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 (t1/2β) 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” (V2) is not routinely reported, and a comparison with the standard volumes, i.e., the initial volume of distribution for a multieponential equation (V1), the volume of the central compartment in compartmental interpretation (V1), or the volume of distribution at steady state (Vss), is difficult if not impossible. Furthermore, because V2 was evaluated from \( V_2 = CL/\beta \), \( V_2 \) 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 if 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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Systemic Thromboses after Cardiopulmonary Bypass: Is It Thrombin or Antithrombin?

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.2 Intravascular 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 intravascular coagulopathy, one may observe bleeding tendency. In both cases that the authors described, the administration of disseminated intravascular coagulopathy, one may observe bleeding tendency. In both cases that the authors described, the administration of deep hypothermic circulatory arrest.4–6 To my knowledge, there is no case report of this phenomenon with bolus anticoagulation.7

In the case of fibrinogenemia 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 hemostasis 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. 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. This area of endeavor is limited not only by a rare incidence and complex etiology, but also by a lack of real-time objective 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 heparin for cardiac surgery with and without cardiopulmonary bypass.

Drs. Tanaka and Sniecinski have correctly highlighted antithrombin deficiency as a possible component in the etiology of systemic thrombosis after cardiopulmonary bypass. The continuing incidence of these rare, but catastrophic cases highlights the clinical necessity for better data, perhaps in the form of an international registry. This would provide a platform for further clinical trials to refine our coagulation management of cardiopulmonary bypass and improve perioperative outcomes for our patients.

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To the Editor.—We read with interest the article by Iselin-Chaves et al.1 in which implicit learning was studied during general anesthesia. Forty words were played 25 times during anesthesia, and each played word was associated with a Bispectral Index (BIS) value recorded at the moment the word was played. The authors showed that implicit learning persists for words played during light (BIS 61-80) and adequate anesthesia (BIS 41-60) but not during deep anesthesia (BIS 21-40). Because the words were repeated 25 times throughout anesthesia, each word was associated with 25 BIS values for each patient, and it is not clear whether the authors, to classify each word in a BIS category (21-40, 41-60, or 61-80), used the mean of the 25 BIS values or used the BIS range of these 25 values to be associated with each word. If the mean BIS value was used, it is possible that some of the word presentations have been played at a higher BIS value than stated in the study. So implicit learning presented as occurring at a BIS below 60 may actually have occurred at a higher BIS.

Moreover, the time for BIS processing was not taken into account; this processing is responsible for a 15- to 30-s delay between raw electroencephalogram recordings and BIS value display (depending on the “BIS Smoothing Rate” setup).2 So each BIS value associated with a 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 can be considered as an adequate anesthesia as stated in the article.

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In Reply—We read with interest the comments by Lequeux et al. about our article, 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.

Irene A. Iselin-Chaves, M.D.,* Sylvie J. Willems, Ph.D. ‡ University Hospital of Geneva, Geneva, Switzerland. irene.iselin-chaves@hcuge.ch

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Succinylcholine-induced Hyperkalemia

To the Editor.—Drs. Martyn and Richtsfeld 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 case report of a patient who developed succinylcholine-induced hyperkalemia. Martyn and Richtsfeld state, “Another report of hyperkalemia was meant to challenge the traditional views of how long extrajunctional neuromuscular receptors persist after traumatic upper motor neuron injury that occurred 14 months, rather than several weeks, before the patient’s upper motor neuron lesion was a traumatic cervical spine injury.” 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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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.1,2 In contrast to the frequent reports of respiratory depression after postoperative intrathecal or epidural opioid administration,3,4 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.2,6–10 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 avulsion 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 mM 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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David C. Warthier, M.D., Ph.D., served as Handling Editor for this exchange.

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Fig. 1. Chest x-ray. White arrows mark elevated left diaphragm. C = colon.

Fig. 2. Computerized, contrast-enhanced, multisliced tomography; coronary reconstruction. White arrows mark the right and left diaphragm; left side elevated diaphragmatic dome with compression atelectasis (*). A = aorta; L = liver; LV = left ventricle; RV = right ventricle.

MN) 8 months previously, he experienced intractable neuropathic pain, including deafferentation pain at the left upper limb, and tactile allodynia at the left chest after a coagulation of the dorsal root entry zone of the substantia gelatinosa (DREZ lesion) 1 yr ago. At time of presentation, the medication included 75 mg amitriptyline, 1,800 mg gabapentin, and an intrathecal infusion of 4 mg morphine per day since 1 yr. The pain relief was insufficient, with a mean pain level of 7 on a numeric rating scale (0–10). In addition, the patient reported increasing dyspnea, severe fatigue, sleep disorder, and depressed mood during the past 8 months. He was unable to walk more than 10 m, he needed permanent administration of oxygen, and partly assisted ventilation (continuous positive airway pressure) became necessary during the past 6 months. The medical and neurologic examination revealed a tired patient with complete paralysis of the left arm, accompanied by atrophy, anesthesia (C4–C7), Horner syndrome, and tactile allodynia of the left chest. Chest x-ray and computed 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 mm; saturation, 80%). Pain started immediately after the accident and was treated by 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, cardiopulmonary resuscitation became necessary. The patient recovered completely 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 tiredness and depressed mood, and the reduced pulmonary function, we suspected chronic opioid intoxication, and consequently the daily intrathecal 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 mm; 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 complete 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 although 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.11,12 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 orthopedic departments with a monodisciplinary approach to pain treatment.13 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 treatment in chronic pain states considering that, in contrast to intrathecal spasmyotic treatment and oral opioid pain treatment,14–16 no randomized controlled trials are available.
The Value of Simulation Training during Anesthesia Residency

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 is still not made even 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 is still not made.


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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 and narrow bore extension tubing (Arrow International Inc., Reading, PA). Roller clamps and manifold stopcocks were opened to allow immediate initiation of therapy as necessary; however, the extension tubing that would eventually connect the manifold to the patient’s central venous line remained clamped.

The patient was brought to the operating room. After induction of anesthesia and preparation for surgery, the extension tubing from the manifold was connected to the infusion port of the central venous catheter (MAC, Arrow International, Inc.). Later, the clamp on the extension tubing was opened to allow the slow infusion of carrier fluid via the manifold.

Almost immediately, and for no readily apparent reason, the patient’s 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 closed 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.

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
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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The authors thank Paul R. Malischke, B.S.E.E. (Anesthesia Equipment Manager, University of Wisconsin Hospital and Clinics, Madison, Wisconsin).

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