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# Do centrally pre-prepared solutions achieve more reliable drug concentrations than solutions prepared on the ward?

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**Abstract** *Purpose:* To compare the concentration conformity of infusion solutions manually prepared on intensive care units (ICU) with solutions from pharmacy-based, automated production. *Methods:* A prospective observational study conducted in a university hospital in Germany. Drug concentrations of 100 standardised infusion solutions manually prepared in the ICU and 100 matching solutions from automated production containing amiodarone, noradrenaline or hydrocortisone were measured by high-performance liquid chromatography analysis. Deviations from stated concentrations were calculated, and the quality of achieved concentration conformity of the two production methods was compared. *Results:* Actual concentrations of 53% of the manually prepared and 16% of the machine-made solutions deviated by >5% above or below the stated concentration. A deviation of >10% was measured in 22% of the manually prepared samples and in 5% of samples from automated production. Of the manually prepared solutions, 15% deviated by >15% above or below the intended concentration. The mean concentration of the manually prepared solutions was 97.2% (SD 12.7%, range 45–129%) and of the machine-made solutions was 101.1% (SD 4.3%, range 90–114%) of the target concentration ($p < 0.01$). *Conclusions:* In this preliminary study, ward-based, manually prepared infusion solutions showed clinically relevant deviations in concentration conformity significantly more often than pharmacy-prepared, machine-made solutions. Centralised, automated preparation of standardised infusion solutions may be an effective means to reduce this type of medication error. Further confirmatory studies in larger settings and under conditions of routine automated production are required.

**Keywords** Medication error · Adverse drug events · Intensive care · Pharmaceutical preparations · Safety management · Quality assurance

## Introduction

Parenteral medication errors are a serious safety problem in intensive care units (ICU) and are recognised as a high-priority health care issue [1–3]. Such errors have been shown to occur commonly across national borders, different ICU settings and health care systems as well as being associated with additional morbidity and mortality [4, 5].

The process from the prescription to the administration of an infusion is complex and thus liable to a number of different errors [6, 7]; for example, Fraind et al. [8] described 41 distinct steps in this process. One source of medication errors arises from the manual preparation of individual infusion solutions by nursing and medical staff [9–12]. This can lead to calculation and preparation of incorrect drug concentrations, use of inappropriate diluents, contamination of solutions, insufficient mixing of ingredients and incorrect labelling of solutions. The variety of potential problems, the complexity of the process and the challenges of performing research in the ICU setting make it difficult to comprehensively evaluate the incidence and prevalence of all types of potential errors. Some of them may not be detected by inspection of medication charts, or by direct observation, and may not be recorded by self-reporting systems because they remain undiscovered [10, 13]. Only a few studies have actually measured drug concentrations of manually prepared infusion solutions in routine ICU practice, and have consistently found clinically relevant deviations from originally prescribed concentrations [14–16]. Automated pre-preparation of infusion solutions has been proposed as a means of reducing the risk of parenteral medication errors [17], and its use was recommended some years ago by the British Audit Commission [18]. Until now, no studies have systematically compared pharmacy production with manual ICU-based preparation.

The objective of this study is to compare the conformity of drug concentrations of ICU-based, on-demand, manually prepared infusion solutions with pre-prepared, machine-made solutions produced in the pharmacy.

## Methods

This prospective observational study was conducted in the Department of Intensive Care Medicine and the Department of Pharmacy of the University Medical Center Hamburg-Eppendorf in Germany from January to March 2008. Four medical and surgical adult ICUs with a total of 40 beds were involved.

Drug concentrations of 100 manually prepared and 100 machine-made standardised infusion solutions (50 ml) for syringe drivers for prescriptions of amiodarone (40 per group), noradrenaline (30 per group) or hydrocortisone (30 per group) were analysed by high-performance liquid chromatography (HPLC). The actual measured concentration was compared with the target concentration, and the conformities of the two production methods were compared.

Both ICU and pharmacy staff gave informed consent to participate in the study. The samples were anonymised before analysis.

### Prescription, preparation and collection of samples

All solutions were prepared according to the department's standardised prescriptions. The standardised prescriptions for amiodarone and hydrocortisone were 21 and 4 mg/ml, respectively. For noradrenaline there were four standard concentrations: 60, 120, 180 and 360 μg/ml.

The manual preparation of solutions was undertaken by ICU nurses as part of their routine care. The nurses were asked to place all used syringes with study-related drug prescriptions into fridges on the ward. The fridges were emptied three times daily. Aliquots of 1 ml from those syringes containing at least 1 ml of residual solution were further stored at −25°C (noradrenaline, hydrocortisone) or 2–8°C with light protection (amiodarone) until a weekly analysis of concentrations. Analysis was performed on consecutive eligible samples until predefined numbers for each of the three substances were reached.

The machine-made solutions were prepared by two pharmacy technicians in the pharmacy under the supervision of a pharmacist. Production was only for the purposes of this study, and the preparations were not used on the ward. As a first step, buffered solutions were manually prepared under laminar airflow from ampoules (amiodarone and noradrenaline) or vials of dissolved dry powder (hydrocortisone). These buffered solutions were then diluted by a mixing machine with appropriate solvents to produce 250 ml bulk solutions with the prescribed drug concentrations. Aliquots of 1 ml per bulk solution were stored at the same conditions as above and were also analysed weekly.

The syringes used during the study (Perfusor™; B. Braun, Melsungen, Germany) comprised polypropylene (wall) and synthetic polyisoprene rubber (plug), which are regarded as compatible with pharmaceutical ingredients.

### Laboratory analysis

All analyses were performed by independent, blinded laboratory technicians at a contract laboratory. Drug concentrations were measured using HPLC [19] (LichroGraph™ Merck-Hitachi; Thermo Fisher Scientific™). Calibration curves, prepared from defined standard concentrations of each of the three drugs, were constructed for each batch (correlation coefficient: 0.99). Triplicate quality-control samples for each of the three drugs were made up in defined concentrations and included in each of the weekly analyses. Accuracy, precision and further details are given in Table 1.

### Statistical analysis

WinSTAT™ (version 2007.1) for Microsoft Excel™ was used for statistical analysis. Drug concentrations were

**Table 1** HPLC analysis of amiodarone, hydrocortisone and noradrenaline

| | Amiodarone | Noradrenaline | Hydrocortisone |
|---|---|---|---|
| Nominal concentration | 21 mg/ml | 60/120/180/360 mg/l | 4 mg/ml |
| HPLC system | LichroGraph (Merck-Hitachi) | LichroGraph (Merck-Hitachi) | Thermo Fisher Scientific |
| Within-day | | | |
| Accuracy (%)[a] | 0.81 | 0.52 | 6.75 |
| Precision (%)[b] | 2.74 | 1.08 | 3.04 |
| 95% CI | 20.6–21.4 mg/dl | 59.6–60.4 mg/l | 3.9–4.1 mg/dl |
| Between-day | | | |
| Accuracy (%)[a] | 1.38 | 0.07 | 0.40 |
| Precision (%)[b] | 1.74 | 1.48 | 3.77 |
| 95% CI | 20.7–21.3 mg/dl | 59.2–60.8 mg/l | 3.9–4.1 mg/dl |

[a] Accuracy expressed as relative difference between mean concentration found and target concentration

[b] Precision expressed as relative standard deviation; 95% confidence interval (CI) of the true mean concentration of an infinite set of measurements

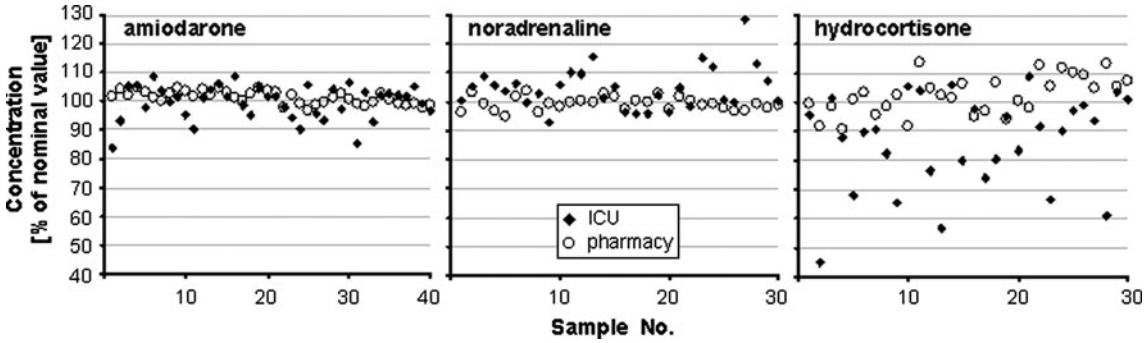


**Fig. 1** Concentration conformity of infusion solutions: 40 amiodarone, 30 noradrenaline and 30 hydrocortisone solutions were prepared both in the ICU (*black diamonds*) and in the pharmacy (*open circles*). Concentrations were analysed by HPLC and are expressed as percentages of the respective targeted standardised prescription concentration

analysed as percentages of the intended target concentration. Student's *T* test for independent variables was used to compare mean concentrations for the two production methods; *p* value <0.01 (two-sided) was considered significant.

## Results

### Overall results

We found that 53 (53%) of the ward-prepared solutions and 16 (16%) of the pharmacy-produced solutions had actual drug concentrations that deviated either above or below the intended concentration by at least 5% (Fig. 1). Deviations of more than 10% were measured in 22 (22%) of the manually prepared samples as opposed to 5 (5%) of the samples from automated production. We found that 15 (15%) of the manually prepared solutions deviated by more than 15% above or below the stated concentration, the maximum deviation being 55% below the declared concentration. The maximum deviation in the machine-made solutions was 14% above the target concentration. The mean concentration of all manually prepared solutions was 97.2% (SD 12.7%, range 45–129%) while that for the machine-made solutions was 101.1% (SD 4.3%, range 90–114%) (Fig. 1). The difference between the two groups was statistically significant ($p < 0.01$).

### Amiodarone

We found concentration deviations of at least 5% in 17 (43%) of the 40 manually prepared amiodarone solutions (9 above, 6 below the target concentration) but in none of the 40 machine-made solutions (Fig. 1). Deviation of more than 10% was measured in two (5%, both below the targeted concentration) of the manually prepared samples. The mean concentration of the 40 manually prepared amiodarone solutions was 99.7% (SD 6.1%, range 83–109%) as opposed to a mean of 101.4% (SD 2.3%, range 97–105%) for the machine-made solutions. The difference between the two groups was not statistically significant ($p = 0.1$).

### Noradrenaline

We found concentration deviations of at least 10% in 6 (20%, all above the target concentration) of the 30 manually prepared noradrenaline solutions but in none of the 30 machine-made solutions (Fig. 1). Another nine (30%, eight above the target concentration) samples of the manually prepared and one (3%) sample of the machine-made solutions deviated between 5% and 10%. The mean concentration of the 30 manually prepared noradrenaline solutions was 104.7% (SD 7.5%, range 92–129%) as opposed to a mean of 99.3% (SD 2.3%, range 94–104%) for the machine-made solutions. The difference between the two groups was statistically significant ($p < 0.001$).

### Hydrocortisone

We found concentration deviations of at least 10% in 14 (47%, all below the target concentration) of the 30 manually prepared hydrocortisone solutions compared with 5 (17%, all above the target concentration) of the 30 machine-made samples (Fig. 1). Another 7 (23%) samples of the manually prepared and 10 (33%) samples of the machine-made solutions deviated between 5% and 10%. The deviations were distributed evenly below and above the target concentration. The mean concentration of the 30 manually prepared hydrocortisone solutions was 86.6% (SD 16.3, range 45–115%) as opposed to a mean of 102.5% (SD 6.7%, range 90–113%) for the machine-made solutions. The difference between the two groups was statistically significant ($p < 0.001$).

## Discussion

In this preliminary study, solutions of amiodarone, noradrenaline or hydrocortisone prepared manually by ICU nurses during routine clinical care frequently showed clinically relevant deviations from the prescribed target concentrations. In contrast, solutions from automated production were significantly less variable and showed better concentration conformity, with only a few samples outside an acceptable limit of 10% deviation above or below the target concentration [20].

Our findings of significant concentration deviations in manually prepared solutions are in line with the findings of three previous studies in ICUs [14–16]. Allen et al. [14] measured concentrations of manually prepared infusions of dopamine, dobutamine and epinephrine in a paediatric ICU. They found significant concentration deviations from ordered concentrations due to preparation inaccuracies. Parshuram et al. [15] examined manually prepared morphine solutions on a paediatric ICU and found relevant concentration deviations in about two-thirds of samples. Wheeler et al. [16] found relevant concentration deviations in the majority of manually prepared solutions of insulin, norepinephrine, dopamine, potassium and magnesium in an adult ICU. However, none of these studies compared concentration conformities of manually prepared solutions with those of solutions from an automated production facility.

Our findings of a higher quality of drug concentrations of solutions prepared by automated production contrast with recent findings of Valentin et al. [5]. In their cross-sectional observational study on parenteral medication errors in ICU, they found a positive association between errors of drug administration and use of pre-prepared solutions. However, interpretation of this finding and comparison with our results is difficult since their cross-sectional results were obtained by means of self-report [20] and errors of drug preparation were not investigated.

Deviations from expected drug concentrations may have clinical implications such as the risk of adverse drug effects associated with overdosing or loss of therapeutic effects due to underdosing. Even for drugs where dosing is titrated to clinical effect, as with noradrenaline, incorrect concentrations can lead to misinterpretation of infusion rates and apparent dosing requirements, resulting in inadequate response and suboptimal clinical management.

By choosing quantitative concentration analysis, we selected an objective measure that is able to reveal preparation errors of concentration accurately, as opposed to investigating medication charts, patient conditions or voluntary error reporting systems. Due to the study design, we were unable to determine individual causes of concentration deviations. Differing results between the three drugs could have been due to specific compounding-related problems, but we can only speculate on the causes.

During the process of collecting consecutive samples, we ignored syringes that contained less than 1 ml solution and could not analyse those that were accidentally or deliberately discarded. The latter may have introduced a bias in favour of the manually produced preparations.

Furthermore, awareness that the study was taking place could have influenced the performance of all involved staff, an effect referred to as a "Hawthorne effect" [21]. However, the facts that the preparation process was not observed directly and that samples were collected anonymously probably reduced such an effect to an acceptable degree.

The ICU solutions were prepared as part of routine patient care, as opposed to the samples that were produced especially for the study in the pharmacy. The level of distraction in the ICU [22] may have introduced a bias in favour of the pharmacist technicians' performance. However, we postulate that, even under conditions of routine pharmacy production, the technicians' work environment would remain less distracting than the busy ICU environment. Moreover, for any routine automated production, as opposed to manual preparation on the

ward, regular and standardised measures of quality assurance are obligatory for each batch of solution.

Our results, in conjunction with the results of previous studies [14–16], raise general concerns about the quality of concentrations of manually prepared parenteral medications used in ICU.

Intensive care units should create awareness about this potential source of error and should ideally evaluate the quality of concentrations of solutions prepared in their unit. Regular, bed-side double-checking of manual preparations by a second nurse (the "four eyes principle") could improve quality but is likely to increase labour costs. The cost-effectiveness of implementing automated production of solutions is not known, and such an analysis would need to consider machine-related investment costs as well as potential savings in labour costs, indirect costs and intangible costs.

In summary, our results suggest that deviations from the prescribed concentration may occur frequently in manually prepared parenteral medications in ICUs and that centralised automated production of standardised infusion solutions may be an effective means of reducing such variation. However, these preliminary results require confirmatory studies investigating the quality of preparations in different and larger settings, under conditions of routine automated production and also focusing on aspects of cost and feasibility.

*Ethical standard:* Because the study was observational and no clinical interventions were performed, no formal approval of the hospital's ethics committee was necessary, according to local regulations. However, informed consent was obtained by all ICU nurses involved in the study and samples were collected anonymously.

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**Conflict of interest** None.

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