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Original Article

On-site production of a dialysis bath from dry salts. Results of solute concentration control by routine clinical chemistry

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Abstract

Background. Dialysis bath production, at least in Europe, is currently based on pre-produced aqueous solutions of dialysis salts (concentrate), which are re-handled by dialysis machines to deliver the final dialysate concentrations. Because of the logistics of aqueous solution creation, a large amount of transportation capacity is needed. Therefore, we changed this process to use pre-produced dry salt containers and to undertake in-clinic dissolution of salts and concentration production. Because no preclinical control for solute concentrations is available so far using this new process, we employed routine clinical chemistry analytics.

Methods. We report the controls of solute concentrations created by these methods for 746 samples of concentrates and 151 dissolution processes. For analysis, absolute and relative deviations from prescriptions and associations between the solute concentrations and the density controls of the concentrates were computed.

Results. A total of 98% of all the concentrates were found to be within a 10% margin of error from the prescriptions. The mean relative deviation of the solute concentrations from the prescriptions was $-0.635 \pm 3.83\%$. Among particular solutes, sodium had the highest maximum deviation of 26 mmol/L from the prescription. Calcium and magnesium (small concentration solutes) exhibited small systematic errors of 1.37 and 1.22%, respectively. Other solute concentrations showed random errors only and no associations with the mean relative deviations of all the solutes within a production batch or with the density controls.

Conclusions. Single solute concentration control by routine clinical chemistry after dry salt production of concentrates is a valuable additional tool for monitoring clinical risk with dialysate concentrates. The analytical random error of clinical chemistry exceeds the weight tolerance of production; therefore, such analytics cannot be used for precision production and control of dry salt containers.

Keywords: dialysis bath; dry salt; quality control; solute concentration

Introduction

Dialysis bath preparation is usually performed by the dilution of pre-produced salt concentrations, which contain solutes in concentrated hydrous solutions. Conventionally, these pre-produced hydrous solutions are delivered to dialysis machines by concentration circuits. The dialysis machine dilutes the solute concentration with conditioned dialysis water and adds hydrogen carbonate. This ready-for-use solution (concentrate + water + hydrocarbonate = dialysate) serves as an electrolyte solution exposed to the 'water side' of the extracorporeal circuit [1, 2].

The delivery of conventional hydrous dialysis salt concentrations to dialysis centres is characterized by difficult weight and volume logistics. For the treatment of a single patient with a dialysate flow rate of 500 mL/min, the delivery of 600–700 L of concentrate must occur over 1 year. If only salt, and not water, is delivered in pre-produced dry containers, the amount can be reduced to <200 kg. Conventional hydrous solution tanks measure 330 kg and yield 300 L of concentrate. Alternatively, dry salt containers measure 220 kg and yield 750 L of concentrate. Therefore, for the same amount of concentrate, almost four times the weight must be handled. The additional weight is water, which could be added at the dialysis unit (on-site). Considerable amounts of fuel, transportation capacity, carbon dioxide liberation and money can be saved using this dry salt approach. The salt containers, which contain dry solutes in pre-specified weight stocks, must be filled and mixed with dialysis water, yielding particular solute concentrations suitable for final bath preparation by dialysis machines. Although there is approved machinery offered on the European market that prepares such solutions from dry solute containers, the quality control process controls only for accurate initial solute weight at the production site and for complete dissolution at the dialysis site. For this purpose, manufacturers use weight control measures and automated density controls for the dissolution process at dialysis sites. There is currently no system available for the

control of single solute concentrations after the dissolution of pre-weighed dry salts. By such means, only the production and dissolution, but not the single solute concentration, can be controlled and no standard procedure is therefore available to control direct patient safety parameters. Of course, measures can be taken to control the dialysate after the handling of the concentrate by dialysis machines. Because every machine dilutes the concentrate separately, no control of all dialysis treatment locations is possible by measuring concentrates after dissolution and before dialysate preparation in daily routine. Laboratory methods and clinically safe concentration thresholds for the dialysate or concentrate measurements have not been standardized. To overcome these shortcomings, we launched a quality control programme to reappraise the single solute concentrations of on-site-produced dialysis concentrates from dry salt containers. All routine dialysis concentrates for ~160 patients from August 2010 to November 2011 were produced by this system and were included in routine chemistry analyses to control for solute stability after the dissolution of dry salts. In addition, we performed a cross-sectional one-point analysis of the dialysate after dilution by haemodialysis (HD) machines, and we compared the results with the corresponding batches before dilution by machines.

Materials and methods

Dry salt containers were produced by an external production company (Intermed Service GmbH, Ostrhauderfehn, Germany) following a certified and approved production procedure. The weights of the ingredients were 158.02 kg of sodium (Na), 28.8 kg of glucose, 5.87 kg of potassium (K) (for 3 mmol/L of final K concentration), 5.21 kg of calcium chloride (Ca), 2.67 kg of magnesium chloride (Mg) and 4.74 kg of acidic acid with allowed tolerance levels of 0.5%. The stocks of each solute were measured, and the solute mixtures were stored in containers (BigCarts) of the same company. These BigCarts were delivered to our dialysis centre. The on-site preparation and dissolution were performed by a preparation apparatus manufactured by the same company (ECOmix). The precision of solute dissolution was controlled by means of an aqua flow sensor with an allowed tolerance of <0.3% and by means of solute density measurements of every produced solute concentrate batch with an allowed tolerance of <2.5%. After dissolution, samples were drawn for external clinical chemistry measurements. Biochemistry tests for the determination of solute concentrations were performed after diluting 1 part concentrate with 34 parts sterile water to simulate the dilution procedure within the dialysis machine. In addition, dialysate samples were analysed after handling of the concentrates by the dialysis machines at five different HD locations and were compared with concentrates from the same production batches. For analysis, a Cobas™ clinical chemistry laboratory system (Roche, Germany) was used for serum samples with ion-selective electrodes (Na and K) and for photochemistry/photo-density (Mg, Ca and glucose). The allowed tolerance levels for sodium, glucose, potassium, calcium and magnesium were 3, 11, 4.5, 6 and 7.5%, respectively. The intermediate precision tests of the manufacturer (intraday variation) of aliquot sera for sodium and potassium were 0.6 and 0.7%, respectively, but not given for glucose, calcium and magnesium. These levels were controlled by continuous inter-laboratory comparison of the serum samples for electrolyte concentrations. Thus, with the goal of having a controlled aqueous solution instead of serum, the results of solute determination were anticipated to be the same concentration levels as dialysis machines provide for the dialysis process.

The dissolved concentrate was stored in 800-L containers and was delivered to the treatment locations by concentrate circuits. At the dialysis machines, the concentrate was diluted with dialysis water at a ratio of 1 part concentrate to 34 volume parts water/sodium hydrocarbonate to obtain ready-to-use dialysate. The final sodium concentration was augmented to 135–140 mmol/L by sodium hydrocarbonate at the machine level, as appropriate. The prescribed amounts of the solutes in the concentrates and dialysates are given in Table 1.

Statistical analysis

Concentration data and density data are presented as the mean, maximum and SD. Continuous variables were compared using Student's two-sided *t*-test.

Errors (F) were determined as deviations in the concentrations from the prescriptions:

$$F = X_{obs} - X_{pres}.$$

To enable comparisons between solutes of different concentrations, we computed the relative error f with regard to 100%:

$$f = \left[(X_{obs} - X_{pres})\right] \times 100\%.$$

The absolute deviation *D* was computed by setting all the negative values of f as positive and by computing these values for the groups as appropriate.

Batch error $\bar{f}$ was computed by summation of all the single solutes f in one dissolution batch:

$$\begin{aligned}
\bar{f} = \big\{ &\left[(X_{obsNa} - X_{presNa})/X_{presNa}\right] \\
&+ \left[(X_{obsGlu} - X_{presGlu})/X_{presGlu}\right] \\
&+ \left[(X_{obsK} - X_{presK})/X_{presK}\right] \\
&+ \left[(X_{obsCa} - X_{presCa})/X_{presCa}\right] \\
&+ \left[(X_{obsMg} - X_{presMg})/X_{presMg}\right] \big\}/5 \times 100\%.
\end{aligned}$$

F, f and $\bar{f}$ are given as the mean and SD.

Correlations were computed with Pearson's *R*. For statistical comparisons and computations, the SPSS® computer program package, version 13.0, was used.

To assure the clinical safety of the concentrates, deviation categories were computed by sorting *D* into categories: >10, 7.5–10, 5–7.5, 2.5–5 and <2.5%. Concentrate samples in categories 1–4 were considered clinically safe without further controls.

Results

Electrolyte results

A total of 746 measurements of seven prescribed solute concentrations were performed over 16 months for 151 production batches. The mean density deviation was −0.011 ± 0.03 (−0.11 to −0.07)%. For the concentration, the absolute error F of the observed concentration from prescription was dependent on the size of the prescribed concentration. F is displayed in Figure 1 and has not been analysed further.

The mean relative concentration deviation of all the solutes from the prescription, i.e. the relative conventional error

Table 1. Prescribed and observed values of solutes in concentrates after 1:34 pre-laboratory dilution

Solute (number of measurements, n)	Prescription (mmol/L)	Observed concentration $\pm$ SD (mmol/L)	Mean relative error f $\pm$ SD (%)	Mean absolute deviation $D \pm$ SD (%)	Maximum absolute deviation D (%)
Na (151)	102[a]	102 $\pm$ 3.07	0.139 $\pm$ 3.01	2.23 $\pm$ 2.02	10.21
K (10)	2	2.11 $\pm$ 0.164	5.50 $\pm$ 8.23	7.16 $\pm$ 6.66	21.82
K (110)	3	3.00 $\pm$ 0.11	−0.06 $\pm$ 3.77	2.84 $\pm$ 2.47	13.90
K (30)	4	3.93 $\pm$ 0.11	−1.74 $\pm$ 2.79	2.29 $\pm$ 2.34	7.55
Ca (151)	1.35	1.37 $\pm$ 0.49	1.37 $\pm$ 3.66	3.06 $\pm$ 2.43	14.23
Mg (151)	0.50	0.51 $\pm$ 0.02	1.22 $\pm$ 3.73	3.00 $\pm$ 2.53	11.61
Glucose (143)	5.50	5.52 $\pm$ 0.23	0.48 $\pm$ 4.16	2.86 $\pm$ 3.04	26.04

[a]Concentrate concentration was augmented to the dialysis concentration of 135–140 mmol/L by hydrocarbonate.
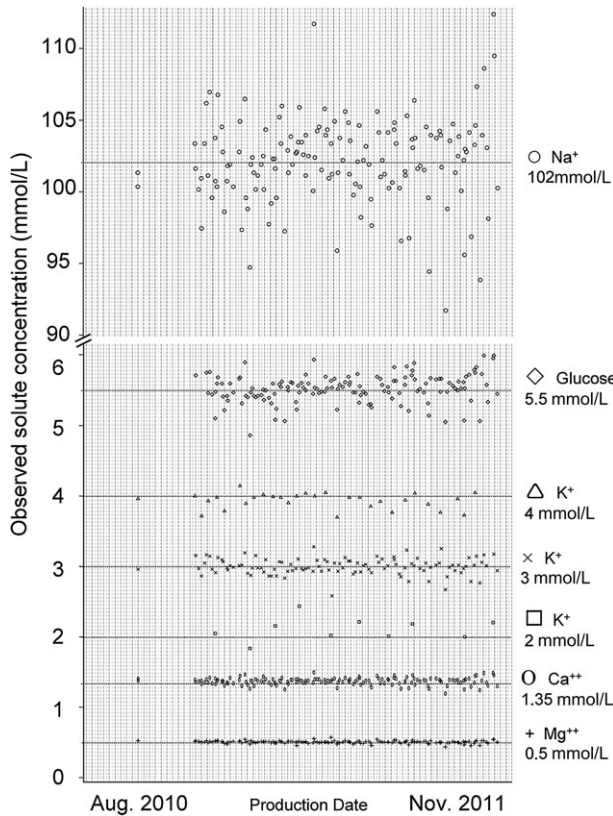

Fig. 1. Observed concentrations of solutes by production dates. Each point on the X-axis represents a production date and batch. The observed concentrations of the solutes belonging to this production (each indicated by an individual symbol) are given on the Y-axis.

Fig. 2. Relative error of solute concentrations by production dates. Each point on the X-axis represents a production date and batch. Errors of single solute concentration f belonging to this production (each indicated by an individual symbol) are given on the Y-axis.

f, was −0.635 $\pm$ 3.83% (Figure 2). The absolute deviation D was 2.83 $\pm$ 2.65%. The mean relative errors and maximum deviations for the observed single solute concentrations are given in Table 1.

The correlation between the concentration errors of single solutes (f) and whole batches (f̄) is shown in Figure 3. The correlation coefficients were 0.372 overall and 0.45 (P < 0.01), 0.14 (P < 0.05), 0.53 (P < 0.01), 0.27 (P < 0.01), 0.81 (P < 0.01), 0.40 (P < 0.01) and 0.32 (P < 0.01) for sodium, glucose, potassium 4 mmol/L, potassium 3 mmol/L, potassium 2 mmol/L, calcium and magnesium, respectively. In other words, only for potassium (2 mmol/L) did we observe an almost complete correlation between the errors of the single solutes and of the batches.
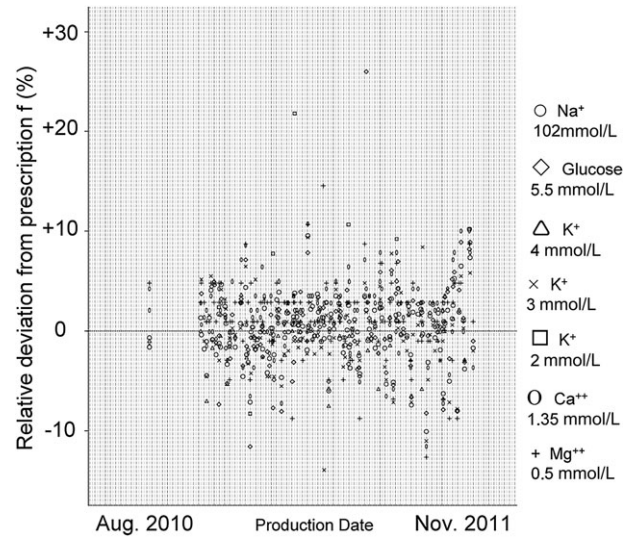
The errors in density and concentration were not correlated (R = 0.063, P = 0.09), either for the single solutes or for the batches.

Relative errors were examined, as they were, in general, independent of the absolute size of the measurements. The results for potassium 2 mmol/L showed an abnormal pattern, with bias towards the higher observed concentrates, compared with the prescribed measurements. For the remaining solutes, the error of the measurement was dependent on the absolute size of the measurements. There was a small error towards higher observed concentrates for the low concentration solutes (magnesium and calcium), no systematic error for potassium 3 mmol/L and a clear systematic error towards lower observed concentrations for potassium 4 mmol/L.

Numbers and percentages of measurements not exceeding 2.5, 5, 7.5 and 10% of deviation are given in Table 2. A total of 86% of all the concentrations were within the range of <5%, whereas 2.1% exceeded the 10% limit.

Direct dialysate measurements, after handling of the concentrates by five different HD machines (and treatment locations), revealed no errors exceeding margins considered 'clinically safe' compared with the prescriptions and solute concentrations of the batch before machine dilution (Table 3).
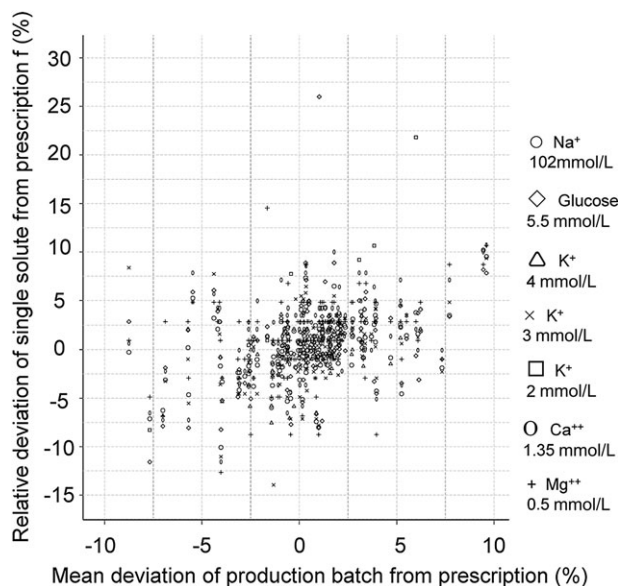
Fig. 3. Relative error of solute concentrations by the relative error of the whole production batch. Each point on the *X*-axis represents the relative error *f* of a whole production batch. Single errors of solute f belonging to this batch error (each indicated by an individual symbol) are given on the *Y*-axis.

Discussion

This quality control programme for on-site dialysate production from dry salts using routine clinical chemistry revealed solute concentrations within a 10% deviation threshold in 98% of the investigated samples. However, this threshold of 'clinical safety' was arbitrarily chosen because medical and regulatory data addressing such issues are not yet available. International guidelines [Kidney Disease: Improving Global Outcomes (KDIGO) and Kidney Disease Outcome Quality Initiative (KDOQI)] do not refer to HD concentrations or to dialysate control. The 'German Dialysis Standard' [3], a recommended but not compulsory standard operating procedure, introduced thresholds of peculiarity and permission of 5 and 10%, respectively, in 2006. Because 2% of our measurements exceeded the 'permitted' thresholds, we re-checked the density controls and manufacturer weights without yielding conspicuous results. No systematic bias was observed if the dialysate solutes were controlled after the dilution of concentrates by dialysis machines and if the permitted thresholds were not exceeded in these fluids, which come into the closest contact with patient's blood.

In the 16 of 746 samples with deviations >10%, the question of clinical safety arises. In these samples of batch production and dissolution, we recommend control

Table 2. Number and percentage of solute measurements within deviation categories

Solute, mmol/L	Deviation	2.5% n, %	2.5–5% n, %	5–7.5% n, %	7.5–10% n, %	>10% n, %
Na 102		107, 70.9%	30, 19.9%	10, 6.6%	2, 1.3%	2, 1.3%
K 2		81, 56.6%	38, 26.6%	13, 9.09%	9, 6.29%	2, 1.4%
K 3		4, 40%	0	0	3, 30.0%	3, 30%
K 4		61, 55.5%	33, 30.0%	10, 9.1%	4, 3.6%	2, 1.8%
Ca 1.35		20, 66.7%	4, 13.3%	5, 16.7%	1, 3.3%	0
Mg 0.5		73, 48.3%	54, 35.8%	14, 9.3%	6, 4.0%	4, 2.6%
Glucose 5.5		63, 41.7%	72, 47.7%	5, 3.3%	8, 5.3%	3, 2.0%
Total		409, 54.8%	231, 31.0%	57, 7.62%	33, 4.4%	16, 2.1%

Table 3. Solute measurements in dialysate after dilution of concentrates by dialysis machines and in corresponding concentrate batches after dissolution and before dilution by HD machines (all units mmol/L)[a]

Prescription (mmol/L)	From batch potassium 4		From batch potassium 3		From batch potassium 2	
	Dialysate mean ± SD; min to max, n = 5	Concentrate	Dialysate mean ± SD; min to max, n = 5	Concentrate	Dialysate mean ± SD; min to max, n = 5	Concentrate
Na 140/102	140.52 ± 3.73; 136.1 to 145.8	110.7	142.64 ± 4.52; 138.5 to 151.0	108.7	141.22 ± 1.74; 139.1 to 144.1	106.0
K 2					2.03 ± 0.03; 2.00 to 2.09	2.02
K 3			3.04 ± 0.10; 2.91 to 3.17	3.16		
K 4	3.84 ± 0.18; 3.51 to 4.00	4.28				
Ca 1.35	1.35 ± 0.03; 1.31 to 1.38	1.47	1.39 ± 0.08; 1.31 to 1.51	1.45	1.35 ± 0.01; 1.33 to 1.36	1.45
Mg 0.5	0.50 ± 0.00; 0.49 to 0.50	0.52	0.50 ± 0.02; 0.47 to 0.53	0.51	0.50 ± 0.02; 0.49 to 0.52	0.50
Glucose 5.5	5.74 ± 0.16; 5.60 to 5.96	5.71	5.80 ± 0.15; 5.62 to 5.94	6.06	5.75 ± 0.05; 5.72 to 5.85	6.06

[a]min, minimum; max, maximum.

with routine chemistry tests and with dialysate control after dilution by machines. None of our samples exceeded the chosen thresholds of these measurements. Random laboratory bias might have been responsible because such laboratory imprecision would have exceeded the allowed weighing tolerances of the manufacturers and the results of on-site density controls, which of course cannot be used for patient safety monitoring. Laboratory imprecision (most likely dilution errors), in general, makes clinical chemistry not fully appropriate for controlling the 'production precision' of dry solutes. The most important bias might be related to the difference between the precision of solute weighing at production and the precision of clinical chemistry measurements (i.e. the measurement error outbalances the suspected production and dissolution bias). Another bias might arise from the imprecision of inter-laboratory quality controls, which are optimized for serum but not for aqueous solutions. However, for clinical safety monitoring, our employed measures provided sufficient information about the vast majority of the test samples.

The question of the usefulness of our method must be addressed, in particular with regard to sodium. The maximum deviation of sodium was as high as 26 mmol/L. This deviation would, of course, generate clinical concerns if it were real. Final sodium concentrations are regulated by dialysis machines via augmentation with sodium hydrocarbonate. Owing to such methods, the prescribed sodium concentrate content is not directly delivered to the patient. Therefore, and following the wide scattering of observed concentrations, we do not recommend using sodium concentration measurements in comparable programmes in the future.

Glucose concentrations did not exceed 5 or 6 mmol/L without systematic bias. We therefore consider glucose control as a useful clinical application for metabolic control of dialysate.

Potassium, in general, had a small random bias, with the exception of the batches containing concentrations of 2 mmol/L of potassium. These productions were small in absolute numbers, and therefore, this error cannot be regarded as definitive.

Small concentrated solutes, such as calcium and magnesium, yielded only a small random scattering of observed values. Of note, in clinical terms, there were small systematic biases for both solutes towards higher than prescribed concentrations. This finding might have been important with regard to calcium because its concentration is crucial for maintaining bone and mineral homoeostasis. In the literature, a range from 1.15 to 1.5 mmol/L [4–6], depending on the clinical indications, is usually recommended. The constraints, within the biological effects that might be expected, could be as low as 0.05 mmol/L. This narrow target imposes large requirements on the delivered concentration of that particular solute. After re-checking with the manufacturer for the delivered original sample weights, we could not confirm our measured error for the calcium concentration. Therefore, a systematic analytical bias, in addition to random error, must be suspected. Following the biological importance of dialysate calcium concentrations, we intend to improve the analysis by calibration with an internal standard and/or more elaborate assays, e.g. spectroscopy or flame photometry.

In summary, quality control of dialysate production from dry salts with routine clinical chemistry for safety monitoring is useful in most test samples of solutes, except for sodium. For optimization of production precision control, in particular with a focus on calcium, better biochemistry tools are needed.

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