

Errors during the preparation of drug infusions: a randomized controlled trial

R. M. Adapa^{1,2}, V. Mani^{1,2}, L. J. Murray³, B. A. Degnan¹, A. Ercole^{1,2}, B. Cadman⁴, C. E. Williams^{1,2}, A. K. Gupta^{1,2,3} and D. W. Wheeler^{1,2*}

¹ Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Box 93, Cambridge CB2 0QQ, UK

² Department of Anaesthetics, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Box 93, Cambridge CB2 0QQ, UK

³ Simulation Centre, Postgraduate Medical Centre, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Box 111, Cambridge CB2 0QQ, UK

⁴ Department of Pharmacy, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Box 104, Cambridge CB2 0QQ, UK

* Corresponding author. E-mail: dww21@cam.ac.uk

Editor's key points

- The authors have addressed an important area of reducing medication error.
- The use of pre-filled syringes in a simulated septic shock patient was studied.
- Pre-filled syringes significantly reduced the likelihood of medication error.
- Although intuitive, these findings provide important evidence of improved patient safety by using pre-filled syringes.

Background. We investigated the extent and frequency of dose errors and treatment delays made as a consequence of preparing drug infusions at the bedside, rather than using pre-filled syringes.

Methods. Forty-eight nurses with critical care experience volunteered to take part in this randomized, blinded, controlled study conducted in the simulation centre of an urban hospital. They assisted in the management of a simulated patient with septic shock. Vasopressor infusions were prepared either by diluting concentrated drugs from ampoules or were provided in syringes pre-filled beforehand by an intensive care unit resident.

Results. The time taken for the infusion to be started and the final concentration of the drugs were measured. We also measured the concentration of infusions prepared by a pharmacist and a pharmaceutical company. Nurses took 156 s to start infusions when using pre-filled syringes compared with 276 s when preparing them *de novo*, a mean delay of 106 s [95% confidence interval (CI) 73–140 s, $P < 0.0001$]. One infusion prepared from ampoules contained one-fifth of the expected concentration of epinephrine; another contained none at all. Medication errors were 17.0 times less likely when pre-filled syringes were used (95% CI 5.2–55.5), and infusions prepared by pharmacy and industry were significantly more likely to contain the expected concentration ($P < 0.001$ for norepinephrine and $P = 0.001$ for epinephrine).

Conclusions. Providing drug infusions in syringes pre-filled by pharmacists or pharmaceutical companies would reduce medication errors and treatment delays, and improve patient safety. However, this approach would have substantial financial implications for healthcare providers, especially in less developed countries.

Keywords: infusions, intravenous; medication errors, prevention and control; safety; vasopressor, compounding

Accepted for publication: 21 May 2012

Administering drugs by i.v. infusion is a mainstay in many fields of medicine. There is a widespread perception that drug infusions are now provided in pre-filled syringes, prepared in bulk by pharmaceutical manufacturers or on a smaller scale in individual hospital pharmacies. While this may be true for some countries or individual institutions, this is a misperception: it is still very common for drug infusions to be prepared on the ward or at the bedside as and when they are needed.

Task analysis has identified 41 potential steps in the process of preparing a drug infusion.¹ It is therefore not surprising that the process is prone to error: on our critical care unit, we found that repeated errors were being made when infusions were prepared from concentrated stock solutions and diluted at the bedside.² These included several instances of patients receiving more than four times the intended dose of magnesium. Even after measures were taken to improve prescription and preparation, more than three-quarters of

infusions still differed from the prescribed concentration by more than 10%.

Medication errors are an important cause of healthcare-associated harm to patients. A patient's risk of experiencing a medication error on an intensive care unit (ICU) is ~10% per day,^{3, 4} and about 10% of these errors are substantial enough to warrant life-sustaining treatments.⁵ On the ICU, many drugs are administered by infusion, which appear particularly prone to error. Medication errors with infusions frequently result from mistakes during preparation, due to inaccuracies in drug-volume calculations, imprecision with volume measurements, inadequate mixing during dilution, or fatigue, excessive workload, or inexperience among staff.^{6–9} Other investigators have also found significant differences between the prescribed and delivered concentrations of drug infusions when they are prepared at the bedside, including vasopressors, opioids, and acetylcysteine.^{7, 10–13} However, the direct clinical consequences of the errors associated with the preparation infusions are more difficult to quantify.

We evaluated the extent and frequency of medication errors made during the preparation and administration of potentially life-preserving drug infusions in an emergency. We measured the time nurses took to institute infusions, comparing the process of drawing up and diluting drugs from ampoules *de novo* with the use of pre-filled syringes. In addition, we measured the extent and frequency of dose errors, comparing the concentration of the delivered infusion with that requested with control infusions made under calm, controlled conditions by physicians, pharmacists, and the pharmaceutical industry. The emergency clinical scenario was that of a critically ill patient, who had become haemodynamically unstable as a consequence of septic shock, recreated in a high-fidelity patient simulator.

Hypotheses

We had two primary (null) hypotheses: (i) that there would be no significant difference between the time taken to prepare and institute infusions when preparing them *de novo* vs using pre-filled syringes, and (ii) that there would be no significant difference in the concentrations of the infusions prepared.

Methods

The study protocol was reviewed by an ethics panel, who decided that formal approval was not needed (UK LREC reference number 05/Q0108/116). The scenario was enacted using an adult mannequin in the hospital's high-fidelity patient simulator centre (Human Patient Simulator, Medical Education Technologies, Sarasota, FL, USA), which was configured as a standard hospital ward. The storage and presentation of the drugs, diluents, filter needles, documents, and other equipment required met the standards of our institution. Hospital-affiliated nurses in our institution with critical care experience volunteered to participate without payment. The Appendix shows the volunteers' briefing.

A randomization sequence of 48 unsorted non-unique numbers ranging from 0 to 1 was generated online (Research Randomizer, Social Psychology Network; available at www.randomizer.org) and implemented by a researcher (L.J.M.) who was not involved in data collection. This determined whether the nurses received pre-filled syringes or were required to prepare the infusions *de novo*.

Nurses were asked to assist a trainee intensive care physician to stabilize a haemodynamically unstable patient with septic shock before transfer from the ward to the ICU. The role of the physician was undertaken by an investigator (R.M.A. or V.M.). Having informed the nurse of the patient's history and requirements, he asked for a 50 ml infusion of norepinephrine at a concentration of 80 µg ml⁻¹. The arterial pressure did not recover despite this infusion, so soon afterwards the nurse was asked to provide a 50 ml infusion of epinephrine at a concentration of 100 µg ml⁻¹. These concentrations are standard in our institution. Requests were timed so as not to coincide with times that the nurse might be busy with other tasks, such as measuring or recording the 'patient's' observations.

The control pre-filled syringes used in the scenarios had been prepared in advance by the investigators (R.M.A. and V.M.) under normal conditions. Nurses required to make up the infusions *de novo* were provided with ampoules of norepinephrine (4 mg in 4 ml, Martindale, Romford, UK), epinephrine (1 mg in 1 ml, Martindale), syringes, needles, and sufficient saline (0.9% NaCl, Baxter, UK) to make up the total volume to 50 ml.

We defined the time taken to prepare an infusion as the time that elapsed between it being requested and its readiness for administration, namely when it was secured in the syringe driver. We measured the concentration of the catecholamine in each syringe, and the concentration of infusions of both drugs prepared in our pharmacy and sourced from the pharmaceutical industry. The concentrations of all infusions were audited against the United States Pharmacopeia (USP) standard that delivered concentrations should be within 10% of that prescribed.¹⁴

Audiovisual recordings of the scenarios were made with integrated time displayed. Having edited out the preparation step, an investigator (C.E.W.) blinded to each participant's randomization status subsequently calculated the time taken for each infusion to be prepared by subtracting the time at which the infusion was requested from the time it was ready. At the end of the scenario, the remnants of the drug solutions in the syringe were removed and stored in sterile containers at -20°C until analysis. All specimens were assayed by enzyme-linked immunosorbent assay (LDN Noradrenaline ELISA kit, Labor Diagnostika Nord GmbH, Germany; IBL Adrenaline ELISA kit, IBL International GmbH, Germany) in triplicate against standard curves of known dilution and positive and negative controls when appropriate, and resolved against four-parameter curve fit models as previously described.¹⁵ Controls were included to ensure that storage at -20°C did not result in appreciable changes in drug concentration. The coefficients of intra-assay variation

after dilution were 3.3% for norepinephrine and 3.9% for epinephrine.

Sample size estimation indicated that 24 participants were required in each group to achieve a significance level of 5% and study power of 80%, based on observations from other studies that suggested differences of 90 s in dose administration time and 30% in the concentration of the catecholamine drugs between the groups.^{2 16} We recorded the time taken from the physician's request for an infusion and it being ready to administer, and report the mean and median values with 95% confidence intervals (95% CI) and the inter-quartile range (IQR), respectively, rounded to the nearest whole second. These data were analysed using the Mann–Whitney test; Gaussian approximations of two-tailed *P*-values are reported.¹⁷ The concentrations of the catecholamine drugs were converted into a percentage of that expected by dividing the measured concentration by the prescribed concentration (80 µg ml⁻¹ for norepinephrine and 100 µg ml⁻¹ for epinephrine), thus 100% represented a drug at its exact expected concentration. We report the mean and median values with 95% CI and the IQR, respectively, and the standard deviation (*sd*) with 95% CI, each to one decimal place.¹⁸ Data were analysed using the Kruskal–Wallis test; Dunn's multiple comparison test was used to compare methods of preparation. We recorded whether the concentration of each infusion lay outside 10% of that expected and thus constituted a medication error as specified in the USP standard (i.e. the concentration was <90% or >110%),¹⁴ used χ^2 analysis to test for statistical significance, and calculated the odds ratio for a medication error. Non-parametric tests were chosen, as data were found not to be normally distributed using the Kolmogorov–Smirnov test. Data were also represented in scatter plots (GraphPad Prism, version 4.0b, GraphPad Software, CA, USA).

Results

The study was initiated and completed in 2009. Forty-eight critical care nurses consented to participate, and were randomized in equal proportions to two groups. All participants completed the scenario. Sixteen infusions were prepared in pharmacy and 16 sourced from the pharmaceutical industry.

Time taken to administer catecholamine infusions

Nurses using pre-filled syringes prepared the infusion more quickly than those who had to draw up the drug from glass ampoules and dilute them (Table 1 and Fig. 1). The mean time from an infusion being requested to a pre-filled syringe being ready to administer was 166 s for norepinephrine and 146 s for epinephrine, including the time it took to label the syringe with patient details and check the prescription chart against the 'patient's' identification wristband. The mean time taken to prepare a norepinephrine infusion *de novo* was 274 s and 277 s for epinephrine. The additional time taken—a statistically significant mean increase of 106 s (95% CI 73–140 s, *P*<0.001)—reflects the time taken

Table 1 The influence of infusion preparation technique on time taken to prepare infusions and drug concentration

Syringe type	Time taken from request to administration		Mean concentration of contents as percentage of that prescribed					
	Norepinephrine		Norepinephrine			Epinephrine		
	Mean time (95% CI) (s)	Mean time (95% CI) (s)	95% CI (%)	sd (95% CI)	Number meeting USP criteria (%)	95% CI (%)	sd (95% CI)	Number meeting USP criteria (%)
Prepared de novo	277 (246–308)	274 (242–306)	90.3 (82.3–98.4)	25.6 (19.9–35.9)	7/24 (29.2%)	80.9 (70.0–91.7)	19.0 (14.8–26.7)	12/24 (50.0%)
Pre-filled by physician	146 (129–164)	166 (134–198)	104.5 (99.9–109.1)	13.0 (10.1–18.3)	18/24 (75.0%)	92.2 (86.6–97.7)	10.9 (8.5–15.3)	16/24 (66.7%)
Pre-filled by pharmacy	—	—	102.8 (99.0–106.5)	8.5 (6.3–13.1)	15/16 (93.8%)	99.8 (95.3–104.3)	7.5 (5.6–11.2)	13/16 (81.2%)
Pre-filled by industry	—	—	102.1 (99.9–104.3)	6.5 (4.8–10.0)	16/16 (100%)	102.9 (99.4–106.3)	4.4 (3.3–6.6)	15/16 (93.8%)

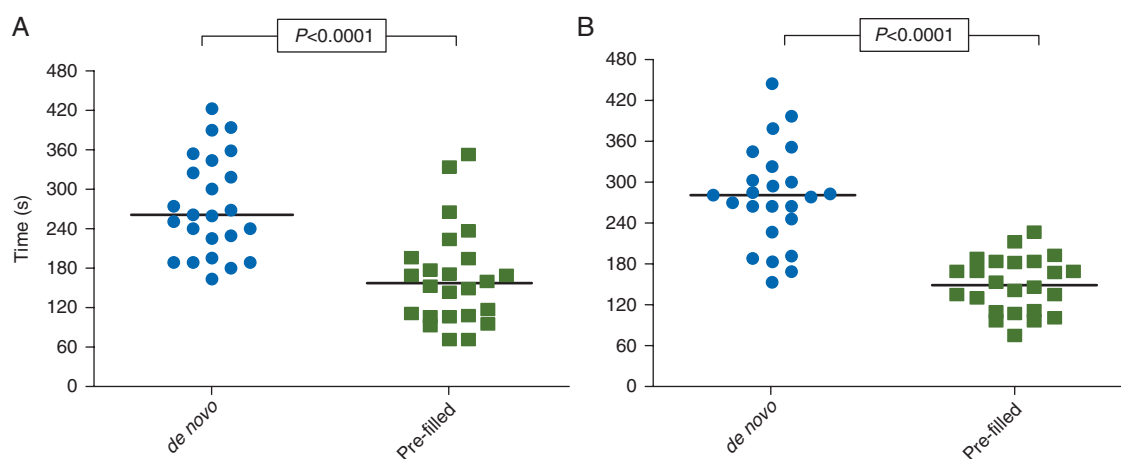


Fig 1 (A) The median time (s), indicated by the bars, taken to ready a pre-filled norepinephrine syringe for administration was 157 s (IQR 107–195 s) compared with 260 s (IQR 211–334 s) for the group of nurses making the infusion *de novo* ($P < 0.001$). (B) For epinephrine, which required more ampoules to be opened, the pre-filled syringes were readied in a median time of 147 s (IQR 107–180 s) while *de novo* preparation took 278 s (IQR 235–311 s) ($P < 0.001$). The adjusted mean time from request to administration was 106 s (95% CI 73–140 s) greater for all infusions made from ampoules rather than pre-filled syringes.

to check and open the ampoules, and dilute their contents to a total volume of 50 ml with 0.9% NaCl.

Concentration of catecholamine administered

Infusions that were made *de novo* in a stressful environment were prepared with less precision. Their mean concentrations and standard deviations were statistically significantly different from pre-filled syringes (Table 1 and Fig. 2, $P = 0.026$ for norepinephrine and $P < 0.001$ for epinephrine). Seven out of 24 (29.2%) norepinephrine and 12 out of 24 (50.0%) epinephrine infusions prepared by the nurses met the USP criteria for a correctly prepared infusion. Table 1 also illustrates the increasing precision with which infusions were prepared by healthcare workers in a calm environment, pharmacists, and the pharmaceutical industry, respectively, with increasingly higher proportions measured as being within 10% of the expected concentration (Table 1, $P < 0.001$ for norepinephrine and $P = 0.001$ for epinephrine). The odds ratio for a medication error when preparing infusions *de novo* was 17.0 (95% CI 5.2–55.5). One infusion was meant to contain epinephrine, but only contained saline. Review of the video recording showed that although the nurse opened the epinephrine ampoules, they were overlooked in the dilution step and not drawn up into the syringe. Another epinephrine infusion was one-fifth of the expected concentration, when reviewed it was clear that only one ampoule had been opened, rather than the five required.

Discussion

Preparing drug infusions at the bedside by diluting the contents of concentrated stock solutions is a process that can result in delays in treatment and clinically significant drug errors, even when experienced healthcare workers are

studied.¹³ It can be argued that requiring someone to undertake a task that requires precision in a stressful situation is bound to lead to errors and delays, and that our findings are predictable. In which case, it is necessary to ask why healthcare workers are expected to do so as part of their normal daily practice, and whether the errors are even more substantial when less experienced nurses and physicians are required to undertake these tasks? We suggest that there is little appreciation of the magnitude, costs, and clinical importance of the errors made. Thus, a combination of institutional resistance to change, and sensitivity to the increased cost of pre-filled syringes for generic drugs, means that the practice continues. Our findings show the magnitude and clinical importance of the errors; further studies will be needed to measure the costs.

The additional time needed to prepare infusions from ampoules is just over 100 s, reflecting the time taken to wipe the ampoules clean, draw the drugs up through a needle, and dilute the contents in the syringe. Good practice states that ampoules should be wiped with an alcohol swab and left to dry for 30 s before opening. We did not record whether nurses followed this procedure, but observed that many did not. This may be because the nurses were hurrying—the patient's arterial pressure was precipitously low—but cannot be sure whether the nurses changed their behaviour because the scenario was simulated. It is difficult to quantify the clinical consequences and long-term sequelae for a patient of a 1.75 min delay in instituting treatment for hypotension, but it would be reasonable to argue that treatments for critically ill patients should be initiated as promptly as possible.

The deviations from the expected concentration of the infusions made by hand were certainly clinically significant. The risk of a medication error was 17 times greater when

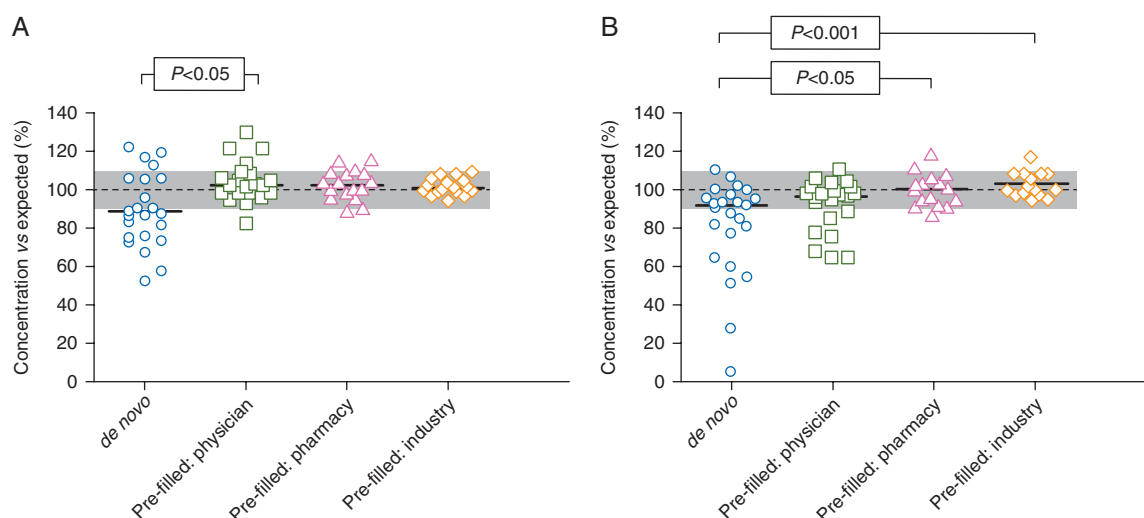


Fig 2 (A) Concentrations of norepinephrine infusions. Bars indicate a median concentration of 88.5% (IQR 75.9–106.3%) of that expected for *de novo* syringes, vs 102.9% (IQR 97.9–109.4%) for those pre-filled by physicians, 102.6% (IQR 96.8–108.8%) for those pre-filled in pharmacy, and 101.0% (IQR 98.9–106.0%) for those pre-filled by industry. The dotted line at 100% indicates the correct concentration; the shaded box represents $\pm 10\%$, the USP standard.¹⁴ Statistically significant differences between groups, on the basis of Dunn's multiple comparison test, are shown. (B) Concentrations of epinephrine infusions. Bars indicate a median concentration of 91.4% (IQR 70.8–96.4%) of that expected for *de novo* syringes, vs 96.4% (IQR 86.6–100.6%) for those pre-filled by physicians, 100.3% (IQR 93.0–105.1%) for those pre-filled in pharmacy, and 101.2% (IQR 97.4–108.4%) for those pre-filled by industry; 100% was the correct concentration. Statistically significant differences between the groups, on the basis of Dunn's multiple comparison test, are shown.

infusions were prepared by hand (95% CI 5.2–55.5). Here, the definition of a medication error is an infusion that differed from its expected concentration by more than 10%, based upon the USP standard, but it can be argued that this standard is too lax: quality control within the pharmaceutical industry would aim for infusions to be prepared with at least three orders of magnitude better precision. Perhaps even more worrying were the two infusions that contained no, or one-fifth of the expected concentration of, epinephrine. Administering these infusions would have had little or no effect on the patient's arterial pressure over some time, with profound implications for the patient's continuing management and eventual outcome. In our opinion, these are serious adverse events, constituting 8.3% of the epinephrine infusions made by hand. The particular problems encountered with epinephrine may have resulted from the increasing workload placed on the nurse towards the end of the scenario. However, it is notable that the physicians also made statistically significant mistakes when preparing the control infusions under normal conditions, perhaps reflecting the difficulty of opening five small ampoules with tiny labels.

A potential limitation of our study was that the emergency scenario was simulated. It is not clear to what extent behaviour is altered by lack of fidelity, or by observing it. We believe that these limitations are outweighed by the benefits of being able to create reproducible and convincing scenarios in which errors made have no clinical consequences, and can be used for study and learning. To ensure that our findings would be relevant beyond the ICU in a

developed country, we chose a case that is common and life-threatening, but the results could be generalized to any other situation in which drug infusions are prepared *de novo*. Another limitation is the challenge of measuring catecholamine concentrations precisely after multiple dilution steps, reflected in the coefficients of variation in our assays. This might explain why one industry-prepared infusion lay outside 10% of the expected concentration. However, although this adds an element of uncertainty to the absolute concentrations quantified and their relation to the 10% margin for error defined in the USP, it does not alter the magnitude of the differences seen between study groups. Finally, as we did not record nurses' seniority or experience, it is conceivable that differences between the groups reflect confounding differences in randomization. Importantly, the experienced physicians also had difficulty preparing infusions precisely under 'elective' conditions, so our findings are more likely to reflect a fundamental problem with the process itself rather than operator skill and experience.

The use of pre-filled syringes is not universal, nor is it standard, even in developed countries. The most compelling argument against using them is the obvious and immediate increased cost of providing less expensive generic drugs in relatively expensive syringes in an era of shrinking healthcare budgets. The pharmaceutical industry presents many drugs in pre-filled syringes, although these are mostly high cost biologicals such as large proteins or monoclonal antibodies. For an expensive drug, the cost of the syringe is a very small proportion of the overall cost. For vasopressors, the cost of the

syringe becomes a much larger proportion of the cost. In 2012, five 1 ml ampoules of epinephrine (1 mg ml^{-1}) cost approximately €3.00 (US\$4.00, £2.55), yet the market cost of a prefilled epinephrine syringe diluted to 0.1 mg ml^{-1} has been estimated at €8.00–€23.00 (\$11.20–\$32.00, £7.00–£20.00). Without absolutely compelling safety data, it is unlikely that these vastly increased costs could or would be met within current healthcare budgets, especially as the costs of the errors made by preparing drug infusions by hand have not been quantified. They could range from the insubstantial, for example, the costs of additional i.v. fluids or vasopressors required to correct the haemodynamic imbalance, to the very substantial, such as the cost impact of treating multi-organ failure, or ischaemic stroke. Even without these data, there are other reasons why wider availability of pre-filled syringes would not solve the problems we encountered. Drugs provided in pre-filled syringes can have a reduced drug shelf life due to interaction with the plastic, rubber bung, or silicone oil.¹⁹ Also, they are generally supplied in 'standard 70 kg adult' doses, so do not cater for small adults, children, and babies.

Our findings strongly favour the argument for making emergency drugs for adults more widely available in pre-filled syringes, produced to pharmaceutical industry standards. For drugs used less frequently, and to cater for children or adults who require individual doses, we recommend small-scale preparation in pharmacy whenever possible. Introduction of robotic technology and improved drug dose calculation and decision support software will further improve the quality of the infusions produced locally.^{20 21}

Declaration of interest

None declared.

Appendix

Briefing

The participant was briefed as follows: 'You have been called to the ward to assist one of the ICU physicians with a critically ill patient. It is thought that the patient has septic shock, and needs to be transferred to the ICU. No bed is currently available, but one should be ready in about 30 min. In the mean time, the ICU resident is stabilizing the patient on the ward. He has begun i.v. fluid resuscitation and placed central venous and peripheral arterial lines for invasive monitoring. Please assist the physician to manage the patient with a view to an imminent transfer to the ICU'.

References

- 1 Fraind DB, Slagle JM, Tubbesing VA, Hughes SA, Weinger MB. Re-engineering intravenous drug and fluid administration processes in the operating room: step one: task analysis of existing processes. *Anesthesiology* 2002; **97**: 139–47
- 2 Wheeler DW, Degnan BA, Sehmi JS, Burnstein RM, Menon DK, Gupta AK. Variability in the concentrations of intravenous drug infusions prepared in a critical care unit. *Intensive Care Med* 2008; **34**: 1441–7
- 3 Valentin A, Capuzzo M, Guidet B, et al. Patient safety in intensive care: results from the multinational Sentinel Events Evaluation (SEE) study. *Intensive Care Med* 2006; **32**: 1591–8
- 4 Herout PM, Erstad BL. Medication errors involving continuously infused medications in a surgical intensive care unit. *Crit Care Med* 2004; **32**: 428–32
- 5 Osmon S, Harris CB, Dunagan WC, Prentice D, Fraser VJ, Kollef MH. Reporting of medical errors: an intensive care unit experience. *Crit Care Med* 2004; **32**: 727–33
- 6 Donaldson TM, Mani V, Wheeler DW. Factors affecting the concentration of electrolyte infusions prepared from stock solutions. *Postgrad Med J* 2011; **87**: 83–8
- 7 Parshuram CS, To T, Seto W, Trope A, Koren G, Laupacis A. Systematic evaluation of errors occurring during the preparation of intravenous medication. *Can Med Assoc J* 2008; **178**: 42–8
- 8 Tissot E, Cornette C, Limat S, et al. Observational study of potential risk factors of medication administration errors. *Pharm World Sci* 2003; **25**: 264–8
- 9 McDowell SE, Ferner HS, Ferner RE. The pathophysiology of medication errors: how and where they arise. *Br J Clin Pharmacol* 2009; **67**: 605–13
- 10 Allen EM, Van Boerum DH, Olsen AF, Dean JM. Difference between the measured and ordered dose of catecholamine infusions. *Ann Pharmacother* 1995; **29**: 1095–100
- 11 Parshuram CS, Ng GYT, Ho TKL, et al. Discrepancies between ordered and delivered concentrations of opiate infusions in critical care. *Crit Care Med* 2003; **31**: 2483–7
- 12 Ferner RE, Langford NJ, Anton C, Hutchings A, Bateman DN, Routledge PA. Random and systematic medication errors in routine clinical practice: a multicentre study of infusions, using acetylcysteine as an example. *Br J Clin Pharmacol* 2001; **52**: 573–7
- 13 Dehmel C, Braune SA, Kreymann G, et al. Do centrally prepared solutions achieve more reliable drug concentrations than solutions prepared on the ward? *Intensive Care Med* 2011; **37**: 1311–6
- 14 United States Pharmacopeial Convention. *USP 797 United States Pharmacopeia*. Rockville, MD: Stationery Office Books, 2007
- 15 Murphy JF, Davies DH, Smith CJ. The development of enzyme-linked immunosorbent assays (ELISA) for the catecholamines adrenalin and noradrenalin. *J Immunol Methods* 1992; **154**: 89–98
- 16 Wheeler DW, Carter JJ, Murray LJ, et al. The effect of drug concentration expression on epinephrine dosing errors: a randomized trial. *Ann Intern Med* 2008; **148**: 11–4
- 17 Sheskin DJ. *Handbook of Parametric and Nonparametric Statistical Procedures*. Boca Raton, FL: Chapman & Hall/CRC, 2007
- 18 R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing, 2007. Available from <http://www.r-project.org/> (accessed 16 February 2012)
- 19 Ludwig DB, Carpenter JF, Hamel JB, Randolph TW. Protein adsorption and excipient effects on kinetic stability of silicone oil emulsions. *J Pharm Sci* 2010; **99**: 1721–33
- 20 Pedersen CA, Schneider PJ, Scheckelhoff DJ. ASHP national survey of pharmacy practice in hospital settings: dispensing and administration—2008. *Am J Health Syst Pharm* 2009; **66**: 926–46
- 21 Lehmann CU, Kim GR, Gujral R, Veltri MA, Clark JS, Miller MR. Decreasing errors in pediatric continuous intravenous infusions. *Pediatr Crit Care Med* 2006; **7**: 225–30