CASE REPORT

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Hypertensive Crisis During Norepinephrine Syringe Exchange: A Case Report

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A 67-year critically ill patient suffered from a hypertensive crisis (200 mm Hg) because of a norepinephrine overdose. The overdose occurred when the clinician exchanged an almost-empty syringe and the syringe pump repeatedly reported an error. We hypothesized that an object between the plunger and the syringe driver may have caused the exertion of too much force on the syringe. Testing this hypothesis in vitro showed significant peak dosing errors (up to +572%) but moderate overdose (0.07 mL, +225%) if a clamp was used on the intravenous infusion line and a large overdose (0.8 mL, +2700%) if no clamp was used. Clamping and awareness are advised. (A&A Case Reports. 2016;8:178–81.)

Adverse events related to intravenous administration of vasoactive medication are relatively common as the result of preparation and prescription errors[1]; however, many errors with vasoactive medications have been related to infusion technology,[2] for example, pump malfunctions.[3] In addition, characteristics of the infusion system may yield dosing deviations after interventions, such as a syringe exchange,[4] flow rate changes,[5,6] and vertical displacement of the pump.[7] In this case report, we describe a critical care patient receiving an accidental overdose of norepinephrine, probably caused by a pump malfunction during a syringe exchange.

Consent for Publication

The patient's family reviewed the case report and gave written permission (informed consent) to the authors to publish the case report.

CASE DESCRIPTION

A 67-year-male patient was admitted to the intensive care unit of the University Medical Center Utrecht, the Netherlands, after a bicycle accident and presented with an out-of-hospital cardiac arrest, a high cervical (C1 and C2) injury, and spinal shock. The patient wished to be treated despite a poor prognosis. The patient's medical history included chronic obstructive pulmonary disease, glaucoma, hypertension, and benign prostatic hypertrophy. Regular home medication included perindopril 8 mg per day. To treat his spinal shock, norepinephrine (0.1 mg/mL by protocol) was administered continuously (5–6 mL/h) with a syringe pump Perfusor Space (B. Braun Perfusor; B. Braun, Melsungen, Germany) to achieve a maintenance dose of approximately 8 to 10 μg/min.

The norepinephrine was administered together with a saline carrier flow of 10 mL/h. Both were first connected to 2 standard 1-m infusion lines (Cair LGL, Civrieux d'Azergues, France) and, subsequently, joined with an "octopus" infusion set (CODAN Medical, Lensahn, Germany). The vascular access device used was a 7-Fr triple-lumen catheter (Argon Careflow, Plano, TX) that entered the patient at the v. femoralis. The norepinephrine and saline were connected to the distal lumen of the catheter, another saline infusion (5 mL/h) was connected to the medial lumen, and venous pressure measurement was performed through the proximal lumen. The syringe pumps were equipped with Omnifix syringes (B. Braun; Figure 1).

When norepinephrine was administered, the syringe pump produced an alert indicating that the syringe would be empty within 10 minutes. On the mounting of the new syringe, the pump signaled "repeat syringe exchange." The full syringe was removed from the pump and remounted. The pump gave the same error message again, 3 times in a row. At the fourth attempt, the syringe was mounted inside a different pump, which did not signal an error. After restart of the infusion, the patient instantly underwent a period of severe hypertension (mean arterial pressure 200 mm Hg, see Figure 2A) lasting for several minutes, strongly suggestive of an inadvertent overdose of norepinephrine. To lower the mean arterial pressure, labetalol was administered. After stabilization, electrocardiogram values were indicative for a myocardial infarction (Figure 2B), and ultrasound confirmed that the anterior heart wall movement was impaired.

Coronary catheterization was conducted, and the planned operation was postponed. Angiography showed a spastic coronary artery, which improved during the angiography procedure, and the patient survived the incident. Blood test results showed a mild increase of serum troponin I with a maximum of 5510 ng/L and creatine kinase MB with a maximum of 27 (<5% creatine kinase activity), indicative of myocardial cell damage.

The case was reported, and the health inspectorate concluded that the incident was investigated carefully and closed

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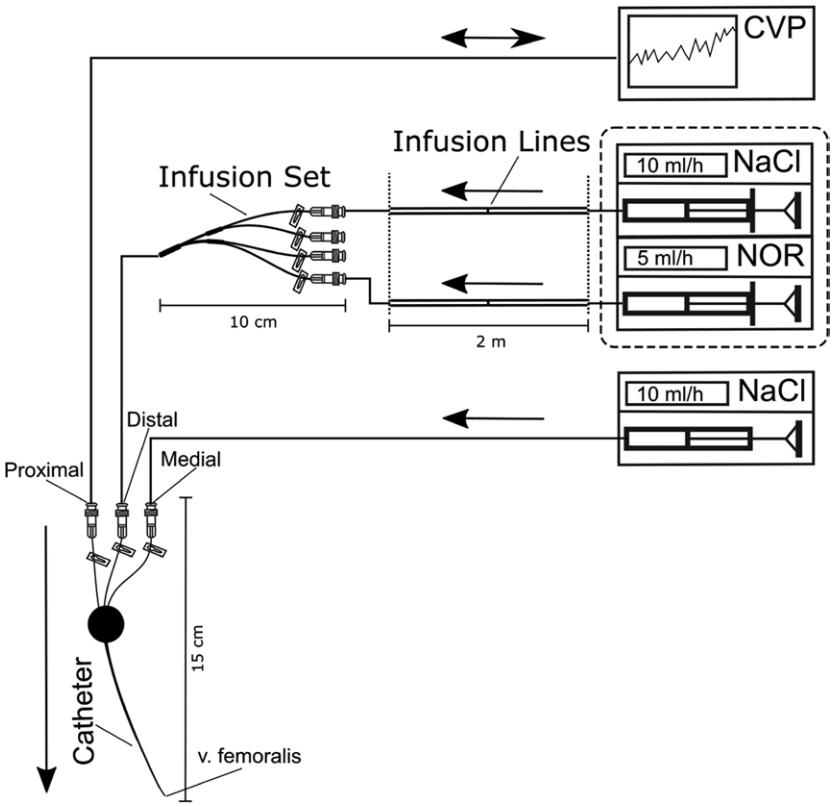

Figure 1. Infusion setup. Within the square area indicated by the dotted lines are the NaCl and norepinephrine (NOR) pumps. Only these pumps were involved in the incident. The drugs from both these pumps were joined with an infusion set and subsequently administered to the patient with the distal lumen of a triple-lumen catheter. An additional central venous pressure (CVP) measurement and NaCl flush, respectively, connected to the proximal and medial lumen of the catheter are indicated as well. The flow rates are denoted in the schematic representations of the infusion pumps. Also indicated are the flow rates during the incident; these were acquired from interviewing the nurse and, in case of the norepinephrine pump, from reading out the pump log files.

the case. No additional results from health care inspectors regarding pump malfunction were issued. All future directions from the authorities and field safety notices will be conspicuously followed, and we advise all pump users to do so as well.

DISCUSSION

After the incident, the pump was inspected by a maintenance engineer, who found no defects, erroneous flow rate settings, or other abnormalities. Our investigation, however, showed that the pump gave the reported error message if an object, such as intravenous tubing curled up next to the gripper, became interposed between the syringe plunger and the syringe driver. In that case, the syringe driver exerts too much force on the syringe plunger (Figure 3). In our hypothesis, this may have occurred repeatedly and caused pressure build up in the syringe, which in turn caused too much flow and thus dosing errors upon release of the clamp, or immediately if no clamp was used.

Measurement Setup

The plausibility of this obstruction hypothesis was tested in a laboratory setting. To reproduce the clinical situation in an in vitro experiment, the infusion setup was reduced to the hardware elements that were relevant to the norepinephrine overdose incident (see the encircled area in Figure 1). The outflow of the triple lumen catheter was submerged in 5 cm of water to simulate the venous pressure. The outflow was measured gravimetrically with a precision (±1 mg) balance (PGW 450, Adam Equipment, Danbury, CT). The sample time was 1 second.

Experiments

First, the syringe exchange was performed according to the clinical protocol described previously. To reproduce the syringe driver obstruction in a systematic manner, the grippers used to grab the plunger were obstructed deliberately with a solid "obstructing object" between the syringe driver and the plunger (Figure 3B). Consequently, the pump signaled the error message and asked the user to repeat the syringe exchange; this procedure was repeated 3 times. Next, the obstructing object was removed, the syringe was mounted correctly, and the clamp was released. The experiment was repeated without the placement of a clamp. Finally, a nominal syringe exchange, that is, a syringe exchange without any obstruction or errors, was investigated.

In each case, the period after the interventions, until the set point of the cumulative flow rates (15 mL/h) was reached again, was recorded. In this period, the "peak error" (mL/h), that is, the greatest value measured minus the nominal value (15 mL/h), and "excess area under the curve," that is, the measured volume minus the nominal volume (mL), were acquired and presented. The set point cumulative flow rate (15 mL/h) or nominal volume delivered (flow rate × time), is considered 100% throughout.

The experiments were repeated 5 times (n = 5). The results can be found in the Table and are presented as mean ± SD. An independent samples *t* test was applied with SPSS, version 21 (IMB Corp, Armonk, NY).

The results show that the syringe exchange always produced an overdose after the pump was started, even in the nominal case; however, it was found that after the pump was obstructed, a significantly larger overdose occurred. The peak error, that is, the greatest measured deviation from set point of 15 mL/h, was 85.8 (+572%) with clamp. During a short period of time (7 seconds), a 225% and 2700% of overdoses were infused to the patient, with and without clamp, respectively.

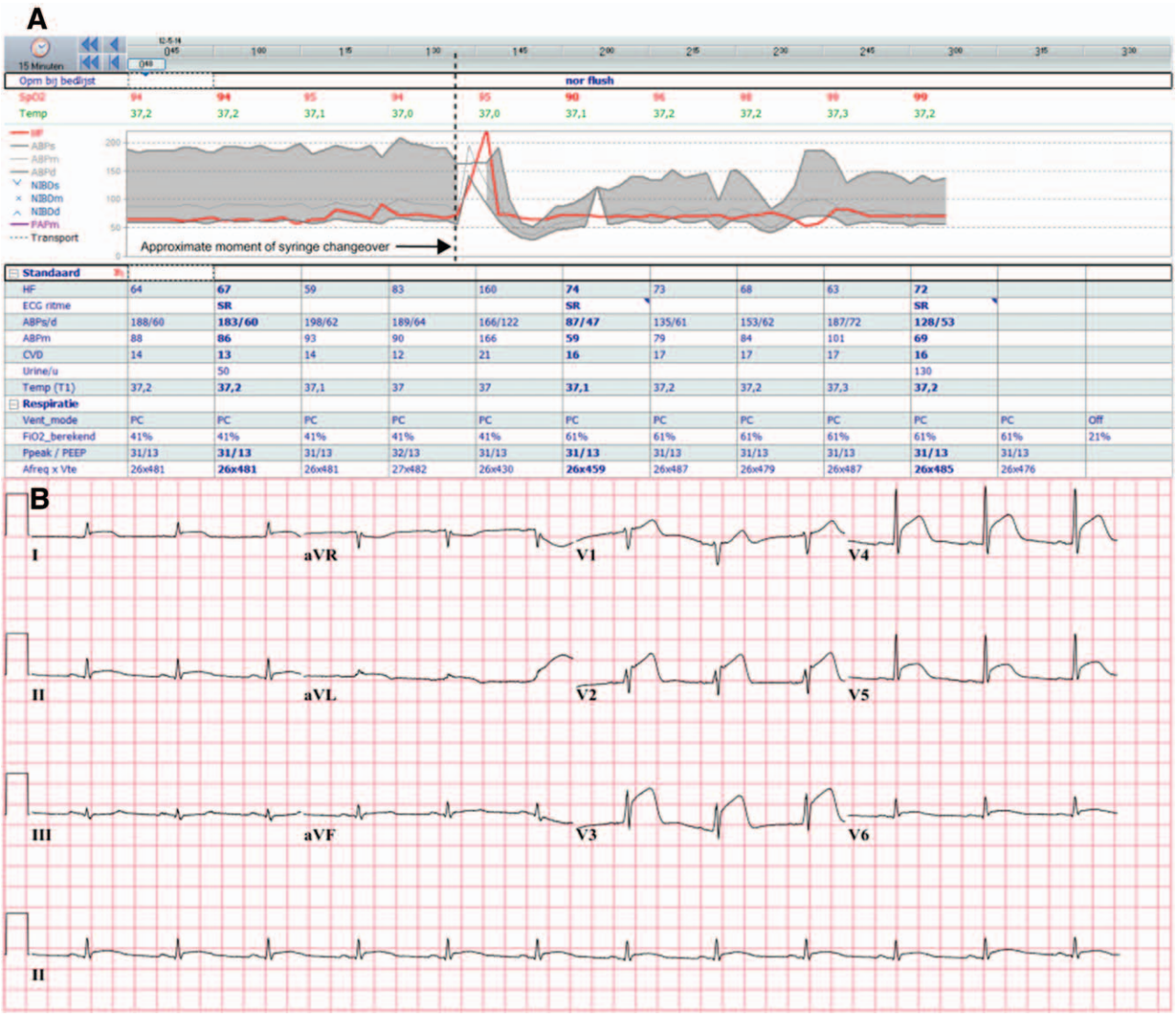

Figure 2. A, Vital signs during the incident in the night from May 11, 2014, to May 12, 2014, at approximately 01:50. Mean arterial blood pressure (MABP) > 200 mm Hg, diastole pressure 150 mm Hg, systole pressure 100 mm Hg, heart rate (HR) > 200 bpm. B, Electrocardiogram (ECG) values approximately 10 minutes after the incident. Clearly visible ST-elevation in nodes I, II, and III is indicative of myocardial infarction directly after the incident. Hearth rate normalized quickly (approximately 70 bpm).

Advice and Clinical Considerations

It is therefore reasonable to assume that there is causality between the syringe exchange procedure and the blood pressure incident. Hypothetical obstruction caused clinically significant overdoses in vitro. If the syringe driver was obstructed, an additional dose of at least 2.33 (with clamp) and 27 µg (without clamp) was delivered in approximately 7 seconds. Although both these quantities exceed the maintenance dose, only the unclamped situation is likely to produce the hypertensive crisis as shown in Figure 2. Moreover, clinicians should note that in these cases, a second overdose may occur because the ratio in concentration between the saline and the norepinephrine pump is temporarily changed at the mixing point of the infusion set along with the flow rate deviation,[6] which only occurred in the norepinephrine pump in the described case.

In clinical practice, it is not unlikely that the syringe driver may indeed become obstructed by an infusion line or some other object; it is therefore important that clinicians are aware of these phenomena. Norepinephrine overdose because of the technical glitch investigated in this study is deemed plausible but avoidable. Technical innovations such as less protruding grippers or reducing the force exerted by the syringe driver might reduce or eliminate the effect of the described malfunction. Clamping the line is, however, essential. Clinicians who were treating the patient in the described case considered the possibility that line was not fully clamped. Failing to clamp the infusion line may produce an overdose for at least 2 reasons. First, free flow may occur. In such a case, the higher situated syringe empties into the patient because gravity "pulls" the medication toward the patient.[8] Second, as the results showed, an obstructed syringe driver may produce an overdose of almost 1 mL if the infusion line is not clamped, despite the fact that a blade-like fixator is placed inside the plunger by the pump.

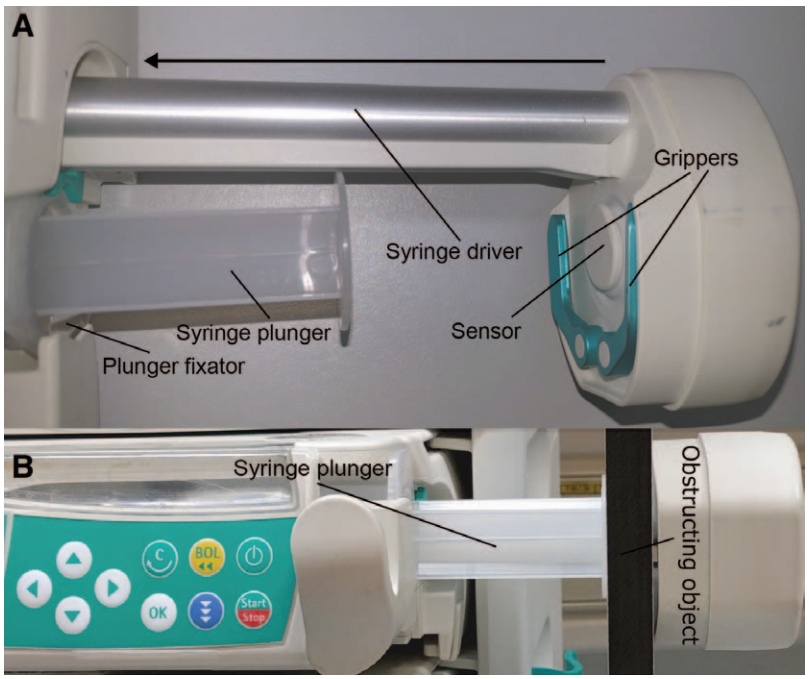

Figure 3. Mechanism of the syringe driver of the syringe pump in the laboratory, identical to the pumps described in the case report. A, After the syringe is placed, the syringe plunger is fixated with a plunger fixator knife. Next, the syringe driver moves toward the syringe plunger until the sensors registers the plunger. After this, the grippers grab the syringe plunger, and the plunger fixator is retracted. The grippers protrude somewhat over the sensor. B, Obstructing object allowing the syringe driver to exert force on the syringe plunger while the thickness of the grippers prevents the sensor to signal the syringe driver to halt. The syringe driver eventually does retract; however, the force exerted is large enough to cause dosing errors.

Table. Experiment Results

	Peak Error (mL/h)	*P* Value	AUC Error (mL)	*P* Value
Obstructed syringe change with clamp	85.8±12.2 (+572%)	[b]*P* < .001	0.07±0.02 (+225%)	[a]*P* < .01
Obstructed syringe change without clamp	926±65.3 (+6173%)	[c]*P* < .0001	0.81±0.07 (+2700%)	[c]*P* < .0001
Nominal syringe change with clamp	45.5±12.0 (+303%)	–	0.03±0.02 (+127%)	–

The results of 3 interventions are shown. In each case, the nominal set point flow rate was considered 100%. The volume delivered by a flow rate of 15 mL/h during time t was considered 100% as well. First, the syringe driver was obstructed and the infusion line clamped. The obstructed syringe driver was allowed to exert force on the plunger 3 times, then the fourth time the syringe driver grabbed the syringe plunger properly and the infusion was continued, after this the flow rate was measured. Second, the experiment was performed without a clamp; in this case, the plunger driver was again obstructed and allowed to exert force on the plunger. Because this produced an overdose immediately, the flow rate was registered during the syringe driver exerted force on the plunger. Finally, a nominal syringe exchange, according to the protocol, was reproduced in the laboratory, in which the pump was not obstructed and no errors or problems occurred. After these 3 interventions, the peak error value and the excess AUC values were acquired from the flow rate data. The AUC is defined as the excess volume delivered from the point after the intervention and during the entire period that the flow rate remained larger than 15 mL/h. The *P* values are comparisons of the nominal and obstructed syringe exchanges; *P* values <.05 were considered statistically significant.

Abbreviation: AUC, area under the curve.

[a]*P* ≤ .01; [b]*P* ≤ .001; [c]*P* ≤ .0001.

CONCLUSIONS

It is plausible that the norepinephrine overdose was because of the potential malfunction, where the syringe driver is obstructed. Partial human error is still a likely alternative explanation, especially because clamping of the infusion was uncertain so that free flow may have occurred. Moreover, if the line is not clamped and the pump is obstructed, the malfunction may produce a significant overdose of almost 1 mL. Therefore, a combination of an obstructing object between the syringe driver and plunger and an unclamped line explains both the severity of the overdose and the error message of the pump described in the case report. This study therefore reinforces the importance of using a clamp during the exchange procedure. In addition, removing the syringe from the pump each time the pump fails to start decreases the risks.

ACKNOWLEDGMENTS/ETHICS STATEMENT

This case has been reported to the Dutch Health Care Inspectorate (registered as number M1006037). The authors thank Dr. R. L. M. Schoffelen for his contribution to possible explanations for the incident.

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