modes and tones on anesthetist vigilance and on the performance of the whole OR team. The entire operating room environment, and not just individual devices, must be considered. Until data are available, any rigidly defined standard would be premature and inappropriate.

In October, the committee developing human factors guidelines for medical devices for the Association for the Advancement of Medical Instrumentation (AAMI) voted unanimously to oppose rigidly defined alarm standards in medical equipment until additional scientific study and significant input from clinicians had been obtained. The Patterson sounds are too strictly defined and may not be the best approach. Mandating their use in all devices prematurely may, in fact, inhibit advances in alarm technology and slow improvement in the dismal ergonomics of the anesthetist's workspace. To participate in the standards development process, write to Mr. Terri Mecholsky, Staff Manager, ASTM, at the following address for membership information: 1916 Race Street, Philadelphia, PA 19103-1187; telephone: (215) 299-5485. Members of the North American anesthesia community are invited to send comments on this topic to me at the address listed below.

MATTHEW B. WEINGER, M.D.
Assistant Professor of Anesthesiology
University of California, San Diego
San Diego VA Medical Center (125)
3350 La Jolla Village Drive
San Diego, California 92161

* Patterson RD: Guidelines for auditory warning systems on civil aircraft. Civil Aviation Authority Paper #82017. London, England, 1982.

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Paralysis after Long-term Administration of Vecuronium

To the Editor:—The publication of Segredo *et al.*[1] has been recently commented on by Pollard[2] and Bachenberg.[3] Both authors[2,3] raise important questions, but there are additional questions that should be clarified before accepting the conclusions of Segredo *et al.*[1]

Dr. Bachenberg's[3] question regarding chronic denervation in patient 1 has been only partially answered by the authors.[4] Segredo *et al.*[1] should have differentiated between multi-organ failure-associated "critical illness polyneuropathy,"[5] Guillain Barré syndrome, and simple inhibition of the neuromuscular transmission. The differential diagnosis between these conditions is a lot more complicated[6] than outlined in the reply[4] to Dr. Bachenberg.

Segredo *et al.*[1] believe the persistent high plasma concentrations of 3-desacetyl vecuronium to be responsible for prolonged neuromuscular blockade observed in their patients. No mention is made, however, whether and how the assay was validated under the conditions of this study, to exclude the possibility of interference of one or more of the numerous drugs, administered simultaneously during the course of paralysis, with the determination of vecuronium and 3-desacetyl vecuronium. This is of importance since because of the specific conditions of this study, blank plasma samples could not be obtained from the patients.

By assumption, the authors linked the persistent high concentrations of 3-desacetyl vecuronium to renal failure and did not exhaustively elaborate the alternative possibility that not only the parent compound but also the 3-desacetyl derivative might depend mainly on hepatic uptake and biliary excretion for its elimination. This view is supported by literature data[7–10] and by the finding that patient 1 had slightly elevated and patient 2 had evidently abnormal direct bilirubin values.

In light of the current knowledge on the elimination pattern of vecuronium, partially generated[11] or reviewed[12] by some of the authors, it is difficult to understand and accept the reasons for the "arbitrary" instead of rational choice of vecuronium for long-term relaxation in a jaundiced patient (patient 2) with liver function disturbances.

Last but not least, for the sake of thoroughness, the authors should have considered (by adding a footnote to their galley proof) the observations by others[13] of just the opposite phenomenon—increased requirements for vecuronium during long-term administration of very high doses, and uneventful recovery in two critically ill patients.

We consider the paper by Segredo *et al.*[1] an important warning signal with regard to the use of muscle relaxants in the critically ill patients. However, most of the assumptions, limited to a population of only two patients, remained unsubstantiated.

SANDOR AGOSTON, M.D., PH.D.
Research Group for Experimental Anesthesiology and Clinical Pharmacology
University of Groningen
P.O. Box 30.001
9700 RB Groningen
The Netherlands

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In Reply:—We appreciate the opportunity to reply to the letter of Dr. Agoston. We are pleased that the description of our two cases has generated so much interest. On the other hand, we believe the temptation to overinterpret our two complicated cases should be resisted. Nevertheless, we will respond to the concerns of Dr. Agoston that we did not adequately analyze the various possibilities of the prolonged paralysis we observed.

We agree that a complete differential diagnosis of prolonged weakness in critical care patients is complicated. However, Dr. Agoston offers no substantive new thoughts regarding the cause. As we stated in our response to Dr. Bachenberg,[1] neostigmine transiently reversed the weakness, which lead us to conclude that a neuropathy or a "Guillain-Barre" type of syndrome was not the diagnosis. A neuropathy certainly does occur in critically ill patients[2] and may have been a contributing, but not a primary, factor.

In addition, because we did not find the other classical causes that could have explained the prolonged neuromuscular blockade (pharmacologic potentiation of neuromuscular blockade, residual levels of vecuronium, acidosis, hypokalemia, hypocalcemia, and hypermagnesemia), we measured the plasma concentrations of vecuronium's putative metabolites. We found very high and persistent levels of 3-desacetylvecuronium, which is 50% as potent as vecuronium as a neuromuscular blocking agent in cats. We therefore concluded that accumulation of 3-desacetylvecuronium was the likely cause of the prolonged paralysis.

Dr. Agoston's concern about the validity of our gas chromatography assay findings, given the lack of blank plasma samples, is reasonable. The specificity of the gas chromatography assay for quaternary ammonium compounds arises from the selectivity of the sample processing, the resolving power of capillary column gas chromatography, and the ability of the nitrogen–phosphorous (NP) detector to respond only to components containing nitrogen or phosphorous.[3] In general, we have found that most other nonquaternary ammonium drugs are removed by sample processing during the prewash or do not form extractable ion pairs with iodide ion. In the rare cases in which we have observed recovery of other nonquaternary ammonium drugs after sample processing, their molecular weights or polarities have been sufficiently different from that of vecuronium or its metabolites to allow complete separation by gas chromatography. Among the drugs specifically tested for interference are atracurium, thiopental, fentanyl, midazolam, diazepam, and vancomycin at the 1-μg/ml level. Nonetheless, analysis of samples from critically ill patients provide unusual analytical challenges not only because of the wide variety of drugs given to these patients, but often also because of elevated plasma levels of endogenous components, particularly in patients with liver and kidney failure. To eliminate concerns about the validity of the gas chromatography data from intensive care unit (ICU) patients, we analyzed selected samples from the gas chromatography analysis by selected ion monitoring gas chromatography mass spectrometry at m/z 557, which is the M^+-57 fragment of the tert-butyldimethylsilyl derivative of 3-desacetylvecuronium. In these experiments, the response at m/z 577 was found to be consistent with that found by gas chromatography, and thus the identity of the 3-desacetylvecuronium peak was confirmed.

Dr. Agoston mentions the very interesting problem posed by the study of the pharmacology of 3-desacetylvecuronium in animals, which strongly suggests that 3-desacetylvecuronium is eliminated mainly by the liver.[4] These animal data should not bias his analysis of our first case report. The patient who remained paralyzed 7 days after discontinuation of vecuronium did not have liver impairment. The very slight perturbation of liver function tests observed are common in the ICU setting, and there was no sign of either liver injury (normal to twofold increased levels of transaminases and normal levels of alanine aminotranferase, throughout the period of prolonged paralysis) or of decreased liver synthesis function (normal prothrombin time throughout prolonged paralysis). The direct bilirubin concentration was slightly elevated during the period of prolonged paralysis, but the value observed 24 h before the discontinuation of vecuronium was normal (total bilirubin = 1.2 mg/dl). Because of its very slight elevation and because the alkaline phosphatase plasma concentrations remained normal throughout the period of prolonged paralysis, we consider the slight increase in bilirubin plasma levels not clinically significant. Therefore, we excluded liver impairment as a cause of 3-desacetylvecuronium accumulation (high, stable concentrations of 3-desacetylvecuronium during the last 5 days of prolonged paralysis). On the other hand, we observed a creatinine clearance of 5 ml/min, indicating renal failure. We also observed a very low creatinine clearance (3.6 ml/min) in our second case, a 40-h, prolonged neuromuscular blockade after discontinuation of a 48-h-long administration of vecuronium, in which the patient also had high plasma concentrations of 3-desacetylvecuronium. This suggested that renal failure may be related to 3-desacetylvecuronium accumulation. This apparent contradiction between human observation and animal data cannot be explained until there is an animal model with which to study the effect of long-term administration of vecuronium on its pharmacokinetics.

We feel confident of our conclusion that prolonged neuromuscular blockade can occur after prolonged administration of vecuronium, and that it may be due to the accumulation of the metabolite 3-desacetylvecuronium.

VERONICA SEGREDO, M.D.
Visiting Research Fellow

MANOHAR SHARMA, PH.D.
Associate Research Chemist

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