argue that, although one cannot precisely predict the duration of
labor for a given patient, the multiparous patient presenting in active-
phase labor with a history of previous uncomplicated vaginal deliv-
eries, on average, would deliver more quickly than the prima gravida
or the multiparous patient presenting in latent-phase labor. In our
study, we found that inserting uniport epidural catheters 2 cm min-
imizes insertion-related complications; however, as Belin notes,
epidural catheters inserted 2 cm within the epidural space are more
likely to subsequently dislodge. Although true, catheter dislodgement
occurred in only 16 of 200 epidural catheters inserted 2 cm within
the epidural space and dislodged an average 6.5 h after insertion,
significantly longer than the reported mean 3.2 h duration of active-
phase labor in the multiparous patient. Therefore, based on these
findings and despite Belin’s argument, I recommend inserting uniport
epidural catheters 2 cm in the multiparous patient presenting in
active-phase labor. In all other patients, I would insert epidural cat-
hetes 6 cm within the epidural space. In addition, as Belin suggests,
I would consider a combined technique in these patients but would
insert the uniport epidural catheter 2 cm within the epidural space
after the subarachnoid injection.

Belin questions our conclusion that epidural catheter manipulation
may be more time-efficient than epidural catheter replacement be-
because 65 min was required to achieve patient comfort in one patient
in whom the epidural catheter was inserted 8 cm within the epidural
space. Belin also suggests that we should have either administered
additional local anesthetic before catheter manipulation or auto-
matically replaced epidural catheters associated with inadequate an-
algiesia. However, as previously stated, one purpose of our study was
to determine the effectiveness of catheter manipulation. Because
Catheter manipulation was effective in 91% of epidural catheters in-
serted >2 cm associated with unilateral analgesia and 50% of catheters
inserted intravenously functioned well after catheter manipulation,
I believe our recommendations regarding catheter manipulation are
justified. I agree that 65 min to achieve patient comfort is an excessive
amount of time. However, 783 other patients became comfortable in
<65 min. In addition, clinical practice is not dictated by strict
research protocol, and our clinical practice uses earlier, more ag-
gressive catheter manipulation. Finally, regarding administration of
additional local anesthetic before catheter manipulation, we know
of no series that has randomly investigated the efficacy of adminis-
tering additional local anesthetic in the presence of unilateral an-
algesia. However, we have observed that this practice, if ineffective,
will delay achieving patient comfort that Belin and we oppose. I
believe the findings of our study can be applied in clinical practice.
Currently, I insert epidural catheters 6 cm within the epidural space.
If analgesia is inadequate 10–15 min after local anesthetic admin-
istration, I withdraw the catheter 3–4 cm and administer local ad-
ditional anesthetic. If the patient is not comfortable within 10 min
after additional drug administration, the epidural catheter is removed
and replaced. As a result, the patient is either comfortable or the
epidural catheter is replaced within 20 min of initial placement.
This practice, I would argue, is expedient for the anesthesiologist
and the patient.

Robert D’Angelo, M.D.
Assistant Professor of Anesthesiology
Section of Obstetric Anesthesia
Department of Anesthesia
Wake Forest University Medical Center
Bowman Gray School of Medicine
Winston-Salem, North Carolina 27157
Electronic mail: rdangelo@bgsm.edu

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Antagonism of Residual Mivacurium Blockade:
Setting the Record Straight

To the Editor.—The studies of Hart et al. 1 and Szenohradsky et
al. 2 raise a number of issues regarding antagonism of mivacurium
blockade. The following comments may be helpful.

The above studies were conducted using the original technique
of Miller and Cronnelly, 3, 4 in which an infusion of relaxant is given
to maintain a steady-state level of paralysis. An antagonist is given
without changing the rate of relaxant infusion to compare case of
antagonism of various relaxants and/or potency and duration of effect
of the antagonists. The technique may have been constructed origin-
ally to obtain purely pharmacodynamic measurements, in the ab-
sence of any kinetic factors. The problem with the model is its ques-
tionable clinical relevance, especially with respect to its application
to mivacurium.

Kinetic factors are of prime importance in any evaluation of anta-
gonism of residual nondepolarizing blockade. What clinicians need
to know is how much antagonist is necessary to restore normal func-
tion within a period of time pertinent to practice. In this respect,
the studies of Hart et al. 1 and Szenohradsky et al. 2 may be misleading.

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Both studies would seem more pertinent if the infusion of mivacurium had been discontinued and then the antagonist given. The then-observed speed of reversal would provide data that would be useful to practitioners.

Because the active isomers of mivacurium have half-lives of less than 2 min, the timing of reversal of mivacurium infusions is key. If the clinician simply waits 2 min after discontinuation of a mivacurium infusion, the plasma concentration will have decreased to approximately 50% of levels present beforehand, thereby making antagonism more facile. (By analogy, no anesthesiologists have been taught to antagonize block by any other relaxant soon after giving a 'topping-up' dose.)

Reversal of all relaxants, including mivacurium, should be viewed as a summation of two processes: the clearance of the relaxant plus the pharmacodynamics of antagonism. In the case of mivacurium, the high rate of clearance due to plasma cholinesterase hydrolysis likely contributes especially to a rapid antagonism of residual blockade. In any discussion of the influence of various factors on the kinetics or dynamics of mivacurium, including reversal, the major consideration is the possible effects of the interventions on plasma cholinesterase activity. This includes the anticholinesterases given for reversal. Both neostigmine and edrophonium do partially inhibit plasma cholinesterase. They presumably do not stop the hydrolysis of mivacurium, however, which is why antagonism is relatively rapid.

Keeping the latter point in mind, explanations may be given for several observations or situations. For example, the increase in plasma concentrations of all mivacurium isomers found by Hart et al. after edrophonium injection during infusion of mivacurium may be explained by an inhibition of plasma cholinesterase.

Reduced plasma cholinesterase activity resulting from genetic or environmental factors likely will result in slower reversal of mivacurium in any patient when such a situation exists, because, in such a case, the large contribution of mivacurium clearance to the pharmacodynamics of reversal will be decreased. We suspect that, in the undocumented cases speculated on by Hart et al. in which "incomplete or delayed" reversal of mivacurium by edrophonium was observed, an undiscovered reduction of plasma cholinesterase activity may have been contributory; in any event, other classic causes of slow or delayed reversal should be sought, such as temperature or electrolyte disturbances and concomitantly administered drugs. This commentary is especially pertinent to the rare patients who are homozygotes for the atypical form of plasma cholinesterase. Reversal of mivacurium in these people, though effective, may be relatively slow (as in the case of any long-lasting relaxant), because the contribution of drug (mivacurium) clearance to the rate of reversal is probably relatively minor in these individuals. Because the plasma cholinesterase in these people is rather inactive to begin with, the administration of anticholinesterases to them is moot.

As Beemer et al. showed, the testing of antagonism of any relaxant at depths of block greater than 90% twitch inhibition is probably inappropriate, because the probability of antagonism to train-of-four >70% is less than 10%. Hart et al. base one of the premises of their study on an abstract by Kao et al. in which mivacurium antagonism was evaluated at 99% blockade of the electromyographic twitch. (1) Kao et al. do not state whether mivacurium infusion was discontinued;

(2) At this depth of block, no twitch would be ordinarily recordable by mechanomyography nor palpable by clinical observation.

A final comment on the structure activity requirements of plasma cholinesterase hydrolysis should help clear up another element of apparent confusion. Mivacurium is a true choline ester, wherein complete hydrolysis yields a dibasic acid and two quaternary amino alcohols. This feature makes the molecule a substrate for the enzyme. Other quaternary esters, such as atracurium, do not yield acids and quaternary amino alcohols on hydrolysis of the ester linkage and are therefore not substrates. Consequently, Hart et al. seem to be way out on a limb in speculating on metabolism of mivacurium by "other esterases or cholinesterases." As they have shown, mivacurium infusion dosage requirements correlate well with plasma cholinesterase activity. The half-life of mivacurium in plasma in vitro and in vivo is less than 2 min, indicating not only that metabolism and clearance occur largely in plasma but also that other possible processes cannot constitute rate-limiting factors.

In summary, in deciding whether or how to "reverse" (i.e., to accelerate recovery from) residual mivacurium blockade, clinicians should use commonly accepted rules of practice, as with other nondepolarizers. Administration should be stopped and spontaneous recovery allowed to proceed to a point when two or more twitches on TOF stimulation are palpable to ensure effective antagonism by anticholinesterases. Clinicians also may apply new predictive information (such as the 5–25% twitch recovery interval) to better guide administration of mivacurium and to help predict whether an antagonist will be necessary to accelerate recovery. If the choice of antagonism is made, the infusion of mivacurium should simply be discontinued, the line flushed, a sign of beginning recovery observed on TOF monitoring, and the antagonist given. In 90% or more of cases, however, the patient may be offered rapid spontaneous recovery from mivacurium, providing an added option and a safety factor that does not exist in practice with other relaxants.

John J. Savarese, M.D.
Cynthia A. Lien, M.D.
Matthew R. Belmont, M.D.
Department of Anesthesiology
The New York Hospital-Cornell Medical Center
525 East 68th Street. A-1050
New York, New York 10021

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In Reply.—We appreciate the interest of Savarese et al. in our publications about antagonism of mivacurium-induced paralysis.1,2 We agree that antagonism of neuromuscular blockade is a complex process that involves both the pharmacokinetics and the inherent “reversibility” of the muscle relaxant. For most nondepolarizing muscle relaxants, administration of either edrophonium or neostigmine presumably does not alter the pharmacokinetics of the muscle relaxant; we demonstrated this for vecuronium.3,4 The observation by Cook et al.5 that “edrophonium . . . [has] no effect on the in vitro metabolism of mivacurium” led to the assumption that mivacurium’s elimination would not be affected in vivo by edrophonium.6 However, our recent studies in patients demonstrate that both edrophonium and neostigmine alter mivacurium’s elimination,1,2 thereby indicating the greater complexity of antagonism of mivacurium. In that mivacurium is eliminated by cholinesterase, we are surprised that so little data regarding the in vivo effects of cholinesterase inhibitors were available before mivacurium’s release to the clinical community.

Savarese et al. question the direct clinical applicability of our studies. Studies are sometimes designed to isolate the contribution of single variables (e.g., intrinsic “reversibility” of the muscle relaxant) while maintaining constant concentrations of the anesthetic, muscle relaxant, and end-tidal PCO2. We have acknowledged this “limitation” of our studies. A common approach to examine antagonism of muscle relaxants is to give an antagonist during recovery from a single bolus dose of a muscle relaxant. Such a design might closely resemble some clinical practice. However, it does not replicate those anesthetics during which a muscle relaxant is given repeatedly or by infusion and cumulative effects of the muscle relaxant (even mivacurium)7 might hinder recovery. To be clinically relevant, studies should examine antagonism under a variety of adverse conditions, including prolonged administration, profound paralysis, organ dysfunction, and hypothermia.

Savarese et al. claim that antagonism of block >90% is probably inappropriate. Although this may be true theoretically, antagonism of profound block is probably common practice, as shown by the existence of several studies in which antagonism of profound paralysis was examined. In the absence of the sophisticated monitoring tools available to researchers, clinicians are probably unable to distinguish between twitch depression <90% and >90%. In support of this, clinicians consistently underestimate residual paralysis during recovery5; however, similar studies to assess profound paralysis are lacking.

Are we "way out on a limb" speculating about other routes of elimination of mivacurium? If so, we are in good company—Savarese et al.6 speculated that their results regarding mivacurium’s duration of action “may suggest additional routes of metabolism and/or elimination.” Finally, Savarese et al. suggest that appropriate antagonism of mivacurium requires stopping mivacurium administration and waiting for the presence of twowitches in a train-of-four. We eagerly await studies of this regimen.


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