Potassium maldistribution revisited

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Objective: This study investigated the maldistribution of concentrated 15% potassium chloride after injection into one-litre, flexible, Ringer’s lactate bags.

Method: Twenty millilitres of concentrated 15% potassium chloride was injected into suspended, flexible, one-litre bags of Ringer’s lactate. The potassium was injected by hand, over either 4- (fast) or 20- (slow) second periods. The effect of two successive bag inversions on maldistribution was also investigated. A simulated infusion at 600 ml per hour was controlled using a volumetric pump. Sampling occurred at five-minute intervals for the first 20 minutes and at 10-minute intervals thereafter, until 90 minutes. Potassium concentrations were measured using an accurate, calibrated wide-range analyser that did not require specimen dilution. This experiment was repeated once. A duplicate set of experiments was performed with Bonney’s blue dye added to the potassium concentrate. Bonney’s blue distribution was evaluated visually.

Results: Significant maldistribution occurred. Maldistribution was not dependent on the injection rate. After 20 minutes to 30 minutes of commencing the infusion, maldistribution resulted in delivery of up to 64% and 85%, respectively, of the available potassium. Two bag inversions effectively homogenised the solution. The distribution of Bonney’s blue-stained concentrated potassium was inconsistent with the measured potassium concentrations.

Conclusion: Point-of-care potassium supplementation is frequently required in cardiac and other surgery. Anaesthesiologists should be cognisant of eliminating not only errors of substitution, but also maldistribution of the concentrated potassium. Potassium infusion rates should be controlled, preferably using an electronic infusion controller.

Keywords: anaesthesia-related death, complication, drug error, dye, homogenisation, hyperkalaemia, indicator, layering, magnesium, maldistribution, mistake, mixing, mortality, potassium, preventable

Introduction

After coronary artery bypass grafting, potassium concentrations lower and higher than 3.3 and 5.2 mmol per liter respectively have been associated with poorer outcome.1 Maintaining adequate levels frequently requires potassium administration by anaesthesiologists. However, medication errors, particularly incorrect identification of concentrated potassium chloride ampoules, have had significant human and financial costs.2,3 Indeed, the Joint Commission and similar national organisations have classified concentrated potassium chloride as a high-alert medication.4-14 One reason for this classification is that the intravenous injection of concentrated potassium, confused with sodium chloride or water to constitute antibiotics or flush intravenous catheters, has resulted in death.15-17 Recently, ampoule similarity resulted in the accidental subarachnoid injection of concentrated potassium, instead of bupivacaine.18 Typical safety guidelines have included the removal of concentrated potassium chloride from clinical areas, and storage only within certain locations (pharmacy, intensive care units and operating rooms); storage within a locked cupboard, as for controlled substances; supplying premixed potassium-containing bags; using easily distinguishable packaging and labels for bags and ampoules; and specifying on-site preparation protocols and administration using volumetric pumps.9,11,17,19,20 It has been argued that while safety guidelines to ensure that potassium administration errors “never occur again” are logical,21 they are not backed by objective evidence of efficacy.22 Safety guidelines may have unexpected effects on the functioning of healthcare systems and could instigate “the next error by trying to prevent the last one”.15,23 In this regard, a local distributor of 15% potassium chloride (Sabax, Adcock Ingram Critical Care, Johannesburg, South Africa) printed instructions in red type on both the box and each ampoule (Figure 1) that the contents must be diluted with more than 50 times its volume before use. However, in developing countries, concentrated potassium solutions for point-of-care dilution are still available in operating rooms and critical care areas.

Our department was consulted by forensic pathology about a hyperkalaemic arrest following combined open prosthetic aortic valve implantation and coronary artery bypass grafting at a hospital in another province. The anaesthesiologist’s report described difficult weaning from cardiopulmonary bypass and detailed potassium concentrations of 4.7 and 3.9 mmol/l immediately before and after successful weaning from bypass, respectively. After bypass, 40 mmol of concentrated 15% potassium chloride (Sabax®, Adcock Ingram Critical Care, Johannesburg, South Africa) were injected into a full litre of Ringer’s lactate and infused using a gravity-dependent infusion controller, at approximately 600 ml/hour. Twenty minutes after commencement of the infusion, asystole occurred, with serum potassium of 16.1 mmol/l measured during successful resuscitation.

We considered that the hyperkalaemia might have been caused by maldistribution of the concentrated potassium added to the Ringer’s lactate. Notwithstanding older descriptions,24-28 we re-investigated this phenomenon.

Method

We designed a series of blinded, randomised, controlled, laboratory experiments to mimic the index scenario, which interrogated factors influencing concentrated potassium distribution after addition to Ringer’s lactate. Institutional ethics committee approval was obtained (Protocol No. S13/05/107). Our null hypothesis was that in the absence of purposeful mixing, concentrated 15% potassium chloride solution distributes evenly.
after injection into a compressible one-litre bag of Ringer’s lactate solution. Twenty millilitres of concentrated 15% potassium chloride was injected via the dependent injection port into a suspended, one-litre lactate container (Viaflex®, Adcock Ingram Critical Care, under license from Baxter International, Johannesburg, South Africa). Each injection was performed using a new 20 ml syringe (Surgiplus®, China) attached to a new 18-G, 40 mm-long, hypodermic injection needle (Surgiplus®, China) inserted into the 40 mm injection port of the Ringer’s lactate container. The concentrated potassium was manually injected either “slowly” over approximately 20 seconds (1 ml/second) or “rapidly” over 4 seconds (5 ml/second). One “slow” injection bag was purposefully mixed, the bag being inverted twice over two seconds. The control was a one-litre bag of Ringer’s lactate, to which 20 ml of normal saline was added over four seconds. Braun Infusomat® fmS pumps (B Braun Melsungen, Melsungen, Germany) using an Infusomat® tubing set (TK 200) were used to control the infusion rate at 600 ml per hour. The infusion set was primed before the addition of solute to the Ringer’s lactate container. The experimental order was randomised by a blind card draw. To avoid bag manipulation, a paper label was attached to each drip hook. Sampling occurred immediately on commencement of the bag manipulation, a paper label was attached to each drip hook.

The rate of potassium delivery was constant in the control and agitate experiments. Potassium concentrations and delivery rates (Table 2 and Figure 2) peaked at the five-minute measurement in both the fast and slow experiments, and decreased progressively thereafter, becoming clinically indistinguishable from the control sometime between the 50- and the 80-minute measurements. Peak potassium concentrations were 165.1 and 268.1 mmol/l in the fast experiments, and 85.2 and 230.1 mmol/l in the slow experiments (Table 2). The potassium dose rates peaked during the second five-minute interval, averaging 9.4 and 7.0 mmol per five minutes for the slow and fast experiments, respectively (Figure 2).

When considering delivery as a percentage of total available potassium, 33 and 25% (representing 15 mmol and 11.1 mmol) would have been administered with the initial 100 ml in the fast and slow experiments, respectively. After 300 ml of fluid delivery, 71% and 67% of the total available potassium had to be within specified standards for analysis to occur. Experiment 1 was repeated one month later. The former and latter experiments were referred to as control 1 and control 2, respectively (Table 1). Data were entered into an Excel® spreadsheet for the calculation and graphing of the delineated scenarios. The trapezoid rule was applied to the measured potassium concentrations to calculate the dose. The primary end-points in experiment 1 were the concentrations and doses of potassium delivered over a 90-minute infusion.

Similar experiments (experiment 2) investigated maldistribution by interrogating the colour distribution occurring after 1 ml of Bonney’s blue, a dye comprising crystal violet and brilliant green (Hospital Supplies, Pretoria, South Africa) was added to 19 ml concentrated 15% potassium chloride or 19 ml normal saline. No formal quantification of this aspect of the study was undertaken. Homogenisation was evaluated by visual inspection of the colour distribution of the Bonney’s blue using photographs taken with a Panasonic® Lumix DMC-FZ18 (Matsishita Electric Industrial Company, Osaka, Japan) before and 5, 30, 60 and 90 minutes after adding concentrated potassium chloride and commencing the simulated infusion. This protocol was not repeated.

### Results

#### Experiment 1: Potassium concentrations

In both the control and agitate experiments, potassium concentrations were constant over the 90-minute experimental period, averaging 5.2 and 45.8 mmol/l, respectively (Table 2). The rate of potassium delivery was constant in the control and agitate experiments.

| Experimental arm | Injection time | Solute | Bag inversion | Timing |
|------------------|----------------|--------|---------------|--------|
| Control 1        | 4 seconds      | 20 ml 0.9% NaCl | No           | Baseline |
| Control 2        | 4 seconds      | 20 ml 0.9% NaCl | No           | 1 month |
| Agitate 1        | 20 seconds     | 20 ml 15% KCl  | Yes          | Baseline |
| Agitate 2        | 20 seconds     | 20 ml 15% KCl  | Yes          | 1 month |
| Slow 1           | 20 seconds     | 20 ml 15% KCl  | No           | Baseline |
| Slow 2           | 20 seconds     | 20 ml 15% KCl  | No           | 1 month |
| Fast 1           | 4 seconds      | 20 ml 15% KCl  | No           | Baseline |
| Fast 2           | 4 seconds      | 20 ml 15% KCl  | No           | 1 month |

**Table 1:** Experiment 1 protocol

| Experimental arm | Injection time | Solute          | Bag inversion | Timing |
|------------------|----------------|-----------------|---------------|--------|
| Control 1        | 4 seconds      | 20 ml 0.9% NaCl | No            | Baseline |
| Control 2        | 4 seconds      | 20 ml 0.9% NaCl | No            | 1 month |
| Agitate 1        | 20 seconds     | 20 ml 15% KCl   | Yes           | Baseline |
| Agitate 2        | 20 seconds     | 20 ml 15% KCl   | Yes           | 1 month |
| Slow 1           | 20 seconds     | 20 ml 15% KCl   | No            | Baseline |
| Slow 2           | 20 seconds     | 20 ml 15% KCl   | No            | 1 month |
| Fast 1           | 4 seconds      | 20 ml 15% KCl   | No            | Baseline |
| Fast 2           | 4 seconds      | 20 ml 15% KCl   | No            | 1 month |

NaCl: sodium chloride solution, KCl: potassium chloride solution
representing 32 mmol and 32.3 mmol of potassium in the fast and slow experiments, respectively, would have been administered (Figure 3).

**Experiment 2: Colour distribution using Bonney’s blue dye**

Photographs of stained potassium chloride five minutes after injection demonstrated a homogenous blue colour in the control and agitate experiments (Figure 4). The colour was distributed in the lower half of the Ringer’s lactate bag in the slow experiment, while the blue colouration spread higher in the fast experiment. Sixty minutes after commencing the infusion, the dye in the slow experiment was completely eliminated, while in the “fast” bag, a small amount of dye was still present (Figure 5).

**Discussion**

Following injection of concentrated potassium chloride into suspended, flexible one-litre Ringer’s lactate infusion bags, clinically concerning maldistribution was observed. Fifteen minutes after commencing a simulated 600 ml per hour infusion, maldistribution would have resulted in fourfold greater potassium delivery than if homogenised. This fourfold difference in the maldistributed compared to the homogenised solutions would have caused 25.4 mmol vs. 7.5 mmol of potassium to be delivered to a patient. Such a substantial dose, possibly in combination with a low cardiac output, was the likely cause of hyperkalaemia and cardiac arrest in the index case. Thus, our null hypothesis was rejected.

Cognitive psychology categorises unintentional drug errors into firstly, failure to execute a good plan, and secondly, into the correct execution of an inappropriate plan.23,29,30 The first type of error is defined as either a “slip” (lack of attention), or a “lapse” (omission owing to memory failure), occurring during routine tasks that require little cognitive input. The latter type of error is termed a “mistake”, which occurs when a normally good plan is misapplied.23,30 Potassium maldistribution conforms to this latter definition.

The number “1” denotes the first performance of the experiment, and the number “2” the second performance thereof. See the “Method” section for an explanation of the slow, fast, agitated, and control experiments. The slightly lower concentration of potassium in the control group was a result of saline dilution. The “0” minute measurement that effectively represents the infusion set prime, is very close to the 5.3 mmol/l potassium concentration expected in the Ringer’s lactate solution. The higher initial concentration measured in the fast experiment was owing to air bubbles activating the pump alarm, necessitating flushing of the giving set.

**Remedial guidelines aimed at eliminating concentrated* potassium errors make little if any mention of maldistribution. Research similar to that performed in this study has invariably followed unintended hyperkalemia due to maldistribution,31 the first report by Williams in 1973 concurring with this impetus. Such experiments (Table 3) have typically involved syringing (13 to 40 mmol) concentrated potassium into flexible intravenous fluid bags. Results generally echo our findings, unmixed bags consistently revealing maldistribution with impressive peak concentrations (e.g. 93031 and 135132 mmol/liter) and the bulk (70 to 80%) of added potassium delivered within 20 minutes of the infusion commencing.**

*The Joint Commission states “For potassium chloride, strengths of 2 mEq/ml or greater (specifically, vials of 20mEq/10ml and 40mEq/20ml) are considered concentrated”. http://www.jointcommission.org/standards_information/jcfaqdetails.aspx?StandardsFaqId=53&ProgramId=47
Maldistribution can also occur with heparin, insulin,32 chlorthiazide, diphenylhydantion,38 or magnesium, 41 the severity of the latter similar to that observed with potassium.41

More rapid injection rates would be expected to induce turbulence and greater homogenisation, but this was not observed in our experiments. Surprisingly, little is known about how the injection rate affects homogenisation as this parameter has been standardised in most experiments. 31, 32, 35, 37 The data variation resulting from the manual potassium injection in our study is nevertheless illustrative of what probably occurs clinically. It also emphasises that maldistribution relates primarily to the difference in density (baricity) of the solute and solvent. Hyperbaric solutions gravitate to the bottom of the intravenous fluid container. The specific gravity of both sodium chloride 0.9% and Ringer’s lactate are 1.045 g/ml,40 while that of 15% potassium chloride is 1.084–1.093 g/ml at 21 °C.34, 37, 39 Anaesthesiologists are conversant with baricity, epitomised by the directionality of intrathecally administered hyperbaric local anaesthetic solutions.18

Maldistribution has previously featured in anaesthesia-related problems being blamed for local anaesthetic neurotoxicity.42, 43 Purposeful mixing largely eliminates solute maldistribution. One,35 two (this experiment)38, 39 three41 and six32, 37 fluid bag inversions all effectively homogenised potassium- or magnesium-containing solutions. Manually shaking a hanging bag also proved to be effective.40 Squeezing or adding the potassium solute initially with the bag on its side, and then hung upright, ameliorates but does not eliminate the problem.37, 44 Thirteen cycles of normal handling, described as the removal of the bag from the drip stand, the addition of potassium and the return of the bag to the hook, were needed to facilitate complete mixing.36 Longer standing times, probably because of Brownian motion,37 improve solute and solvent mixing by between 10.5%40 and 50%,37 but on its own this is unreliable.34 Combining a short (10-second) injection time, initial horizontal bag position, and the needle parallel rather than at 45° to the long axis of the bag, afforded the least maldistribution. However, this combination was still insufficient to guarantee adequate, safe mixing.46 Maldistribution is aggravated by longer injection ports, short needles and partial (< 1 cm) insertion of the needle into the bag.31, 32, 35, 36 It is likely that wave reflection explains the good homogenisation invariably observed after potassium is injected into rigid (glass) or semi-rigid (polyolefin) containers.31, 32, 35, 37, 38 Nowadays, intravenous resuscitation fluids are seldom presented in glass containers.

In the index case, the potassium supplementation rate was intended to be 0.34 mmol/kg/hour, this being at the upper end of Evers’ and Maze’s46 recommended range of 0.2–0.4 mmol/kg/hour. The exact infusion rate should be based on serum potassium levels and the presence of hypokalaemia-related complications. Intravenous supplementation at the previously mentioned rates should be accompanied by monitoring of ECG rhythm and morphology, and frequent potassium serum concentrations.
The Synchron® CX 5 system used in this study to measure potassium concentrations had a measurement range that was wide enough not to require sample dilution. This avoided error magnification, a significant advantage over previous similar studies. Potassium measurement techniques in similar studies have included a flame photometer,32, 35, 38 the former specifying 200-fold sample dilution, a digital refractometer37 and a potassium ion-specific electrode requiring 1 000-fold dilution.39 Another study measured chloride concentrations with a formula used to derive potassium concentrations.40

Various coloured dyes (methylene blue31 and indigo carmine33) have been used to visually evaluate potassium distribution. Despite objective measurements not clouding our visual assessment, the distribution of potassium and Bonney’s blue appeared to be inconsistent. This discrepancy intimates that distribution depends on the independent densities of the solute.41 The potentially valuable suggestion of including coloured indicators to solutes needs to take their relative densities into consideration.

Study limitations include non-standardisation of the potassium chloride injection rate as we did not have a device capable of simulating the addition of 20 ml of potassium over either 20 or 4 seconds. This would have necessitated infusion rates of 3 600 and 18 000 ml/hour, respectively. Nonetheless, this limitation was revealing with regard to factors that influence solute maldistribution.

Statistical analysis was not performed as the experiment was aimed at reproducing index case events and interrogating the hypothesis. Furthermore, the aim was not to perform a descriptive, population-based study, but to highlight and demonstrate an important issue. The duplicate experiments produced close enough results, further experiments being superfluous. Financial and resource constraints also limit study repetitions. The double inversion technique should be further investigated as a reliable, simple method of potassium and other solute homogenisation.

In conclusion, remedial guidelines have hitherto focused on eliminating errors of potassium substitution, rather than maldistribution.21 The potential gravity of concentrated solute maldistribution was highlighted by the index case and confirmed in the experiment.49 A significant driver of this study was to highlight these dangers. To our knowledge, premixed solutions specifically for intravenous potassium supplementation are not commonly supplied by South African in-hospital pharmacies. Physicians and nurses in critical care areas in South Africa (and possibly in many other developing countries) are still likely to mix the solutions for potassium supplementation themselves.

The inversion of intravenous fluid containers at least twice after solute addition appears to be a simple and effective method of eliminating maldistribution. Other cornerstones of safe therapy include not treating mild, uncomplicated hypokalaemia, and monitoring plasma concentrations and ECG during intravenous potassium administration. Ideally, the rate of solutions that contain significant potassium concentrations should be regulated with an electronic infusion controller. The maximum dose recommendations of 0.2–0.4 mmol/kg/hour should be respected.

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### Table 3: Publications found regarding homogenization of potassium chloride. (Note that inversion is the only reproducible method ensuring adequate mixing)

| Author        | Publication date | Case study | Homogenization of potassium chloride in polyvinyl/chloride (PVC) bags compared to either glass or polyolefin semi rigid containers or syringes |
|---------------|-----------------|------------|----------------------------------------------------------------------------------------------------------------------------------|
| Williams      | 1973            | Yes (2 patients) | Mixing only adequate in PVC container that was inverted whilst adding solute |
| Lankton       | 1973            | Yes        | Mixing adequate in glass container Mixing in PVC container depends on needle position in injection port |
| Bigley        | 1974            | No         | Mixing only adequate with inversion |
| Schuna        | 1979            | No         | No bag inversion Used non rigid containers from different manufacturers Comparing side or dependent injection ports and needle position in port |
| Thompson      | 1980            | No         | Mixing only adequate after inverting bag 6 times |
| Bergman       | 1982            | No         | Mixing only adequate after inverting bag 6 times |
| Drew          | 1986            | No         | Mixing technique not investigated specifically |
| Deardorff     | 1993            | No         | Mixing most effective after inverting bag twice |
| Donaldson     | 2011            | No         | Concentrations in PVC bags were less variable compared to syringes. Vigorous mixing and allowing preparation to stand or 24 hours also improved homogeneity |
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