Muscle Relaxants and Electroencephalogram

To the Editor:
I was surprised to read in the report of Ueyama et al. the erroneous statement, “A muscle relaxant itself does not have an effect on electroencephalogram.” We described an increase in duration of electroencephalography isoelectric interval during burst suppression after the administration of pancuronium in dogs anesthetized with isoflurane. This effect was then reversed by antagonism of neuromuscular blockade with neostigmine. The failure of Ueyama et al. to control for neuromuscular blockade in their study of pregnant patients may present a confounding variable.

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References

In Reply:
Thank you for your interest in our article. Schwartz et al. reported that pancuronium increased the duration of isoelectricity produced by isoflurane during burst suppression in experiments with canines. When a burst and suppression pattern was observed in a clinical situation, the anesthetic level was considered too deep. Contrary to this, Ge et al. reported that vecuronium did not alter the bispectral index during isoflurane anesthesia. Grief et al. also showed that mivacurium did not affect the bispectral index value during propofol anesthesia. In these reports, the index (BIS) in Ge et al. and bispectral index in Grief et al. was approximately 40–50, which indicated the usual clinical level of anesthesia. The authors analyzed many electroencephalograms and concluded that vecuronium did not change electroencephalographic waveforms or derivatives during sevoflurane/opioid anesthesia in the usual clinical settings. The authors speculated that the phenomenon that Schwartz AE et al. observed was specific for pancuronium or in a deep anesthetic level.

It is well known that contamination of electromyograms may falsely increase electroencephalographic derivatives, and administration of a neuromuscular blocker restores them. In our study, the level of electromyograms was kept adequately low, thereby making the possibility that muscle afferents might alter the level of consciousness unlikely. The authors believe that muscle relaxants would not affect our results.

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Ethics and Human Experimentation

To the Editor:
I thank James Eisenach, MD for asking Edward Domino, MD to provide us with a fascinating historic overview of the development of ketamine, a compound for which new uses are being found almost 50 yr after its introduction into US clinical practice. I commend Eisenach for asking Susan Palmer, MD,2 to provide an ethical commentary about the experimentation on prisoners that was used to test the safety of phencyclidine and then ketamine. I agree with Palmer’s conclusion that the results of Domino’s experiments should be retained in the research literature. On the other hand, I respectfully disagree with her statements that respect for patient autonomy was not clearly defined in 1965 and that a clear understanding of a researcher’s obligation to human subjects was achieved only after the development of federal regulations and their publication in the Code of Federal Regulations.

First, the Nuremberg Code, a response to unethical human experimentation on prisoners, clearly described informed consent and “free power of choice” in its first article in 1947. Second, the Declaration of Helsinki, as adopted by the World Medical Association in June 1964, clearly described what is needed for informed consent in patients, such as prisoners, who are in a dependent relationship with the investigator. Meanwhile, one anesthesiologist, Henry K.
Beecher, MD, was at the forefront of identifying ethical problems with human experimentation; he reported his findings and opinions in several prominent journals, including this one.6,7 Finally, although not relevant to Domino’s experiments, the Belmont Report was published in 1979.8 Therefore, I would argue that the definitions and obligations were available before the 1980s; the problem was that they were being ignored.

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References
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In Reply:
Although I thank Dr. Butterworth for his comments concerning my commentary,1 I do not agree with his opinion that US medical researchers consistently obtained informed consent from human subjects before the 1980s. The Nuremberg Code (1947), the Declaration of Helsinki (1964), and Beecher (1966)2 describe research without consent from human subjects and were all published before the 1980s. However, printed copies of these documents were not readily available to US physicians. Until the 1980s, even fewer physicians thought that the Nuremberg Code or Helsinki Declaration had much to do with medical research or clinical practice within the United States.

The Nuremberg Code was composed subsequent to the conviction of Nazi physicians who defended their horrific research, claiming it was similar to medical research being done all over the world.3 That code stated as its very first basic principle that human experimentation should involve the “voluntary consent of the subject.”

The World Medical Assembly meeting in Helsinki published what became known as the Declaration of Helsinki. It contained 22 “basic principles” for guiding human subject research. The Declaration was later revised in 1975 and 1983.

The medical community did not develop sanctions for researchers who disregarded the Nuremburg Code or the Helsinki Declaration.

Beecher’s2 comments in the New England Journal of Medicine were not welcomed by some in the medical research community because prominent researchers thought his ideas about obtaining informed consent from human subjects would stifle medical research. His article was originally refused publication in JAMA4 and the New England Journal of Medicine agreed to publish it only after more than half of the cases he described were removed.

I agree with Butterworth that Beecher—along with many of his distinguished anesthesiologist colleagues—rightly deserves a place of honor in the development of the understanding of clinical research ethics. However, I certainly did not know specifically of Beecher’s New England Journal of Medicine article2 when I started doing human subject research in 1976. It was not until I took the time and effort to research ethical issues in anesthesiology practice that I began to understand the development of medical ethics in the United States.

The medical literature of the 1970s is, unfortunately, replete with clinical studies that did not meet the standards of the Declaration of Helsinki.5 Even today, many physicians do not value the study of medical ethics because they do not believe it is an academic discipline. Many surgeons believed that consent was not routinely required and that medical ethics was a waste of time that served only to “raise doubts where there were none before.”6 Multidisciplinary panels that composed Federal regulations for human research had more ethicists and members of the public than physicians because US society wanted consistent treatment of human subjects of research.

The community of professional physicians failed to agree on required elements of consent or enforce consistency in obtaining patient consent. Beecher2 himself stated that achieving truly “informed consent” was probably not possible. He acknowledged the pressure on researchers to publish combined and an explosion of research funds to coerce researchers to proceed without trying too hard to fully inform research subjects.

Federal standards were defined in the late 1970s, published in 1981, and enforced thereafter. They defined the requirements for informed consent for research subjects, which, until that time, were pretty much up to individual researchers—some of whom had more defensibly ethical practices than others.

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