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First Human Exposure to Org 25969

To the Editor.—We read with great interest the article by Dr. Gijsenbergh et al.1 about the reversal of rocuronium-induced neuromuscular block by Org 25969. The described reversal mechanism is highly promising both for the clinical application and in research endeavors.

This being the first description of the pharmacokinetics of Org 25969, we hoped to reconstruct the time course of the plasma concentrations of Org 25969 using the provided data. Unfortunately, the combination of the pharmacokinetic parameters (tables 6 and 7) does not permit such a reconstruction, in part due to a nonstandard method of analysis. The authors do not mention whether an exponential equation or a compartmental model was fitted to the concentrations of Org 25969 in plasma. Was either approach even attempted? The terminal elimination half-life \( t_{1/2,\beta} \) could be appropriate for either a biexponential or a triexponential equation. The reported values for the areas under the plasma concentration curves are, in concept, dose dependent, and the reported values apparently reflect this. Presumably, the authors used areas under the plasma concentration curves to justify the claim of “dose-linear pharmacokinetics,” but this was not explicitly stated in the text. The reported “volume of distribution during the terminal phase” \( V_2 \) is not routinely reported, and a comparison with the standard volumes, i.e., the initial volume of distribution for a multieponential equation \( V_0 \), the volume of the central compartment in compartmental interpretation \( V_1 \), or the volume of distribution at steady state \( V_{ss} \), is difficult if not impossible. Furthermore, because \( V_2 \) was evaluated from \( V_2 = CL/\beta, V_2 = V_{ss} \) is a function of \( t_{1/2,\beta} \) and, hence, provides no additional information. Of the routinely reported parameters, the authors provide only the estimates for the systemic clearance (CL) and the mean residence time. These two parameters do not suffice to reconstruct the time course of the plasma concentrations.

It would have been informative had the authors compared the doses of Org 25969 with the dose of rocuronium using molar units. The dose of rocuronium, 0.6 mg/kg, corresponds to approximately \( 1 \times 10^{-6} \text{ mol} \cdot \text{kg}^{-1} \). Given the molecular weight of Org 25969 of 2,000 Da,2 the doses of Org 25969, 0.1 to 8.0 mg/kg, correspond to \((0.05 \text{ to } 4) \times 10^{-6} \text{ mol} \cdot \text{kg}^{-1} \). If one molecule of Org 25969 binds to one molecule of rocuronium and assuming that the whole dose of rocuronium is still present in the body 3 min after injection, then Org 25969 doses of less than \( 1 \times 10^{-6} \text{ mol} \cdot \text{kg}^{-1} \), corresponding to less than 2 mg/kg, would, on theoretical basis, have little chance to reverse the neuromuscular block completely. As documented by the authors, only the molar doses of Org 25969 higher than the molar dose of rocuronium produced the desired reversal. Therefore, Org 25969 doses of 4.0 and 8.0 mg/kg efficiently reversed the block (table 9); on the molar basis, the two doses are two and four times higher than the dose of rocuronium. The Org 25969 dose of 2 mg/kg is equimolar to that of rocuronium and produced only a marginal reversal of neuromuscular block. Consideration of the doses in molar terms strengthens the authors’ conclusion and explains why lower doses of Org 25969 could not have produced the reversal (table 9).

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In Reply.—We appreciate the interest of Nigrovic et al. in our work. The pharmacokinetic parameters that are presented in our article1 are the results of a noncompartmental pharmacokinetic analysis. The authors of the letter are looking for parameters of a pharmacokinetic modeling analysis and wonder whether such an approach was attempted. The answer is yes. In addition to the descriptive manner in which the pharmacokinetic data of this trial were presented in the article, the plasma concentration-time data of sugammadex (Org 25969) and rocuronium were also analyzed elaborately as part of a mechanism-based pharmacokinetic–pharmacodynamic modeling analysis. The model developed in the latter analysis describes not only the time course of plasma concentrations of sugammadex, rocuronium, and the complex formed between sugammadex and rocuronium, but also the resulting time course of neuromuscular block. The results of the development and validation of that model will be the subject of a separate publication.

With regard to the second point that was raised, we agree that it may have been informative from a scientific point of view to discuss the doses in molar units, but because in practice sugammadex is dosed in units of mg/kg, we believe that it is more appropriate to use that unit in publications.

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Reference

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To the Editor.—We read with interest two case reports of fatal thrombotic complications after cardiopulmonary bypass.1,2 However, there are several unclear issues that the readers should become aware of. First, it is not clear whether adequate heparin levels were maintained during cardiopulmonary bypass (CPB) because activated clotting time (greater than 400–600 s*) does not necessarily reflect the efficacy of heparin anticoagulation.3 Heparin insensitivity due to antithrombin deficiency may be masked by thrombocytopenia, hypofibrinogenemia, or other coagulation factor defects. At our institution, we administer hourly bolus doses of 100 U/kg heparin during CPB to prevent the decrease of plasma heparin levels. Furthermore, we frequently replete antithrombin during prolonged CPB (approximately 3 h) in suspected antithrombin-deficient cases by adding fresh frozen plasma or antithrombin concentrate (Thrombate III®; Talecris Biotherapeutics, Research Triangle Park, NC). We have previously shown that reduced antithrombin levels greatly enhance the rate and peak level of thrombin generation.4 In patients with endocarditis, prolonged CPB, or both, plasma antithrombin levels may become critically low.5 Intraocular fluidity, however, may be maintained by the balance between low procoagulant (fibrinogen, platelet) and low anticoagulant levels (antithrombin, protein C and S, thrombomodulin). Under such conditions consistent with disseminated intraocular coagulopathy, one may observe bleeding tendency. In both cases that the authors described, the administration of hemothostatic blood products, platelet concentrate,1 and cryoprecipitate2 after heparin reversal seemed to have triggered thrombotic complications. Rapid extensions of thrombi suggest that uncontrolled “thrombin generation” occurred, and it is questionable whether thrombi could have been quickly dissolved by endogenous fibrinolytic system even in the absence of aprotinin or other antifibrinolytic agents.6 In the case of afibrinogenemia referenced by the authors, it is possible that normal anticoagulant function and short CPB time (36 min) limited thrombus formation locally (i.e., graft occlusion) without systemic thrombus extension.7

To further stress the importance of adequate anticoagulation, the incidence of deep venous thromboses does not seem to be increased with intraoperative use of aprotinin in the orthopedic surgery when prophylaxis for deep venous thromboses (e.g., low-molecular-weight heparin) is implemented.8 These two catastrophic cases highlight the importance of balancing procoagulant and anticoagulant components of coagulation to achieve localized hemoestasis while avoiding thrombotic complications. Further clinical trials must be conducted to improve our current anticoagulant strategy.9

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multifactorial, including genetic factors such as factor V Leiden.\textsuperscript{2} Antithrombin deficiency may be another factor in this multifactorial etiology. The role of aprotinin is still to be elucidated, because there is recent evidence of an association with thrombotic risk after cardiopulmonary bypass.\textsuperscript{10} This area of endeavor is limited not only by a rare incidence and complex etiology, but also by a lack of time-sensitive coagulation monitoring data. This information would allow analysis of the coagulation/anticoagulation imbalance to localize the lesion and direct further inquiry.

The role of antithrombin deficiency should also be interpreted in light of the thrombin inhibitor. Until recently, heparin, an indirect thrombin inhibitor, was the main anticoagulant for cardiopulmonary bypass. This will certainly shift in the future, given the arrival of bivalirudin, a direct thrombin inhibitor, as a clinical alternative to bypass. This will certainly shift in the future, given the arrival of bivalirudin, a direct thrombin inhibitor, as a clinical alternative to bypass.

Forty words were played 25 times during anesthesia, and each played word should have actually been associated with the word played 15–30 s earlier. This could have changed the assumption that implicit learning occurs with a BIS below 60. Indeed, during word presentation, BIS was above 60 during 18.5% of the time, which is far from what learning occurs with a BIS below 60. Indeed, during word presentation, BIS was above 60 during 18.5% of the time, which is far from what...
Succinylcholine-induced Hyperkalemia

To the Editor:—Drs. Martyn and Richtsfeld1 have provided a great deal of useful information in their recent review article titled “Succinylcholine-induced Hyperkalemia in Acquired Pathologic States.” However, clarification is warranted regarding their statement concerning my 2000 case report of a patient who developed succinylcholine-induced hyperkalemia.2 Martyn and Richtsfeld state, “Another report of hyperkalemia with succinylcholine implicating pancreatitis as the etiologic factor actually had an upper motor neuron lesion of several weeks’ duration.” Actually, in my article, little attempt was made to implicate pancreatitis as the causal pathologic state. As was stated in my report, the patient’s upper motor neuron lesion was a traumatic cervical spine injury that occurred 14 months, rather than several weeks, before the hyperkalemic response to succinylcholine. The discussion that followed was meant to challenge the traditional views of how long extrajunctional neuromuscular receptors persist after traumatic upper motor neuron injury. In their review, Martyn and Richtsfeld have provided important information regarding the duration of these changes in acquired states. Importantly, they have made clear succinylcholine’s potential morbidity when used in critically ill patients who experience muscle atrophy, whether due to pharmacologic denervation or bed rest from critical illness (our patient had been critically ill for approximately 30 days and, in retrospect, resulting muscle atrophy was the most likely etiology of the patient’s hyperkalemic response.) The question that cannot be answered definitively by the review article of Martyn and Richtsfeld is, at what point does the risk/benefit ratio of a medication become unacceptable? As the potential morbidity of a therapy increases, the indications for that therapy become narrower. However, it remains difficult to determine when the risk of a therapy becomes absolutely prohibitive. My case report presented the conundrum of an obese, hypoxemic, uncooperative patient who required tracheal intubation and who, by examination, had a potentially difficult airway. This type of patient encounter occurs sporadically and unpredictably and cannot be studied prospectively in any meaningful way. In 22 yr of clinical practice, I have personally witnessed several near airway catastrophes that followed the alternative use of long-acting nondepolarizing muscle relaxants in similar situations. Therefore, I continue to express the opinion offered in the last paragraph of my case report: “Recognizing that the hyperkalemic response to succinylcholine is unpredictable and that there are currently no criteria to establish those definitively at risk, it is uncertain that alternative administration of a long-acting nondepolarizing muscle relaxant would result in less overall morbidity when administered to a series of patients under similar circumstances.” Unfortunately, clinicians will continue to face these difficult therapeutic decisions, albeit with more wisdom instilled by the work of Martyn and Richtsfeld and others.

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In Reply:—We read with interest the comments by Lequeux et al. about our article,1 and we agree with them. As mentioned in the Discussion, our positive memory results, even with adequate anesthesia, may be related to learning during a period of lighter anesthesia that was “missed” by our Bispectral Index (BIS) recording and also by our BIS analysis. More precisely, to classify each word in a BIS category, we used the mean of the BIS values associated with each word played during anesthesia. Therefore, it is possible that some of the words have been played at a higher BIS value than reported in the study. Moreover, as suggested by Lequeux et al., because of the time requirement for BIS processing, the first BIS values associated with a word should have been associated with the word played earlier. We have thus reanalyzed our data regarding memory performance for the different levels of anesthesia, eliminating the BIS values associated with the 30 first seconds of each word presentation. Moreover, we have considered only the highest value of BIS associated with each word (and not the mean of BIS values). These “Maximal BIS” values were categorized as BIS 21–40, 41–60, and 61–80, and memory scores (C and A) were recalculated. We globally replicated our results despite these changes. That is, we found no evidence of memory during deep anesthesia (BIS 21–40, C = 0.05 ± 0.1 and A = 0.09 ± 0.14). However, memory for words was significant during adequate anesthesia (BIS 41–60), with a significant contribution of implicit memory, because the automatic influence score was significantly greater than the base rate (P < 0.05; A = 0.18 ± 0.19). During light anesthesia (BIS 61–80), the automatic influence was greater than the base rate, but not significantly (P = 0.09; A = 0.17 ± 0.17). However, this nearly significant result for light anesthesia can be explained by the insufficient number of words that could be included in this analysis of memory performance. Finally, we found no evidence of explicit memory contribution regardless of the level of anesthesia (C = 0.04 ± 0.09 at BIS 41–60 and C = 0.04 ± 0.09 at BIS 61–80). This last analysis emphasizes the necessity of further investigations on persistence of implicit memory during light and adequate anesthesia.

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In Reply.—Dr. Matthews takes exception to a statement in the review that refers to his publication. The statement reads as follows: “Another report of hyperkalemia with succinylcholine implicating pancreatitis as the etiologic factor actually had an upper motor neuron lesion of several weeks’ duration.” Dr. Matthews claims that little attempt was made to implicate pancreatitis as the causal pathologic state in their case report.

His report is titled “Succinylcholine-induced Hyperkalemia and Rhabdomyolysis in a Patient with Necrotizing Pancreatitis.” The end of the first paragraph of that report makes the following statement: “We report a case of succinylcholine-induced hyperkalemic cardiac arrest and subsequent myoglobinemic renal failure occurring in a patient with severe necrotizing pancreatitis.” Based on these statements, I concluded that pancreatitis was being implicated as the etiologic factor for the hyperkalemic response.

The risk–benefit ratio of the utility of a drug cannot be generalized and applied to all clinical situations. The decision to proceed or not with the administration of the drug (succinylcholine) has to be individualized based on the available information at that time for that patient with repeated evaluation of the situation with change of time and clinical scenario. Dr. Matthews had firsthand information and opportunity to evaluate the patient and, having weighed the pros and cons of the risks and benefits, decided to use succinylcholine. One cannot question that judgment call. He, in fact, considered alternative approaches, including fiberoptic and blind nasal approaches to intubation. However, it is stated, “titration of alternative drug, such as propofol, was felt to be too time consuming.”

Regardless of whether neuronal lesion is of several weeks’ or several months’ duration, succinylcholine-induced hyperkalemia has been observed after full recovery of motor function. In the patient described, Dr. Matthews noted that residual spasticity was still present and the patient needed the use of a cane to ambulate. This patient was initially intubated because of respiratory failure on the fifth day of admission with no adverse events. The report does not provide an account of what drugs were used to facilitate intubation the first time. Was a relaxant used at all? If not, how was the intubation achieved in this obese, hypoxemic, uncooperative patient? These data would have clarified the limitations and advantages of the technique used, and whether in fact the residual effects of spinal contusion were still present, if succinylcholine was used the first time. Unfortunately, only the intubation technique used the second time is reported.

Gronert and Theye wrote the first review of succinylcholine-induced hyperkalemia in 1975. Almost two decades later, based on new and relevant information, the subject was comprehensively reviewed in 1992. Information regarding acetylcholine receptor (AChR), its isoforms, and their responses to agonists and antagonists continues to accumulate. This was the basis for the recent review. During his 22 yr of clinical practice, Dr. Matthews has “personally witnessed several near airway catastrophes that followed the use of longacting nondepolarizing relaxants in similar situations.” In the case reported, the use of a depolarizing relaxant also had a catastrophic consequence. As demonstrated by the observations of Dr. Matthews, sometimes the choices deliberately made, with the best of intentions, can still result in adverse outcomes. Even 40 yr after the original reports of succinylcholine hyperkalemia, we are still uncertain, in some situations, whether it would be safe to administer or desist from succinylcholine. It is possible that persistent pancreatitis (or inflammation) by itself may up-regulate AChRs even in the absence of immobilization. Clinical observations, such as that of Matthews, and basic studies may answer these questions in the future and guide us better.

On another note, I wish to modify my thinking on a statement made on page 164 of the review. It states that 100 mg succinylcholine is capable of releasing 0.56 mol choline, a concentration outside the physiologic range and sufficient to activate α7 AChRs. We now realize that this approximate concentration of choline when redistributed would result in a much smaller concentration at the neuromuscular junction. Although this does not preclude the mechanism suggested for succinylcholine and its metabolites (succinylmonocholine and choline) to stimulate α7 AChRs, the importance of the latter in the stimulation of the α7 AChRs becomes less significant. I thank William J. Perkins, M.D. (Associate Professor, Department of Anesthesiology, Mayo Clinic College of Medicine, Rochester, Minnesota), for bringing this to my attention on January 24, 2006, in a personal communication via e-mail.

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Long-term Respiratory Depression Induced by Intrathecal Morphine Treatment for Chronic Neuropathic Pain

To the Editor.—Intrathecal opioid treatment has become a widely used approach in cancer and chronic pain, particularly for the treatment of patients with neuropathic pain, failed back syndrome, and mixed-type pain. In contrast to the frequent reports of respiratory depression after postoperative intrathecal or epidural opioid administration, there are only a few reports of severe drug-related complications under chronic intrathecal treatment using an intrathecal drug delivery system (IDDS) with a regular dosage. Particularly, to our knowledge, no case of a slowly increasing chronic respiratory depression after IDDS implantation has been reported. We report the case of a 41-yr-old man referred to our pain clinic 6 yr after a motorcycle accident leading to a C4–C7 root transection with attributed medullar and cervical plexus lesion. Despite implantation of an IDDS (IsoMed-60 ml; Medtronic, Inc., Minneapolis, Minneapolis, 2006: 105:431–3

Support was provided solely from institutional and/or departmental sources.
of oxygen, and partly assisted ventilation (continuous positive airway
pressure), sleep disorder, and depressed mood during the past 8 months. He
declared that his pain level of 7 on a numeric rating scale improved
since 1 yr. The pain relief was achieved with 75 mg amitriptyline, 1,800 mg
gabapentin, and an intrathecal infusion of 4 mg morphine per day. At the
time of presentation, the patient experienced deafferentation pain at
the left upper limb, and tactile allodynia of the left chest. Chest x-ray
tomography of the chest demonstrated a left elevated diaphragm as a
consequence of phrenic nerve paralysis (figs. 1 and 2). Arterial blood gas
analysis revealed respiratory acidosis (in arterial blood: partial pressure
of oxygen [PaO2], 47.0 mmHg; partial pressure of carbon dioxide [PaCO2],
65.1 mmHg; pH, 7.33; base excess, 5.3 mmol/L; saturation, 80%). Pain started
immediately after the accident and was treated with several combinations of
opioids and other analgesics, which the patient did not remember in
detail. An IDDS was implanted in January 2004, with an initial daily dose
of 14 mg morphine and 0.15 mg clonidine. Nearly 2 weeks later, catheter
leakage and dislocation provoked a withdrawal syndrome, and after
replacement of the catheter with the previous dose of morphine, cardio-
pulmonary resuscitation became necessary. The patient recovered com-
pletely from this intervention. Subsequently, the morphine dosage was
reduced to 2 mg/day. The exact time course of dose changes within the
following months is unknown, but the dose finally increased to 4 mg
morphine per day. During these last months, the patient’s psychiatric state
and general condition worsened significantly.

Because of the psychological symptoms, particularly the severe tired-
ness and depressed mood, and the reduced pulmonary function, we
suspected chronic opioid intoxication, and consequently the daily intra-
the cal morphine dose was reduced from 4 to 1 mg within 3 weeks and
subsequently was switched to a concomitant oral medication (12 mg/day
hydromorphone). In addition, 0.6 mg/day clonidine was substituted for 5
weeks, and pregabalin (300 mg/day) was substituted for gabapentin.

Under this medication, the patient reported a considerable improvement
in pain level, tiredness, and psychological state, and the dyspnea and
respiratory function recovered to normal (in arterial blood: PaO2, 126.7
mmHg; PaCO2, 41.8 mmHg; pH, 7.424; base excess, 2.8 mmol/L; saturation,
98%). Obviously, the morphine effects on respiration were facilitated by
(1) consequences of the accident, including phrenic nerve paralysis,
elevation of the diaphragm, and atelectasis, and (2) the reduced vigilance
after dose escalation. However, the key role of intrathecal morphine for
the chronic deterioration of the patient’s condition was proven by com-
plete recovery not only of the tiredness and other psychiatric symptoms
but also by return to normal in all respiratory parameters and the physical
capacity after morphine reduction and change to oral opioid treatment.

One reason for this case presentation was the remarkable fact that all
involved physicians (neurosurgeons, neurologists, rehabilitation and pain
specialists) did not recognize the correlation of increasing morphine dose
without any analgesic improvements, the increasing fatigue, exercise dyspnea,
and the deterioration of pulmonary function step-by-step for several months al-
though respiratory depression with intrathecal opioids is well known. The
missing anticipation of respiratory risk under long-term intrathecal morphine
medication is matched by missing precautions in the cited European and
German guidelines. In consequence, physician awareness is apparently
limited only to acute signs of intoxication (such as bradypnea, respiratory
arrest). There is an increasing number of reports such as this one revealing
potentially life-threatening side effects or persistent neurologic sequelae of
IDDS, and there are no controlled trials evaluating the frequency of more
moderate respiratory depression or increased sleep apnea syndrome in
chronic pain patients. The current patient is one of several referred to our
pain clinic and treated intrathecally because of a supposed resistance to
therapy. These patients were mainly diagnosed in neurosurgical or orthope-
dic departments with a monodisciplinary approach to pain treatment. Most
of them—like the current patient—could be treated sufficiently without
IDDS using multimodal nonmedical protocols and medical treatment, mainly
including oral opioids. Therefore, treatment resistance should be diagnosed
very cautiously. We recommend a reevaluation of intrathecal opioid treat-
ment in chronic pain states considering that, in contrast to intrathecal spas-
molytic treatment and oral opioid pain treatment, no randomized con-
trolled trials are available.
To the Editor:—It is hard to measure the intangibles of skilled anesthesia management such as leadership, planning, and dynamic problem solving, let alone to link them unequivocally to specific patient outcomes. Although simulation training has been advanced as a method to help develop crisis management and other “nontechnical” skills, proof of this link has been advanced as a method to help develop crisis management and other “nontechnical” skills, proof of this link has been lacking. As a result, training programs are likely to continue to use simulation to help develop and teach these skills, despite the lack of evidence supporting their efficacy.

I'd been there before. In my early years as a resident, I was put in charge of a patient who was having difficulty breathing during anesthesia. I was able to quickly assess the situation and take appropriate actions to ensure the patient's safety. This experience taught me the importance of being able to think quickly and in a calm, thoughtful manner when faced with a crisis.

The Value of Simulation Training during Anesthesia Residency

The personnel management of this situation focused on dispatching personnel to maintain alveolar anesthetic and oxygen levels while freeing hands to prepare for an intravenous anesthetic. Accordingly, further ventilation was temporarily suspended, and the sidestream carbon dioxide sampling line was disconnected and capped (so as not to waste oxygen from the circuit). Fortunately, a pulse oximeter was available.

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To the Editor—The use of “smart” intravenous infusion pumps incorporating microcomputer technology holds the promise of safer medication administration and is endorsed by ECRI (formerly the Emergency Care Research Institute). A sophisticated feature of smart pumps is the medication library for particular patient types or care venues. Drugs in the library are given absolute (hard) or advisory (soft) preprogrammed dosing limits. The user selects the appropriate library, drug, and concentration, thereby invoking the limits for that medication. If a limit is breached, an alarm is both seen and heard. An “anesthesia mode” within each library allows prolonged pause, alarm management, and dose limits specific for the operating room.

After an intensive multidisciplinary study that included review of safety data, a return-on-investment analysis, a failure mode and effects analysis, and a usability trial, the University of Wisconsin Hospital and Clinics selected and implemented the Alaris Medley Medication Safety System intravenous pump (ALARIS Medical Systems, Inc., San Diego, CA) in October 2003. Before use in the operating room, training to highlight pump safety features, setup, programming, and capabilities was mandated for all anesthesia providers.

The failure mode and effects analysis team was aware, via an Internet discussion group and discussions with the manufacturer, of reports describing incorrect loading of the pumping segment of the Alaris intravenous tubing. Two types of misloads involving a hard plastic upper fitment were described. The first resulted from lifting the upper fitment as the pump door was closed, thereby stretching the silicone plastic pumping segment, typically causing an underinfusion. The second type of misload was less well understood and difficult to reproduce. It was thought to involve trapping the upper fitment in a tilted position as the pump door was closed. Because of these reports, preimplementation training specifically focused on correctly loading the upper fitment.

Three weeks after pump implementation, a 58-yr-old man presented for elective coronary revascularization as the first case of the day. Preoperative anesthesia equipment setup included Alaris intravenous pumps mounted at eye level to facilitate reading the programming screen. One tubing set was primed with nitroglycerin, the roller clamp was closed, the tubing was loaded, and the pump module door was closed and latched. The pump was turned on; the infusion was programmed and placed into prolonged pause as indicated by a yellow light at the top of the pumping module. The tubing was connected to a primed carrier fluid system that included a stopcock manifold. The tubing was off or paused, the fingers press the tubing against the door and controls flow. When the tubing is loaded as designed and the pump is off or paused, the fingers press the tubing against the door and completely prevent flow. In this event, the reticulating fingers could not reach the door, the tubing was not occluded, and free flow occurred.

Review of the downloaded pump databases revealed that during the setup, the pump alarmed twice before the audio and visual alarm indicators were cancelled when the pump was placed in prolonged pause. The alarm message displayed was “Fluid side occlusion.”

Three issues are particularly concerning. First, the failure mode and effects analysis conducted before the implementation of the pumps was lengthy and thorough but did not predict the failure mode causing arterial pressure decreased and required repeated treatment with bolus administration of vasopressors by syringe. Transesophageal echocardiography revealed a marked decrease in left ventricular end-diastolic volume and function. The blood pressure recovered within minutes. Only then was the nitroglycerin bottle supplying the infusion pump found to be completely empty. A free-flow malfunction of the pump was suspected.

Close examination of the nitroglycerin pump module revealed a gap at the top of the door (fig. 1). The pump in question was removed and sequestered. Surgery proceeded without incident. Postoperatively, the patient was found to be neurologically at baseline and without untoward sequelae.

The sequestered pump was photographed, and the databases within the control and pump module were downloaded. Visual examination revealed that part of the intravenous tubing, the upper fitment, a molded hard plastic flange designed to be loaded from above into a recess, had been “front loaded” and held in place by the flange as the door was closed. The door was sufficiently to latch and to open the flow-stop slide clamp below the pumping mechanism. The tubing flange held the door away from the reticulating finger pumping mechanism that normally sequentially occludes the tubing and controls flow. When the tubing is loaded as designed and the pump is off or paused, the fingers press the tubing against the door and completely prevent flow. In this event, the reticulating fingers could not reach the door, the tubing was not occluded, and free flow occurred.

Almost immediately, and for no readily apparent reason, the patient’s
the frank free flow we report. Second, the alarm message displayed during setup indicated an occlusion as opposed to a potential free flow, a message that did not alert the user to the fault. Finally, this event occurred despite intensive user training before implementation that emphasized correct upper fitment loading.

We believe other factors also contributed to this event. Because the pump was mounted at eye level, the door gap at the top was not visible. It is likely that time pressure, distraction from other setup activity in the operating room, and the practitioner’s inexperience clinically with the new pump increased the likelihood of this event.

Clinical introduction of new products may result in unanticipated consequences despite preintroduction evaluation, institution-specific usability testing, and carefully planned user training. Such training cannot be relied on to overcome design flaws in equipment.

This incident was reported through the US Food and Drug Administration reporting system. The manufacturer has since modified the pump module and error messages to reduce the risk of free flow from this cause.

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