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Review

Potassium maldistribution revisited

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Abstract:

Background: This study investigated maldistribution of concentrated 15% potassium chloride after injection into one-liter, flexible, Ringer's lactate bags.

Methods: Twenty milliliters of concentrated 15% potassium chloride was injected into suspended, flexible, liter bags of Ringer's lactate. The potassium was injected by hand, over either four ("fast") or twenty ("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 5-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 analyzer not requiring 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 to 30 minutes of commencing the infusion, maldistribution resulted in delivery of up to 64 to 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 measured potassium concentrations.

Conclusions: In cardiac and other surgery, point of care potassium supplementation is frequently required. Anaesthetists should be cognisant of eliminating not only errors of substitution, but also maldistribution of concentrated potassium. Potassium infusion rates should be controlled, preferably using an electronic infusion controller.

Keywords: potassium, hyperkalemia, anaesthesia related death, drug error, maldistribution, layering, complication, preventable, mixing, homogenization, mortality, magnesium, dye, indicator, mistake

Introduction

Medication errors contribute significantly to human and financial costs.[1-4] One of these errors involves incorrect identification of concentrated potassium chloride ampoules. 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.[5] Maintaining adequate levels frequently requires potassium administration by anesthesiologists. Indeed, the Joint Commission and similar National organizations have classified concentrated potassium chloride as a high alert medication.[6-14] 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 accidental subarachnoid injection of concentrated potassium instead of bupivacaine.[18] Typical safety guidelines have included the removal of concentrated potassium ampoules 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, 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 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 has printed instructions in red type on both the box and each ampoule (Figure 1) that contents must be diluted with more than fifty 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 hyperkalemic arrest following combined open prosthetic aortic valve insertion and coronary artery bypass grafting at a hospital in another province. The anesthesiologists' report described difficult weaning from cardiopulmonary bypass

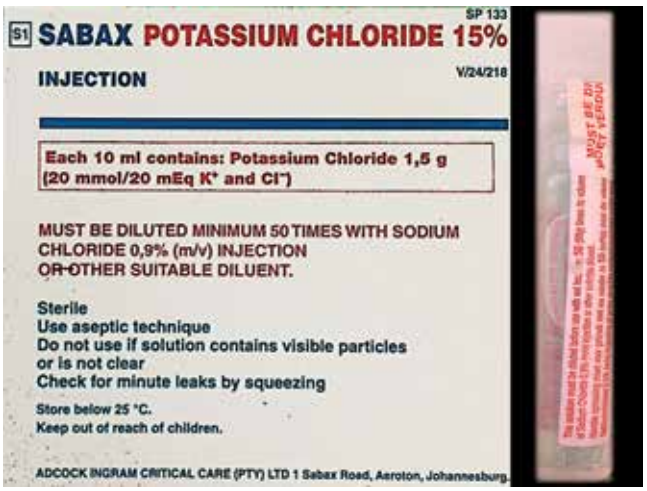

Figure 1: Concentrated potassium chloride box and ampoule indicating instructions for dilution before point of care use.

and detailed potassium concentrations of 4.7 and 3.9 mmol/L immediately before and after successful weaning from bypass respectively. After bypass, forty millimoles of concentrated 15% potassium chloride (Sabax, Adcock Ingram Critical Care, Johannesburg, South Africa) were injected into a full liter 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 the hyperkalemia 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.

Methods

We designed a series of blinded, randomized, 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 number S13/05/107). Our null hypothesis was that in the absense of purposeful mixing, concentrated 15% potassium chloride solution distributes evenly after injection into a compressible liter bag of Ringer's lactate solution. Twenty milliliters of concentrated 15% potassium chloride (Sabax, Adcock Ingram Critical Care, Johannesburg, South Africa) was injected via the dependent injection port into a suspended, one liter (Viaflex®) Ringer's lactate container (Adcock Ingram Critical Care under license from Baxter International Inc., Johannesburg, South Africa). Each injection was performed using a new 20 ml syringe (Surgiplus®, China) attached to a new 18 gauge, 40 millimeter 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 (1ml/s) or "rapidly" over 4 seconds (5ml/s). One "slow" injection bag was purposefully mixed, the bag being inverted twice over 2 seconds. The control was a liter bag of Ringer's lactate to which 20 ml of normal saline had been added over 4 seconds. Braun Infusomat® FM pumps (Infusomat fmS, B Braun Melsungen AG, Melsungen, Germany) using Infusomat® tubing set (TK 200) were used to control the infusion rate at 600 ml per hour. The infusion set was primed before addition of solute to the Ringer's lactate. The experimental order was randomized by blind card draw. To avoid bag manipulation, a paper label was attached to each drip hook. Sampling occurred immediately on commencement of the infusion, thereafter every 5 minutes for the first 20 minutes, and at 10-minute intervals for the following 70 minutes. Five-milliliter samples were collected in barcoded, sterile. plastic laboratory test tubes. Potassium concentrations were analyzed within 2 hours of samples collection. Analysis was performed using a SYNCHRON CX 5 System (Beckman Coulter, Fullerton, CA, USA.) with a potassium analytical range between 2.0 to 200.0 mmol/liter. Samples were not diluted. SYNCHRON CX 5 calibration and quality control results, performed immediately prior to sample analysis, were to be within specified standards for analysis to happen. Experiment 1 was repeated one month later, the former and latter experiments referred to for example as "Control 1" and "Control 2" respectively (Table I). Data was entered into an Excel® spreadsheet (Microsoft Excel® for MAC 2011, Microsoft Corporation, Redmond, USA) for calculation and graphing of the delineated scenarios. To calculate dose, the trapezoid rule was applied to the measured potassium concentrations. The primary endpoints 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 color distribution occurring after 1 ml of

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 is sodium chloride solution; KCl is potassium chloride solution.

Bonney's blue, a dye comprising crystal violet and brilliant green, (Hospital Supplies, Pretoria, South Africa) had been added to 19 ml concentrated 15% potassium chloride or 19 ml of normal saline. No formal quantification of this aspect of the study was made. Homogenization was evaluated by visual inspection of the color distribution of the Bonney's blue using photographs taken with a Panasonic Lumix DMC-FZ18, 18 x Optical Zoom, (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.

In both the "Fast" and "Slow" experiments, potassium concentrations and delivery rates (Table 2, Figure 2) peaked at the five minute measurement, and decreased progressively thereafter, becoming clinically indistinguishable from control sometime between the 50 to 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). 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 15.0 and 11.1 mmol) would have been administered with the initial 100 millilitres in the Fast and Slow experiments respetively. After 300 millilitres of fluid delivery, 71 and 67% of the total available potassium represeting 32.0 and 32.3 mmol of potassium in the Fast and Slow experiments respectively, would have been administered (Figure 3).

Experiment 2: Colour distribution using Bonneys blue dye

Photographs of stained potassium chloride 5 minutes after injection demonstrated a homogenous blue color in the "Control" and "Agitate" experiments (Figure 4). In the "Slow" experiment, the colour was distributed in the lower half of the Ringer's lactate bag while in the "Fast" experiment, the blue colouration spread higher. Sixty minutes after commencing the infusion, the dye in

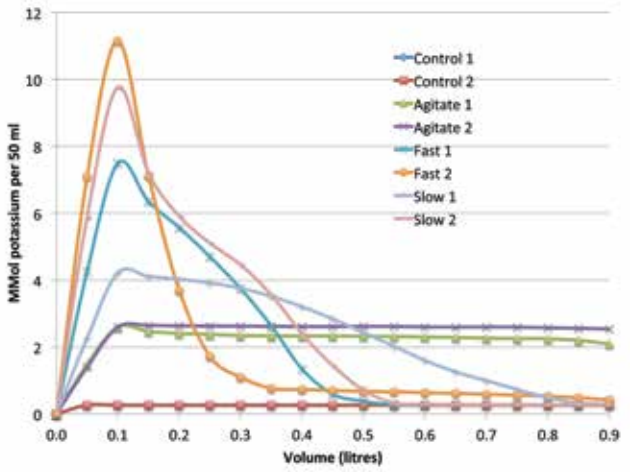

Figure 2. Potassium dose rate (mmol per 5 minutes) versus time at an infusion rate of 600 ml per hour. In all Fast and Slow experiments, a peak in the potassium dose rate was observed at the ten minute interval. At peak rates in this graph, more than half an ampoule of concntrated potasssium would have been delivered over a five minute period. The extremely rapid dose rate decline is indicative of severe maldistribution. The similar shape of the curves is indicative of the interactions between density and turbulence, these factors promoting maldistribution and homogenization respectively. The constant dose rate in the "Agitate" and "Control" bags is indicative of potassium homogenization.

Table 2: The measured potassium concentrations (mmol/l) in fluid discharged from each liter Ringer's Lactate container. The number "1" denotes the first performance of the experiment and the number "2" the second performance of the experiment. See "Methods" section for explanation of slow, fast agitated and control experiments. The slightly lower oncentration of potasium in the control group is a result of saline dilution. The "0 minute" measurements that effectively represent infusion set prime, are very close to the 5.3 mmol/l potassium concentrations expected in ringers lactate. The higher initial concentration measured in the "fast" experiment was due to air bubbles activating the pump alarm, necessitating flusing of the giving set.

Time (mins)	Slow 1	Slow 2	Fast 1	Fast 2	Control 1	Control 2	AgitateAg 1	Agitate 2
0	5.31	5.28	5.27	15.68	5.28	5.28	5.82	5.28
5	85.19	230.05	165.05	268.14	5.18	5.16	53.62	50.70
10	83.39	160.55	134.69	177.77	5.09	5.17	50.21	52.99
15	81.09	127.85	119.34	106.90	5.13	5.18	48.49	52.78
20	80.01	108.61	103.49	40.75	5.15	5.18	47.84	52.64
30	73.45	82.72	65.39	15.72	5.09	5.17	46.63	52.43
40	60.91	36.25	13.96	14.25	5.13	5.13	46.63	52.15
50	44.55	6.81	5.49	13.36	5.09	5.23	46.38	52.43
60	27.82	5.65	5.46	12.53	5.15	5.24	45.95	51.87
70	17.18	5.56	5.42	11.56	5.16	5.19	45.09	52.08
80	7.14	5.56	5.44	10.33	5.13	5.17	44.91	51.39
90	5.54	5.51	5.49	7.87	5.17	5.20	41.03	50.63

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-liter Ringers 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 homogenized. This fourfold difference in the maldistributed compared to the homogenised solutions would have caused 25.4 versus 7.5 mmol of potassium to be delivered to a pateint. Such a substantial dose, possibly in combination with a low cardiac output, was the likely cause of hyperkalemia and cardiac arrest in the index case. Our null hypothesis was thus rejected.

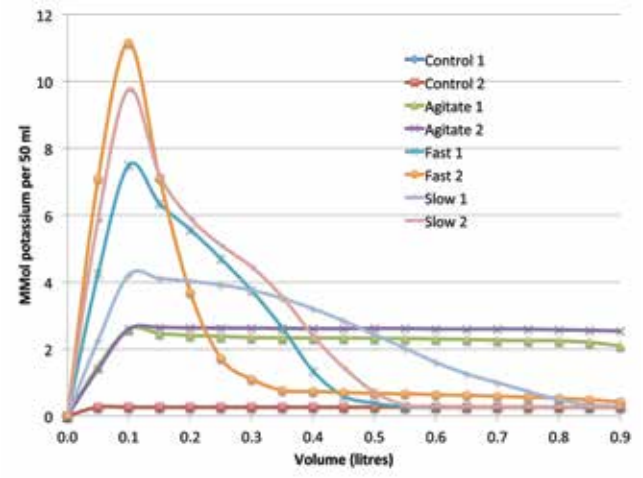

Figure 3. Percentage of total potassium available in the liter of fluid infused versus volume infused. With the worst maldistribution, approximately 80% of the available potassium would potentially have been delivered to the patient in the first 250 ml of carrier fluid. The almost straight line relationships in the Control and Agitated experiments indicate a constant potassium infusion rate.

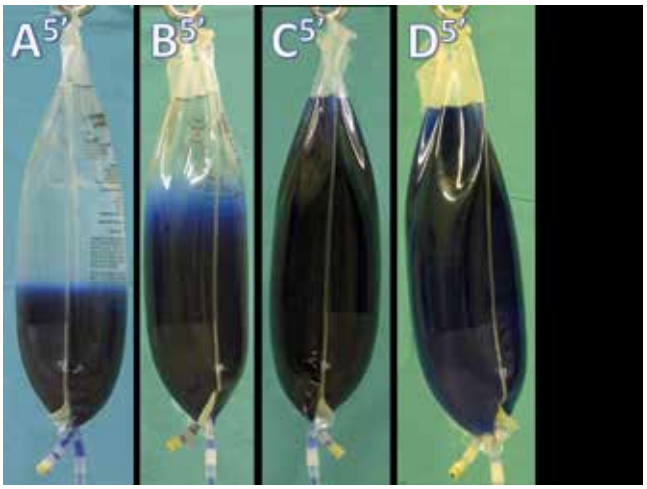

Figure 4. Distribution of potassium chloride stained with Bonney's blue in ringers lactate five minutes after commencing infusion. A homogenous blue color is visible in the "Agitate C5'" and "Control D5'" experiments. In the "Slow A5'" experiment, the colour was distributed in the lower half of the bag while in the "Fast B5'" experiment, the blue colouration spread higher.

Cognitive psychology categorizes unintentional drug errors into firstly, failure to execute a good plan and secondly, correct execution of an inappropriate plan.[23,29,30] The first type of error is defined as either "slips" (lack of attention), or "lapses" (omission due to memory failure), occurring during routine tasks requiring little cognitive input. The latter type of error are termed "mistakes" which occur when a normally good plan is misapplied,[23,30] potassium maldistribution conforming to this definition.

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,[31-38] the first report by Williams in 1973 concurring with this impetus. Such experiments (Table III) 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. 930[31] and 1351[32] mmol/liter) and the bulk (70 to 80%) of added potassium delivered within 20 minutes of the infusion commencing.[31,32,36-40] 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 homogenization, but this was not observed in our experiments. Surprisingly little is known about how injection rate affects homogenization as most experiments standardized this parameter.[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 emphasizes maldistribution is primarily related to difference in density (baricity) of solute and solvent, hyperbaric solutions gravitating to the bottom of the intravenous fluid container. The specific gravity of both sodium chloride 0.9% and Ringer's lactate are 1,0045 g/ml(40) while that of 15% potassium chloride is 1,084 to 1,093 g/ml at 21°C.[34,37,39] Anesthesiologists are conversant with baricity, epito-

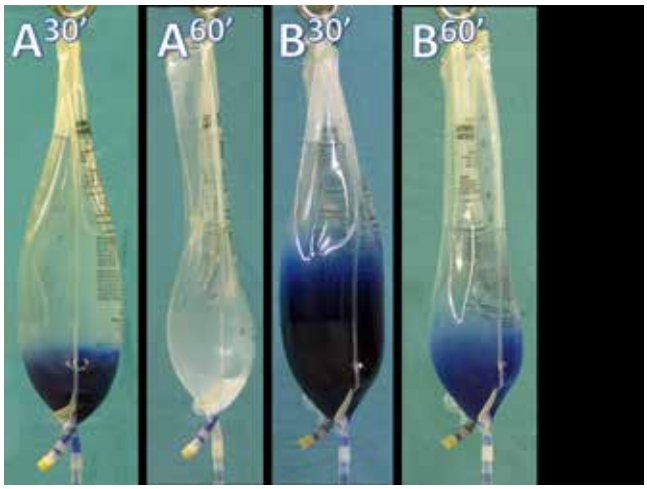

Figure 5. Distribution of potassium chloride stained with Bonney's blue in ringers lactate thirty and sixty minutes after commencing infusion in the Fast and Slow experiments. Sixty minutes after commencing the infusion, the dye in the "Slow A60'" experiment was completely eliminated while in the "Fast B60'" bag, a small amount of staining was still present

mized by the directionality of intrathecally administered hyperbaric local anesthetic solutions.[18] Maldistribution has previously featured in anesthesia related problems, being blamed for local anesthetic neurotoxicity.[42,43]

Purposeful mixing largely eliminates solute maldistribution. One,[35] two (this experiment)[38,39] three[41] and six[32, 37] fluid bag inversions all effectively homogenized potassium or magnesium containing solutions. Manually shaking a hanging bag also proved effective.[40] Squeezing or adding the potassium solute with the initially bag on its side and then hung upright, ameliorates but does not eliminate the problem.[37,44] Thirteen cycles of normal handling, described as a removal of the bag from the drip stand, addition of potassium, and return of the bag to the hook, were needed to facilitate complete mixing.[40] Longer standing times, probably due to Brownian motion,[37] improve solute and solvent mixing by between 10.5[40] to 50%,[37] but on its own, is unreliable.[34] Combining a short (10 second) injection time, horizontal initial bag position, and 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.[40] Maldistribution is aggravated by longer injection ports, short needles, and partial (<1 cm) insertion of the needle into the bag.[33,35,36] Wave reflection likely explains the good homogenization invariably observed after potassium is injected into rigid (glass) or semirigid (polyolefin) containers.[31,32,35,37,38] Intravenous resuscitation fluids are seldom presented in glass containers.

In the index case, potassium supplementation rate was intended to be 0.34 mmol/kg/hour, this being at the upper end of the Evers and Maze's(46) recommended range of 0.2 to 0.4 mmol/kg/hour. Exact infusion rates should be based on serum potassium levels and the presence of hypokalemia related complications. Intravenous supplementation at abovementioned rates should be accompanied by monitoring of EKG 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 wide enough not to require sample dilution. This avoided error magnification, a significant advantage over 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 refractometer[37], and a potassium ion specific electrode requiring 1000 fold dilution.[34] Another study measured chloride concentrations with a formula used to derive potassium concentrations.[40]

Various coloured dyes (methylene blue,[31] indigo carmine[33]) have been used to visually evaluate potassium distribution. Despite objective measurements not clouding our visual assessments, distribution of potassium and Bonney's blue appeared inconsistent. This discrepancy imitates that distribution depends on the independent densities of solute, an important consideration when implementing the potentially valuable suggestion of adding dye to indicate solute maldistribution.[41] The potentially valuable suggestion of including coloured indicators to solutes needs consideration of their relative densities.

Study limitations include non-standardization of the potassium chloride injection rate as we did not have a device capable of simulating addition of 20 milliliters of potassium over eiether 20 or 4 seconds, this necessiating infusion rates of 3600 and 18000 ml/hour respectively. Nonetheless, this limitation was revealing regarding factors influencing 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 were thus regarded as superflous, and financial and resource constraints also limited study repetitions. The double bag inversion should be further investigated as a reliable, simple method of potassium and other solute homogenization.

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,[45] a significant driver of this study being 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 many other developing countries, likely still mix solutions for potassium supplementation themselves. 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 hypokalemia, and monitoring plasma concentrations and EKG during intravenous potassium administration. Solutions containing significant potassium concentrations should ideally have their rate regulated with an electronic infusion controller. The maximum dose reccomendations of 0.2 to 0.4 mmol/kg/hour should be respected.

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