Preparing Drugs for Infusion Via Syringe Pump: A Key Step to Ensure Homogeneous Concentration

Bruno Garrigue, RN, MS
Yann Dehu, MS
Fabrice Girault, RN
Bruno Figadère, PhD
Karine Leblanc, MS
Nicolas Briole, MD
Georges Antoine Capitani, MD
Steven Lagadec, RN
François-Xavier Laborne, MD, MPH

OBJECTIVE Preparation of drug solutions used with electronic syringe infusion pumps plays a crucial role in the delivery of an accurate drug concentration. Is there a correlation between drug concentrations during syringe pump infusion and preparation protocols?
METHOD Norepinephrine, insulin, and sufentanil were prepared in 3 different ways: (1) the drug was taken from the vial, then the solvent was added followed by an air bubble, and mixing was performed by turning the syringe top-to-bottom in a 180° shaking movement 5 consecutive times; (2) the drug was taken from the vial, then the solvent was added and not mixed; and (3) the solvent was taken from a stock solution, then the drug was added and not mixed. Concentrations of drugs were determined at different times during administration by reverse-phase high-performance liquid chromatography with ultraviolet detection. All analyses were performed in triplicate and were based on measurement of peak areas.
RESULTS With no shaking of the syringe, the concentration of the injected drugs varies widely. In any case, mixing of the syringe contents by turning the syringe in a top-to-bottom 180° shaking movement 5 times with an air bubble would ensure administration of the drug at a constant concentration.
CONCLUSIONS Without mixing, the concentrations of all drug solutions varied widely when administered via an electronic syringe infusion pump. Mixing syringe contents should be made part of the compulsory curriculum for administering medications at all levels of medical education. (*Critical Care Nurse*. 2016;36[4]:36-45)

The use of electronic syringe infusion pumps to administer therapeutic agents is common practice in hospitals, particularly among patients who require slow injection treatments. For these patients and their practitioners, it is crucial that the administration of drugs (especially for those having a small therapeutic index) via the syringe pump be consistent, predictable, and reliable. It has been documented that when, for instance, catecholamine blood concentration varies even for a short time, there is a strong adverse effect on patients.[1-4] Thus, it stands to reason that the use of syringe infusion

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pumps for any such time-lapsed drug administration must be reliably stable and accurate throughout the procedure.[5]

In current practice, it is nurses who are responsible for preparing and administering drugs via syringe pumps,[6] but the steps between the prescription and administration of the drug involve many participants, not only nurses. This multiplicity of actors and actions increases the risk of error.[7] Thus, researchers in several studies have reported large differences between the expected concentrations of the drug and the concentrations delivered.[8]

Material factors that have been identified as potential causes of drug-concentration discrepancies with syringe pumps include nonstandardized use of equipment such as tubes, valves, injectors, and syringes.[9-11] Documented human causes of inconsistent drug concentrations include drug mislabeling and improper manipulation of syringes.[12-14] Errors often found include confusion between 2 products and poor transcription of the prescription, all exacerbated by stress and fatigue.[15] Calculation errors and dilutions are also cited as contributing factors in failure rates.[16,17]

Authors

Bruno Garrigue is an anesthesia nurse and head of the prehospital emergency medicine service at Centre Hospitalier Sud-Francilien, Corbeil-Essonnes, France.

Yann Dehu is an anesthesia nurse working in a surgical unit and a clinical research associate at Centre Hospitalier Sud-Francilien.

Fabrice Girault is a registered nurse working in a prehospital emergency medicine service, Centre Hospitalier Sud-Francilien.

Bruno Figadère is a medicinal chemist at Centre Nationale de Recherches Scientifiques (CNRS)/Universite Paris Sud-Faculte de Pharmacie Joint Laboratory, Chatenay-Malabry, France.

Karine Leblanc is a chemical engineer at CNRS/Univ Paris Sud-Faculte de Pharmacie Joint Laboratory.

Nicolas Briole is an emergency medicine physician at Centre Hospitalier Sud-Francilien.

Georges Antoine Capitani is head of the acute care department at Centre Hospitalier Sud-Francilien.

Steven Lagadec is a nurse in the prehospital emergency service and a clinical research associate at Centre Hospitalier Sud-Francilien.

François-Xavier Laborne is a prehospital emergency practitioner and a methodologist and biostatistician in the clinical research unit of the Centre Hospitalier Sud-Francilien.

Corresponding author: Bruno Garrigue, RN, MS, SAMU 91/SMUR de Corbeil, Centre Hospitalier Sud-Francilien, 116, boulevard Jean Jaurès, 91106 Corbeil-Essonnes Cedex, France (e-mail: bruno.garrigue@ch-sud-francilien.fr).

To reduce the incidence of these types of negative interventions, several authors recommend the standardization or even centralization of preparation of drugs to be administered via a syringe pump.[18-21]

In a study[22] on intravenous administration of an aqueous potassium solution, researchers reported that mixing of the solution was crucial.[22] The notion of stirring a medication to prepare it for administration is found more often in the case of a powder to be diluted. Control of the dissolution can be visual. Authors rarely discuss agitation of drug solutions in their preparation protocols.[23]

In another recent study[24] conducted in 100 French nursing schools, researchers reported a variance in recommended approaches being taught in preparation of drugs for infusion via a syringe pump: 40% of instructors recommended taking an aliquot portion of the drug before mixing it with the solvent, 24% recommended filling the syringe first with the solvent and then with the drug, and 32% did not recommend any particular method. Once both drug and solution were in the syringe, only 26% recommended shaking the solution, but without any specified method for doing so.[24] In the same study, the researchers also tracked 100 nurses working in hospitals and reported that 64% of these nurses took an aliquot of the drug before the solvent, 18% did the inverse, and 18% were unaware of their method. Among these 100 professionals, once the drug and solution were in the syringe, only 34% used a mechanical method to mix it.[24]

These results motivated this study: Is there a correlation between preparation protocols and drug concentrations during administration by syringe pump? If so, as we postulate and demonstrate here, recommendations must be disseminated among health professionals for more reliable, safe, and efficient infusion of drugs by syringe pump.

Methods

Drugs Tested

Three compounds that met the following 3 key criteria were chosen for testing:

- Use of the drug requires a syringe pump.
- Dilution of the drug in a solvent is necessary.
- The drug has a narrow therapeutic index, which requires strong control of the drug concentration to avoid adverse effects on the patient.

Norepinephrine is often used in emergency departments for patients with hemodynamic instability. Thus delivery of norepinephrine must be stable and at a constant concentration. Norepinephrine (8 mg, 4 mL) must

Table 1 Products used for the study and presentation

Generic name	Commercial name	Laboratory	Concentration
Norepinephrine	Noradrenaline	Mylan	2 mg/mL
Insulin	Umuline	Lilly	100 IU/mL
Ropivacaine	Ropivacaine KABI	Fresenius	2 mg/mL
Sufentanil	Sufentanil	Renaudin	5 µg/mL
Sodium chloride solution	Chlorure de sodium 0.9%	Macopharma	9 mg/mL
Glucose solution	Glucose 5%	Macopharma	50 mg/mL

be diluted with 5% glucose (28 mL) so as to reach a concentration of 0.25 mg/mL.

Insulin must be continuously administered at a constant rate to patients hospitalized for critical glycemic disorders, which could eventually lead to death if untreated.[25] Insulin (0.5 mL of 1000 IU/10 mL) is diluted with 49.5 mL saline (0.9% sodium chloride solution) so as to obtain a 1 IU/mL solution.

Sufentanil is a synthetic opioid used to potentiate anesthetics during childbirth with epidural analgesia.[26] A study has shown that variations of sufentanil concentration during the delivery process may significantly influence the quality of analgesia.[27] Thus we decided to use ropivacaine (37.5 mL of 0.2% aqueous solution) diluted with saline (0.9% sodium chloride solution, 7.5 mL) and sufentanil (25 µg, 5 mL) so as to obtain 0.5 µg/mL of sufentanil.

High-performance liquid chromatography was used to assess drug concentrations.

Preparation of Drug Solutions

All solutions were prepared by nurses under the standard conditions used in hospitals. One nurse prepared the solution and another controlled the process by double-checking the work of the first nurse to ensure that the drug concentration was correct. The preparation did not include any complex calculations of doses. Stock solutions, syringes, and drugs were purchased from regular sources and used in the usual way (Table 1).

The material used consisted of Agilia brand electronic syringe infusion pumps (Fresenius SE and Co). This equipment was used in accordance with the factory-directed protocol.

The syringes and needles used were as follows:

- 50-mL syringe (B Braun Medical Inc)
- 1.1 × 40 mm needle (Beckton Dickson BD Microlance).
- 0.5-mL syringe (Terumo Medical Corp) graduated in international units and milliliters with incorporated needle to collect the desired amount of insulin.

Method of Mixing

We chose a mixing method after visual tests had been done with some physiological saline solutions, with the drug being replaced by a coloring agent (methyl alcohol blue). We varied several factors such as the number of reversals of the syringe, the movement of the syringe, and the presence or absence of an air bubble during the agitation. Better results were obtained with the following method: addition of a 5-mL air bubble in the syringe and 5 successive reversals of 180°.

Preparation 1: the drug was taken from the vial, then the solvent was added followed by an air bubble, and mixing was performed by turning the syringe top-to-bottom in a 180° shaking movement 5 consecutive times.

Preparation 2: the drug was taken from the vial, then the solvent was added and not mixed.

Preparation 3: the solvent was taken from a stock solution, then the drug was added and not mixed.

A 0.5-mL syringe was used to draw up the insulin for the preparations so that the precise dose required could be collected. In all cases, air was purged after the sample was prepared.

Sample Collection

For both norepinephrine and insulin, the same procedure was used to test all 3 preparations. The flow rate of the syringe pump was set to 8 mL/h, and aliquots were collected as follows:

- For norepinephrine, at time zero and then every hour for 4 hours until the syringe was empty.
- For insulin, at time zero and then every 70 min until the syringe was empty.
- Every experimental sequence was repeated 5 times.

For the sufentanil/ropivacaine mixture only, preparations 1 and 2 were compared by the following method. Boluses of 3 minutes were collected at a flow rate of 100 mL/h every 10 minutes. Thus, 9 boluses were collected. Four aliquots were taken from each bolus every minute (0, 1, 2, and 3) and analyzed 6 times by means of high-performance liquid chromatography (HPLC).

HPLC Analyses

Concentrations of drugs were determined by reverse-phase HPLC with ultraviolet detection. Calibration was set for a range of known concentrations of drugs (0-0.8 mg/mL for norepinephrine, 0-2 IU for insulin, and 0-1 µg/mL for sufentanil). Linearity and reproducibility were ascertained for each drug. All analyses were performed in triplicate, based on the measure of peaks area.

For norepinephrine, a diphenyl Pursuit column (4.6 × 150 mm, 5 µm, Varian) was used with a Waters HPLC (600E quaternary pump, automatic sampler 717 and PDA 2996 ultraviolet detector). The mobile phase was H_2O + 0.05% trifluoroacetic acid/methanol (95:5) at 1 mL/min flow rate. Peak analysis (retention time = 207 min) was performed at 278 nm.

For insulin, a C18 Sunfire column (4.6 × 150 mm, 5 µm, Waters) was used with Agilent HPLC (1200 Infinity, ultraviolet detector). The mobile phase was H_2O + 0.1% trifluoroacetic acid/methanol (40:60) at 1 mL/min flow rate. Peak analysis (retention time = 4.2 min) was performed at 270 nm.

For sufentanil, a C18 Sunfire column (4.6 × 150 mm, 5 µm, Waters) was used with Agilent HPLC (1200 Infinity, ultraviolet detector). The mobile phase was H_2O + 0.1% trifluoroacetic acid/acetonitrile (69:31) at 1 mL/min flow rate. Peak analysis (retention time = 8.2 min) was performed at 230 nm.

Statistical Methods

Statistical analyses were performed by using R version 3.0.3 (R Foundation for Statistical Computing). For each drug studied, the intrasyringe variability in concentration is expressed by the relative standard deviation, and the mean concentration measurements at each time are compared with one another by the Friedman test. For each preparation method, concentration variability is represented by the overall standard deviation of the measured concentrations. Preparation methods are compared with one another by an overall test of variances comparison (Levene test, based on a nonparametric approach), then by pairwise comparisons, adjusting the *P* values with the Holm method. The level of significance (type I error) retained is 5%. Numerical results are presented in Tables 2 through 4.

Results

Norepinephrine

Results are summarized in Figure 1 and Table 2. Best results were obtained for preparation 1, all concentrations are close to the expected concentration (0.25 mg/mL) along the time of administration when the syringes are mixed, with less than 0.3% variation in concentration. For preparations 2 and 3, without shaking, norepinephrine concentrations are different either at the beginning or at the end of administration. Indeed, for preparation 2, 21% of variation of concentration was observed for a single syringe, and for preparation 3, the variation was as high as 33% for 1 syringe.

Insulin

Insulin concentrations were measured for the 3 preparations and results are reported in Table 3 and Figure 2. Best results were obtained for preparation 1 (with shaking); those concentrations are close to the expected value (1 IU/mL) at any time of the experiment with less than 1% variation. In preparation 2, where solvent was added to the drug, some variations were observed, especially at the beginning of the administration. However, for preparation 3, where insulin was added after the solvent and without shaking, a variation in the concentration of insulin was observed, up to 57% for the same syringe.

As long as the solution is well mixed, it does not matter whether drug or solvent is introduced first.

Sufentanil

For sufentanil, shaking was crucial for the concentration (Table 4 and Figures 3 and 4). However, in all cases, the first measure (first minute of the first bolus) always showed a lower value than expected (0.5 µg/mL). Furthermore, we observed a slight difference between the 5 syringes that could be due to an experimenter factor (2 persons performed these experiments), and for 1 syringe, an error occurred (the volume of sufentanil was probably lower than expected). In the experiments run without shaking, sufentanil concentration reached the expected value only after the fourth or fifth bolus and finished above the expected concentration by 10% to 30%.

Table 2 Norepinephrine/glucose 5%

Preparation	Concentration, mean (SD), mg/mL	Minimum-maximum	95% CI	Relative SD, %	*P*
Norepinephrine then glucose 5% with shaking					
1-1	0.2517 (0.0007)	0.2501-0.2530	0.2514-0.2521	0.26	.86
1-2	0.2486 (0.0005)	0.2479-0.2492	0.2483-0.2488	0.18	.15
1-3	0.2516 (0.0006)	0.2508-0.2528	0.2512-0.2520	0.25	.03
1-4	0.2469 (0.0007)	0.2460-0.2479	0.2465-0.2473	0.28	.03
1-5	0.2506 (0.0003)	0.2503-0.2514	0.2505-0.2508	0.13	.31
Norepinephrine then glucose 5% without shaking					
2-1	0.2581 (0.0319)	0.2363-0.3191	0.2398-0.2764	12.35	.02
2-2	0.2627 (0.0394)	0.2360-0.3221	0.2432-0.2822	12.94	.02
2-3	0.2706 (0.0569)	0.2329-0.3793	0.2380-0.3032	21.04	.02
2-4	0.2507 (0.0167)	0.2369-0.2827	0.2412-0.2603	6.65	.02
2-5	0.2537 (0.0086)	0.2442-0.2697	0.2488-0.2587	3.40	.02
Glucose 5% then norepinephrine without shaking					
3-1	0.2533 (0.0113)	0.2367-0.2708	0.2468-0.2598	4.46	.02
3-2	0.2581 (0.0650)	0.1889-0.3637	0.2208-0.2953	25.17	.02
3-3	0.2636 (0.0567)	0.2003-0.3642	0.2311-0.2961	21.51	.02
3-4	0.2535 (0.0304)	0.2029-0.2893	0.2360-0.2709	12.01	.02
3-5	0.2405 (0.0787)	0.1274-0.3633	0.1953-0.2856	32.74	.02

Table 3 Insulin/saline

Preparation	Concentration, mean (SD), mg/mL	Minimum-maximum	95% CI	Relative SD, %	*P*
Insulin then saline with shaking					
1-1	1.0257 (0.0053)	1.013-1.030	1.0226-1.0287	0.52	.02
1-2	1.0287 (0.0064)	1.016-1.036	1.0250-1.0324	0.63	.02
1-3	1.0446 (0.0096)	1.030-1.056	1.0391-1.0501	0.92	.02
1-4	1.0364 (0.0060)	1.027-1.044	1.0330-1.0399	0.58	.02
1-5	1.0214 (0.0090)	1.007-1.030	1.0163-1.0266	0.88	.02
1-6	1.0192 (0.0096)	1.004-1.032	1.0138-1.0247	0.94	.02
Insulin then saline without shaking					
2-1	1.0150 (0.0235)	0.9999-1.0960	1.0015-1.0285	2.32	.03
2-2	1.0498 (0.0346)	1.0130-1.1130	1.0300-1.0696	3.29	.02
2-3	1.0365 (0.0230)	0.9980-1.0690	1.0233-1.0496	3.47	.02
2-4	1.0374 (0.0085)	1.0220-1.0450	1.0326-1.0423	2.21	.03
2-5	0.9968 (0.0336)	0.9338-1.0290	0.9776-1.0161	0.82	.02
2-6	0.9999 (0.0169)	0.9672-1.0170	0.9902-1.0096	1.69	.02
Saline then insulin without shaking					
3-1	1.2367 (0.7078)	0.8327-2.5990	0.8310-1.6425	57.23	.02
3-2	1.1324 (0.2253)	1.0000-1.5720	1.0033-1.2615	19.89	.02
3-3	1.0725 (0.0483)	1.0250-1.1620	1.0448-1.1002	4.50	.02
3-4	1.1023 (0.3314)	0.7521-1.6500	0.9123-1.2923	30.07	.02
3-5	1.0424 (0.0140)	1.0270-1.0670	1.0343-1.0504	1.34	.02
3-6	1.0083 (0.0397)	0.9460-1.0510	0.9855-1.0311	3.94	.02

Discussion

Our results show that the drug solutions had to be shaken before being infused with the syringe pump in order to obtain a constant drug concentration during the infusion. Indeed, the starting point of this study was to evaluate the effect of mixing and stirring on homogenization of drug solutions used with electronic syringe infusion pumps.

After having reviewed the literature on various errors in drug administration, we set out to develop a practice to minimize such errors. We set up an experimental

Table 4 Ropivacaine/sufentanil

Preparation	Concentration, mean (SD), mg/mL	Minimum-maximum	95% CI	Relative SD, %	*P*
Ropivacaine, then saline, then sufentanil, with shaking					
1-1	0.5415 (0.0090)	0.4933-0.5537	0.5398-0.5432	1.66	<.001
1-2	0.5097 (0.0142)	0.4260-0.5223	0.5069-0.5124	2.79	<.001
1-3	0.5289 (0.0099)	0.4712-0.5385	0.5270-0.5308	1.86	.001
1-4	0.5562 (0.0133)	0.4799-0.5686	0.5536-0.5588	2.38	.01
1-5	0.5048 (0.0122)	0.4401-0.5445	0.5025-0.5071	2.41	.002
1-6	0.4491 (0.0111)	0.3852-0.4631	0.4470-0.4513	2.48	<.001
Ropivacaine, then saline, then sufentanil, without shaking					
2-1	0.4734 (0.0712)	0.2762-0.5497	0.4597-0.4870	15.04	<.001
2-2	0.5243 (0.1912)	0.2079-0.6560	0.4877-0.5609	36.46	<.001
2-3	0.5658 (0.0196)	0.4836-0.6004	0.5620-0.5696	3.47	<.001
2-4	0.5298 (0.0597)	0.3482-0.5763	0.5184-0.5413	11.26	<.001
2-5	0.5375 (0.0150)	0.4628-0.5613	0.5347-0.5404	2.78	<.001
2-6	0.5700 (0.1134)	0.2788-0.6599	0.5482-0.5917	19.90	<.001

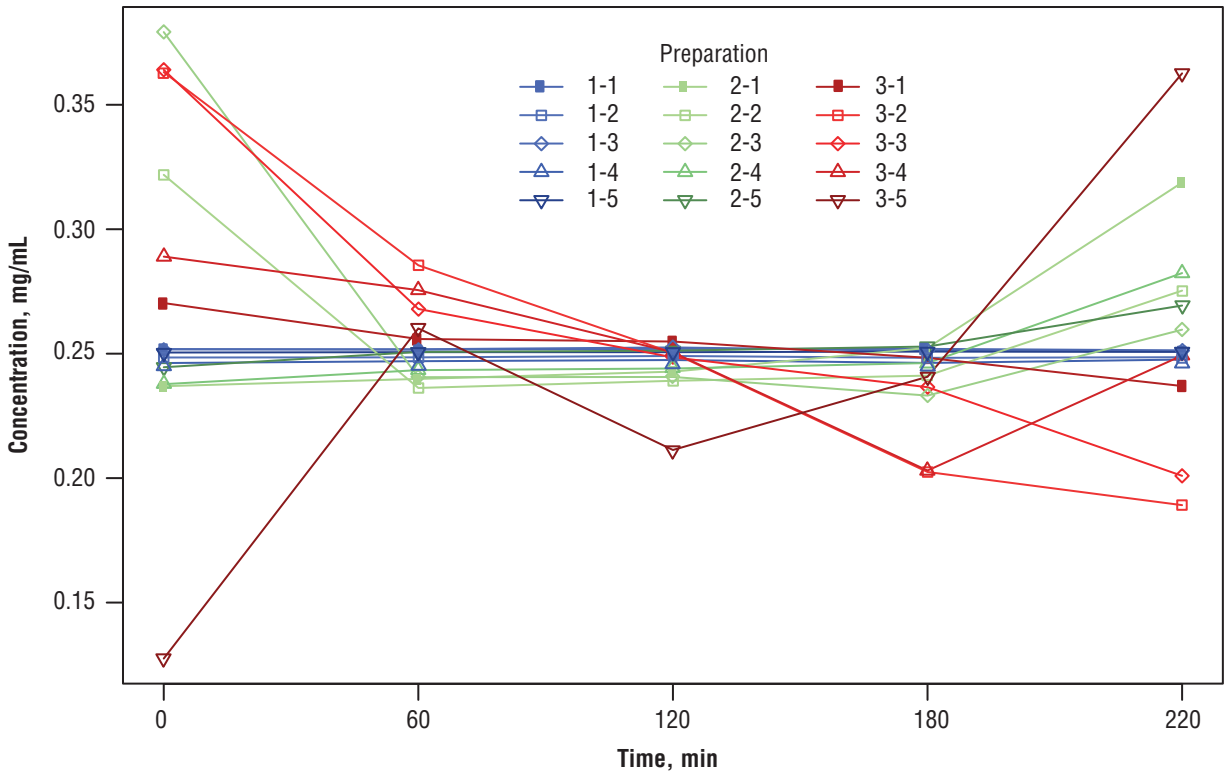

Figure 1 Norepinephrine concentration versus time according to the method of preparation.

protocol wherein pairs of nurses were invited for the study, and within each pair, the following controls were set in place: simple and straightforward calculations were used; the protocol applied by one nurse was checked by the other; and solvents were chosen in light of preestablished recommendations.

In the case of norepinephrine administration, the observed variation (21% for preparation 2 and 33% for preparation 3) is much higher than acceptable variations in drug concentrations (10%).[28] These concentration discrepancies could have a highly negative effect on patients who are in unstable hemodynamic

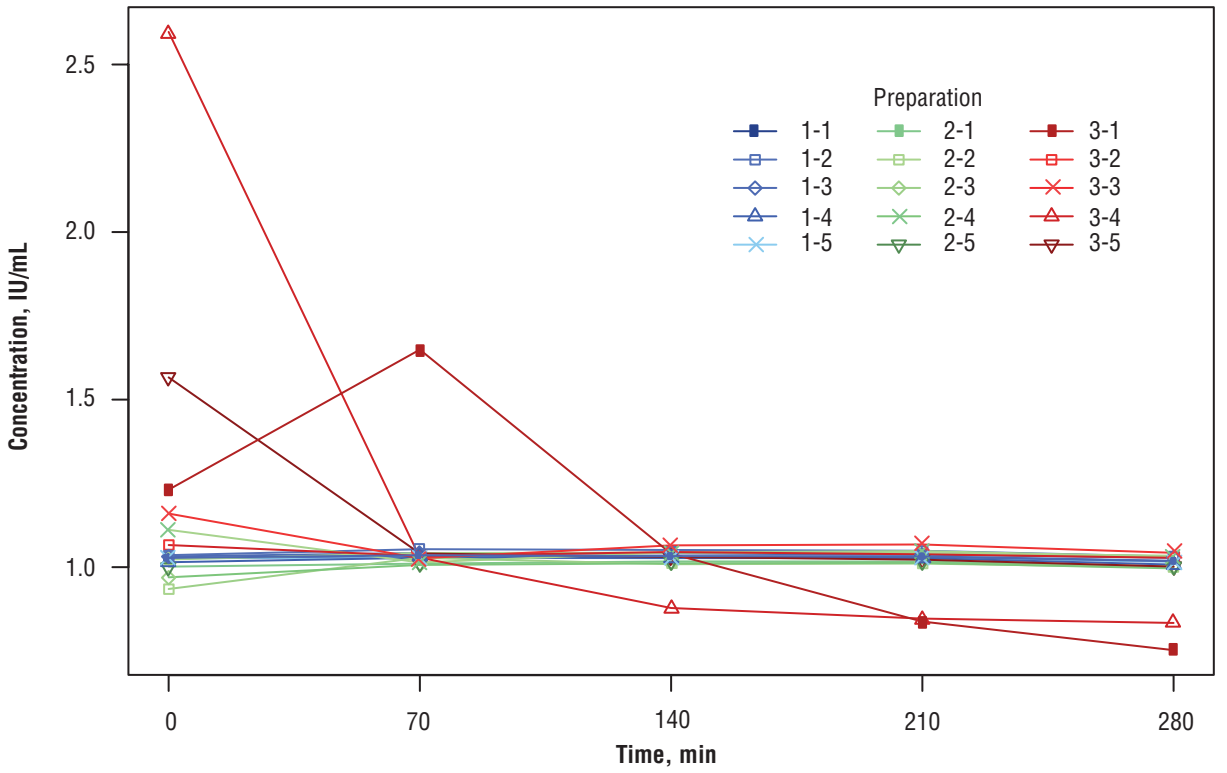

Figure 2 Insulin concentration versus time according to the method of preparation.

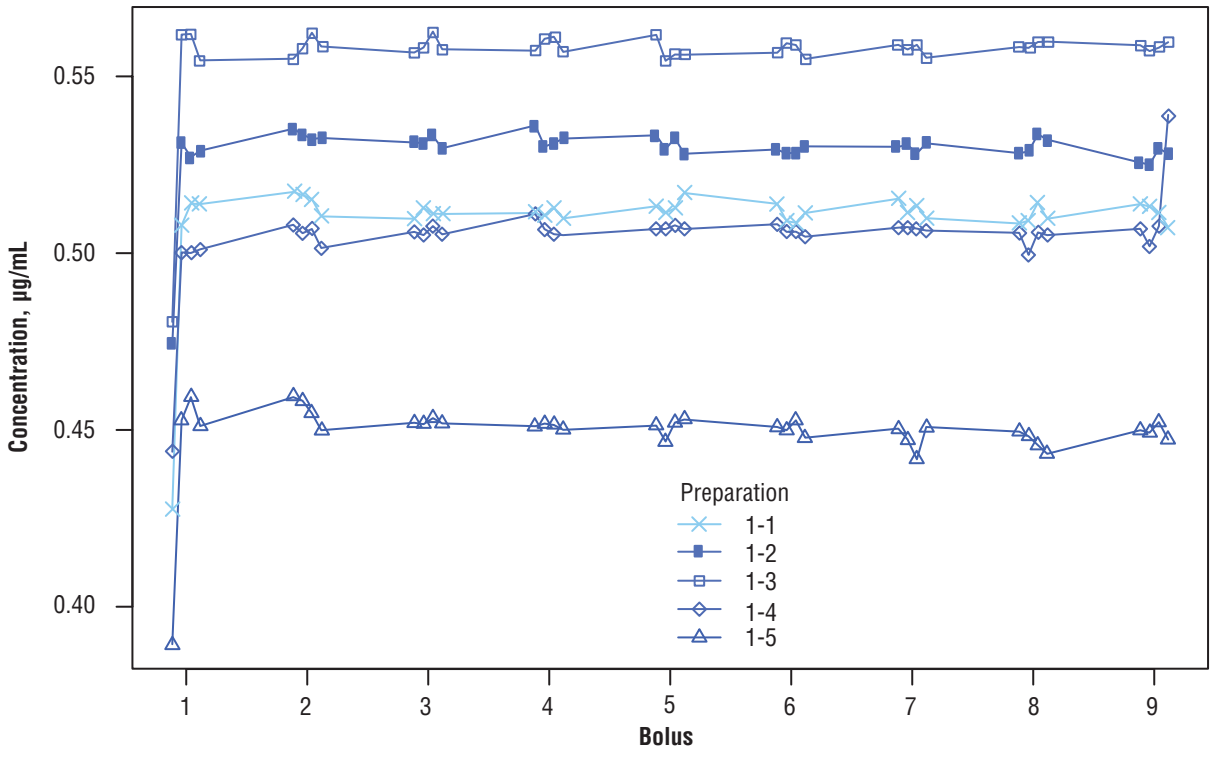

Figure 3 Sufentanil concentration versus time according to the method of preparation, with shaking.

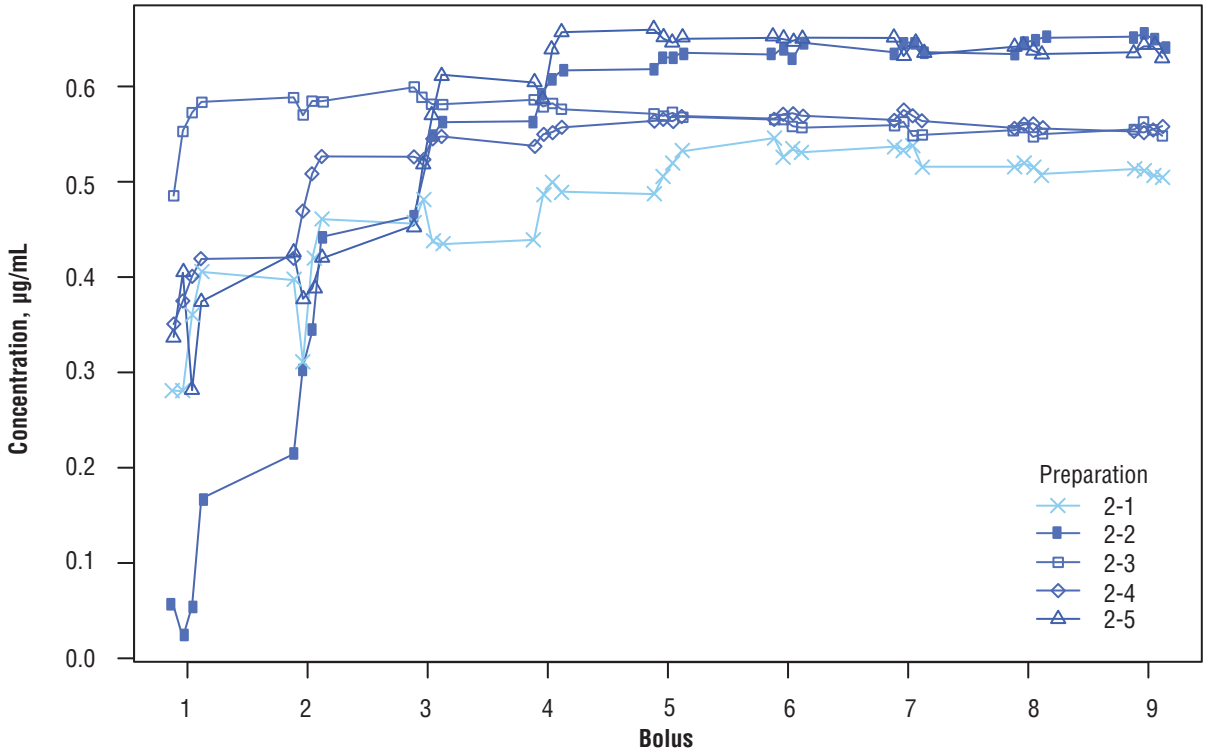

Figure 4 Sufentanil concentration versus time according to the method of preparation, without shaking.

condition, requiring inappropriate adjustment of the administered doses.

For insulin administration, the concentration variation (up to 57%) is even more significant during preparation 3. These differences in drug concentration, compared with the expected insulin concentration, could have severe deleterious glycemic effects on treated patients.

For sufentanil, these concentration variations (10% to 30% for the nonshaking preparation) are observed before the third bolus. This factor may explain the loss of analgesic effects observed when ropivacaine/sufentanil mixture is epidurally administered via a syringe pump to women in labor. Failure to reach the analgesic concentration is one of the causes of ineffectiveness of an epidural analgesic.[29]

It is important to note that all of the drug solutions were shaken with (1) an air bubble and (2) mixing by turning the syringe top-to-bottom in a 180° shaking movement 5 consecutive times. To our knowledge, these 2 measures have never been recommended. This method is reproducible and easy to teach in nursing schools.

The differences observed for the drug concentrations between preparations 2 and 3 may be explained by several factors that have been not studied: viscosity, density, and speed of solvent introduction. However, all things being equal, stirring of the 3 drug solutions allowed us to obtain constant concentrations throughout an infusion via a syringe pump.

Limitations

Several limitations affected our work:

- Syringes whose contents were intended to be mixed were prepared according to the habits of the nurses, thus according to both proposed methods (some nurses added solvent first, some added drug first). The results after mixing were comparable, so we did not differentiate between the initial preparations.
- The intermittent samplings do not correspond to reality, except in the case of sufentanil. Continuous tests could be done for more precise results.
- We used 50-mL syringes, which are typically used in France; nevertheless, some teams may use 20-mL syringes, which could yield different results.
- Our study was limited to 3 drugs, but as the viscosity of other drugs of interest may vary, results with other drugs could be different.

Conclusions

This is an experimental study that calls for clinical studies to confirm the effects of mixing the drug solutions in the syringes on the patients. Proper preparation of drug solutions infused via electronic syringe pumps is crucial for the delivery of an accurate drug concentration, just as improper preparation contributes to multiple types of errors. For drugs with a narrow therapeutic index, control of the drug concentration is often required for the drug to be effective and to avoid complications. In certain cases, commercially available drug solutions would be an ideal target that would eliminate preparation problems (eg, viscosity, solubility) resulting from human error. In any case, mixing of the syringe contents by shaking the solution in a top-to-bottom 180° shaking movement 5 times with an air bubble would be an ideal compromise and would ensure that the drug is administered at a constant concentration. The mixing technique described here is simple, quick, and does not cost anything, so we encourage adoption of this technique for preparing drug solutions for infusion via a syringe pump. We strongly recommend that this practice become part of the compulsory curriculum at all levels of medical education. This study demonstrates that there is more to discover about and correct within even our most mundane practices. CCN

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Preparing Drugs for Infusion Via Syringe Pump: A Key Step to Ensure Homogeneous Concentration

Preparation of drug solutions used with electronic syringe infusion pumps plays a crucial role in the delivery of an accurate drug concentration. Is there a correlation between drug concentrations during syringe pump infusion and preparation protocols?

- Norepinephrine, insulin, and sufentanil were prepared in 3 different ways: (1) the drug was taken from the vial, then the solvent was added followed by an air bubble, and mixing was performed by turning the syringe top-to-bottom in a 180° shaking movement 5 consecutive times; (2) the drug was taken from the vial, then the solvent was added and not mixed; and (3) the solvent was taken from a stock solution, then the drug was added and not mixed.
- Concentrations of drugs were determined at different times during administration by reverse-phase high-performance liquid chromatography with ultraviolet detection. All analyses were performed in triplicate and were based on measurement of peak areas.
- With no shaking of the syringe, the concentration of the injected drugs varies widely. In any case, mixing of the syringe contents by turning the syringe in a top-to-bottom 180° shaking movement 5 times with an air bubble would ensure administration of the drug at a constant concentration.
- Proper preparation of drug solutions infused via electronic syringe pumps is crucial for the delivery of an accurate drug concentration, just as improper preparation contributes to multiple types of errors. For drugs with a narrow therapeutic index, control of the drug concentration is often required for the drug to be effective and to avoid complications.
- In certain cases, commercially available drug solutions would be an ideal target that would eliminate preparation problems (eg, viscosity, solubility) resulting from human error.
- The mixing technique described here is simple, quick, and does not cost anything, so we encourage adoption of this technique for preparing drug solutions for infusion via a syringe pump.
- Without mixing, the concentrations of all drug solutions varied widely when administered via an electronic syringe infusion pump. Mixing syringe contents should be made part of the compulsory curriculum for administering medications at all levels of medical education.
- This study demonstrates that there is more to discover about and correct within even our most mundane practices. CCN

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