kang H, Choi YS, et al. Pre- and intraoperative lidocaine injection for preemptive analgesics in laparoscopic gastrectomy: a prospective, randomized, double-blind, placebo-controlled study. *Journal of Laparoendoscopic and Advanced Surgical Techniques and Videoscopy* 2013; **23**: 663–8.
46. Kim HO, Lee SR, Choi WJ, Kim H. Early oral feeding following laparoscopic colorectal cancer surgery. *Australia and New Zealand Journal of Surgery* 2014; **84**: 539–44.
47. Tikuisis R, Miliauskas P, Samalavicius NE, Zurauskas A, Samalavicius R, Zabulis V. Intravenous lidocaine for post-operative pain relief after hand-assisted laparoscopic colon surgery: a randomized, placebo-controlled clinical trial. *Techniques in Coloproctology* 2014; **18**: 373–80.
48. Yang SY, Kang H, Choi GJ, et al. Efficacy of intraperitoneal and intravenous lidocaine on pain relief after laparoscopic cholecystectomy. *Journal of International Medical Research* 2014; **42**: 307–19.
49. Cepeda MS, Africano JM, Polo R, Alcala R, Carr DB. What decline in pain intensity is meaningful to patients with acute pain? *Pain* 2003; **105**: 151–7.
50. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996; **17**: 1–12.
51. Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain: a systematic review of randomized controlled trials. *Pain* 2006; **126**: 91–101.
52. Walker KJ, Smith AF. Premedication for anxiety in adult day surgery. *Cochrane Database of Systematic Reviews* 2009; (4): CD002192. https://doi.org/10.1002/14651858.CD002192.pub2.
53. Forget P, Borovac JA, Thackeray EM, Pace NL. Transient neurological symptoms (TNS) following spinal anaesthesia with lidocaine versus other local anaesthetics in adult surgical patients: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2019; (12): CD003006. https://doi.org/10.1002/14651858.CD003006.pub4.
54. Walker KJ, McGrattan K, Aas-Eng K, Smith AF. Ultrasound guidance for peripheral nerve blockade. *Cochrane Database of Systematic Reviews* 2009; (4): CD006459. https://doi.org/10.1002/14651858.CD006459.pub2.
55. Jüni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. *British Medical Journal* 2001; **323**: 42–6.
56. Pasquina P, Tramèr MR, Walder B. Prophylactic respiratory physiotherapy after cardiac surgery: systematic review. *British Medical Journal* 2003; **327**: 1379.
57. Chalmers TC, Smith H, Blackburn B, et al. A method for assessing the quality of a randomized control trial. *Controlled Clinical Trials* 1981; **2**: 31–49.
58. Jüni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *Journal of the American Medical Association* 1999; **282**: 1054–60.
59. Moore RA, Mhuircheartaigh RJN, Derry S, McQuay HJ. Mean analgesic consumption is inappropriate for testing analgesic efficacy in post-operative pain: analysis and alternative suggestion. *European Journal of Anaesthesiology* 2011; **28**: 427–32.
60. Myles PS, Christelis N. Measuring pain and analgesic response. *European Journal of Anaesthesiology* 2011; **28**: 399–400.
61. Jewer JK, Wong MJ, Bird SJ, Habib AS, Parker R, George RB. Supplemental perioperative intravenous crystalloids for postoperative nausea and vomiting. *Cochrane Database of Systematic Reviews* 2019; (3): CD012212. https://doi.org/10.1002/14651858.CD012212.pub2.
62. Blessberger H, Lewis SR, Pritchard MW, et al. Perioperative beta-blockers for preventing surgery-related mortality and morbidity in adults undergoing cardiac surgery. *Cochrane*

Database of Systematic Reviews 2019; (9): CD013435. https://doi.org/10.1002/14651858.CD013435.
63. Grady MV, Mascha E, Sessler DI, Kurz A. The effect of perioperative intravenous lidocaine and ketamine on recovery after abdominal hysterectomy. *Anesthesia and Analgesia* 2012; **115**: 1078–84.
64. Ahn E, Kang H, Choi GJ, et al. Intravenous lidocaine for effective pain relief after laparoscopic colectomy: a prospective, randomized, double-blind, placebo-controlled study. *International Surgery* 2015; **100**: 394–401.
65. Dewinter GBE, Teunkens A, Vermeulen K, Al Tmimi L, Van de Velde M, Rex S. Systemic lidocaine fails to improve postoperative pain, but reduces time to discharge readiness in patients undergoing laparoscopic sterilization in day-case surgery: a double-blind, randomized, placebo-controlled trial. *Regional Anesthesia and Pain Medicine* 2016; **41**: 362–7.
66. Maquoi I, Joris JL, Dresse C, et al. Transversus abdominis plane block or intravenous lignocaine in open prostate surgery: a randomized controlled trial. *Acta Anaesthesiologica Scandinavica* 2016; **60**: 1453–60.
67. De Oliveira CMB, Sakata RK, Slullitel A, Salomao R, Lanchote VL, Issy AM. Effect of intraoperative intravenous lidocaine on pain and plasma interleukin-6 in patients undergoing hysterectomy. *Revista Brasileira de Anestesiologia* 2015; **65**: 92–8.
68. Ortiz MP, Godoy MC, Schlosser RS, et al. Effect of endovenous lidocaine on analgesia and serum cytokines: double-blinded and randomized trial. *Journal of Clinical Anesthesia* 2016; **35**: 70–7.
69. Weinberg L, Rachbuch C, Ting S, et al. A randomised controlled trial of peri-operative lidocaine infusions for open radical prostatectomy. *Anaesthesia* 2016; **71**: 405–10.
70. Yon JH, Choi GJ, Kang H, Park JM, Yang HS. Intraoperative systemic lidocaine for pre-emptive analgesics in subtotal gastrectomy: a prospective, randomized, double-blind, placebo-controlled study. *Canadian Journal of Surgery* 2014; **57**: 175–82.
71. Afshari A, Wetterslev J, Smith AF. Can systematic reviews with sparse data be trusted? *Anaesthesia* 2017; **72**: 12–6.
72. Shah A, Smith AF. Trial sequential analysis: adding a new dimension to meta-analysis. *Anaesthesia* 2020; **75**: 15–20.
73. Foldes FF, Malloy R, McNall PG, Koukal LR. Comparison of toxicity of intravenously given local anaesthetic agents in man. *Journal of the American Medical Association* 1960; **172**: 1493–8.
74. Bromage PR, Robson JG. Concentrations of lignocaine in the blood after intravenous, intramuscular, epidural and endotracheal administration. *Anaesthesia* 1961; **16**: 461–78.
75. Gianelly R, von der Groeben JO, Spivack AP, Harrison DC. Effect of lidocaine on ventricular arrhythmias in patients with coronary heart disease. *New England Journal of Medicine* 1967; **277**: 1215–9.
76. Sawyer DR, Ludden TM, Crawford MH. Continuous infusion of lidocaine in patients with cardiac arrhythmias. *Archives of Internal Medicine* 1981; **141**: 43–5.
77. Rowland M, Thomson PD, Guichard A, Melmon KL. Disposition kinetics of lidocaine in normal subjects. *Annals of the New York Academy of Sciences* 1971; **179**: 383–98.
78. LeLorier J, Grenon D, Latour Y, et al. Pharmacokinetics of lidocaine after prolonged intravenous infusion in uncomplicated myocardial infarction. *Annals of Internal Medicine* 1977; **87**: 700–6.
79. Martin F, Cherif K, Gentili ME, et al. Lack of impact of intravenous lidocaine on analgesia, functional recovery, and nociceptive pain threshold after total hip arthroplasty. *Anesthesiology* 2008; **109**: 118–23.
80. Insler SR, O'Connor M, Samonte AF, Bazaral MG. Lidocaine and the inhibition of postoperative pain in coronary artery bypass patients. *Journal of Cardiothoracic and Vascular Anesthesia* 1995; **9**: 541–6.
81. Striebel H, Klettke U. Is intravenous lidocaine infusion suitable for postoperative pain management? *Schmerz* 1992; **6**: 245–50.
82. Birch K, Jørgensen J, Chraemmer-Jørgensen B, Kehlet H. Effect of i.v. lignocaine on pain and the endocrine metabolic responses after surgery. *British Journal of Anaesthesia* 1987; **59**: 721–4.
83. El-Tahan MR, Warda OM, Diab DG, Ramzy EA, Matter MK. A randomised study of the effects of perioperative i.v. lidocaine on hemodynamic and hormonal responses for caesarean section. *Journal of Anesthesia* 2009; **23**: 215–21.
84. Grigoras A, Lee P, Sattar F, Shorten G. Perioperative intravenous lidocaine decreases the incidence of persistent pain after breast surgery. *Clinical Journal of Pain* 2012; **28**: 567–72.
85. Lee EH, Lee HM, Chung CH, et al. Impact of intravenous lidocaine on myocardial injury after off pump coronary artery surgery. *British Journal of Anaesthesia* 2011; **106**: 487–93.
86. Lie KI, Wellens HJ, van Capelle FJ, Durrer D. Lidocaine in the prevention of primary ventricular fibrillation. *New England Journal of Medicine* 1974; **291**: 1324–6.
87. de Oliveira CMB, Issy AM, Sakata RK. Intraoperative intravenous lidocaine. *Revista Brasiliera de Anestesiologia* 2010; **60**: 325–33.
88. Thomson PD, Melmon KL, Richardson JA, et al. Lidocaine pharmacokinetics in advanced heart failure, liver disease, and renal failure in humans. *Annals of Internal Medicine* 1973; **78**: 499–508.
89. Weinberg L, Peake B, Tan C, Nikfarjam M. Pharmacokinetics and pharmacodynamics of lignocaine: a review. *World Journal of Anesthesiology* 2015; **4**: 17–29.
90. Pfeifer HJ, Greenblatt DJ, Koch-Weser J. Clinical use and toxicity of intravenous lidocaine. A report from the Boston collaborative drug surveillance program. *American Heart Journal* 1976; **92**: 168–73.
91. Dale GJ, Phillips S, Falk GL. The analgesic efficacy of intravenous lidocaine infusion after laparoscopic fundoplication: a prospective, randomised, double-blind, placebo-controlled trial. *Local and Regional Anesthesia* 2016; **9**: 87–93.
92. De Oliveira K, Eipe N. Intravenous lidocaine for acute pain: a single-institution retrospective study. *Drugs – Real World Outcomes* 2020; **7**: 205–12.
93. Smith AF, Plunkett E. People, systems and safety: resilience and excellence in healthcare practice. *Anaesthesia* 2019; **74**: 508–17.
94. Maclennan A, Smith AF. An analysis of critical incidents relevant to paediatric anaesthesia reported to the UK National Reporting and Learning System, 2006–2008. *Pediatric Anesthesia* 2011; **21**: 841–7.
95. Smith AF, Pope C, Goodwin D, Mort M. Communication between anesthesiologists, patients and the anesthesia team: a descriptive study of induction and emergence. *Canadian Journal of Anaesthesia* 2005; **52**: 915–20.
96. Smith AF, Shelly MP. Communication skills for anaesthetists: a practical introduction. *Canadian Journal of Anaesthesia* 1999; **46**: 1082–8.
97. Lin T, Smith T, Pinnock C (eds.) *Fundamentals of Anaesthesia*, , 4th edn. Cambridge: Cambridge University Press, 2016.
98. Anon. The licensing of medicines in the UK. *Drug and Therapeutics Bulletin* 2009; **47**: 45–7.
99. Cohen P. 'Off-label' use of prescription drugs: legal, clinical and policy considerations. *European Journal of Anaesthesiology* 1997; **14**: 231–5.
100. Singh S, Bansal P, Dureja J. Off-label use of drugs in regional anesthesia: a need for setting up policies. *Journal of Anaesthesiology and Clinical Pharmacology* 2017; **33**: 448–9.

101. General Medical Council, Good practice in prescribing. https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines#paragraph-70 (accessed 21/06/2020).
102. Sokol DK. Update on the UK law on consent. *British Medical Journal* 2015; **350**: h1481.
103. UK Department of Health. Drug safety update. Off-label or unlicensed use of medicines: prescribers' responsibilities, 2014. https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities (accessed 14/04/2020).
104. Schug SA, Palmer GM, Scott DA, Halliwell R, Trinca J. *Acute Pain Management: Scientific Evidence*, 4th edn. Melbourne: Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine, 2015.
105. Hoegberg LCG, Bania TC, Lavergne V, et al. Systematic review of the effect of intravenous lipid emulsion therapy for local anesthetic toxicity. *Clinical Toxicology* 2016; **54**: 167–93.
106. Association of Anaesthetists. Management of severe local anaesthetic toxicity. 2010. https://www.aagbi.org/sites/default/files/la_toxicity_2010_0.pdf (accessed 14/04/2020).

Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. Extended version of the 'effectiveness' and 'safety' sections of the main guideline.

Appendix S2. An example of a hospital standard operating procedure for the use of intravenous lidocaine.

Appendix S3. Sample educational material for training nurses and operating theatre staff in the recognition of local anaesthetic toxicity.