

Changing Outcome from Aneurysmal Subarachnoid Hemorrhage

Another Step Closer

IN this issue of *Anesthesiology*, Weiss *et al.*¹ report their observations regarding prognostic validity of measuring blood S100B concentrations in patients with aneurysmal subarachnoid hemorrhage (SAH). Their key finding is that this neurochemical marker of acute brain injury, tracked noninvasively during the first few days after ictus, can provide useful information in prognosticating quality of neurologic outcome at 6 months after hemorrhage.

Aneurysmal subarachnoid hemorrhage remains a lethal or disabling disease. Approximately 10–15% of patients experience sudden death.² The probability of full neurologic recovery among those receiving medical attention is low.³ This morbidity is attributable to several factors, including direct damage to the brain from hemorrhage, surgical clipping and coiling complications, and vasospasm.

Because the disease presents multiple complex mechanisms of injury, it is of no surprise that little progress has been made in alleviating SAH morbidity. Treatment of unruptured intracranial aneurysms is largely restricted to those discovered incidentally or those causing a mass effect on adjacent structures such as the optic nerves. Therefore, the potential for preventive therapy is limited. There has been some advance in the management of ruptured aneurysms. Certainly, neuroimaging modalities have vastly improved, particularly computerized tomographic angiography, which provides exquisite three-dimensional preoperative images defining location, structure, parent blood vessels, and regional brain anatomy and can be important in identifying vasospastic vessels amenable to angioplasty. Another advance has been endovascular aneurysm coiling. The sizes, shapes, and locations of aneurysms amenable to this therapy continue to increase. A recent prospective randomized investigation found that risk of death or dependence at 1 yr after hemorrhage was reduced by 7.4% in patients treated with coiling compared with craniotomy and clipping.⁴ However, coiling may carry a greater incidence of

rebleeding⁴ and does not seem to decrease the incidence of cerebral vasospasm.⁵

In most respects, treatment of vasospasm has changed little during the past 25 yr. Standard management now includes monitoring for spasm with serial transcranial Doppler ultrasonography, prevention and treatment of spasm with L-type calcium channel blockers, and treatment of spasm-induced neurologic deficits with hemodilutional hypervolemic hypertensive therapy or angioplasty, all of which were introduced in the early 1980s.^{6–9}

Vasospasm is a complex process. It exceeds simple physiologic arterial contraction in response to hemorrhage. Although not fully elucidated, it is becoming clearer that vasospasm represents a vasculopathy characterized by increased concentrations of endothelin (a potent and long-acting vasoconstrictor), depleted nitric oxide (attributable to increased consumption by reaction with superoxide and depressed nitric oxide synthesis due to inhibited endothelial nitric oxide synthase), disequilibrium of pro- and antiproliferative growth factors, inflammation, and endothelial injury. Definition of this multifactorial response to hemorrhage has presented numerous novel targets for pharmacologic intervention, and therefore, there is reason to believe that therapeutic breakthroughs will occur. However, such advances require complex and expensive human trials, which must occur in a stepwise progression to cause changes in practice.

One problem with such trials is lack of validated surrogate markers that define therapeutic efficacy. The key dependent variable in any such intervention is long-term neurologic outcome. However, for screening purposes, it is important to first identify responses to intervention that indicate a pathomechanism has been modified.

S100B is calcium-binding protein in astrocytes, oligodendrocytes, and Schwann cells and therefore is present in large quantities in the human central nervous system. S100B can be measured in blood, cerebrospinal fluid, urine, or microdialysates. During the past 5 yr, it has been reported that extracellular S100B is increased in patients with cerebral pathology including traumatic brain injury, stroke, chemical or infectious encephalopathy, cardiac surgery, subarachnoid hemorrhage, major depression, multiple sclerosis, and other disorders. In most of these scenarios, a neurochemical marker is not necessary to diagnosis brain injury, which can readily be determined by neurologic or neurocognitive evaluation.

This Editorial View accompanies the following article: Weiss N, Sanchez-Peña P, Roche S, Beaudoux JL, Colonne C, Coriat P, Puybasset L: Prognosis value of plasma S100B protein levels after subarachnoid aneurysmal hemorrhage. *ANESTHESIOLOGY* 2006; 104:658–66.

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What S100B offers is a potential repeatable estimate of the severity and progression of injury. This can have value in terms of prognostication and perhaps more important as a sentinel marker of changes in neurologic condition. If something as simple as a S100B blood test could detect neurologic change (for better or worse), and that change in S100B has been shown to be predictive of outcome, substantially greater opportunity would be present to track efficacy, titrate doses, and screen novel vasospasm therapies.

The work of Weiss *et al.*¹ provides information as to whether measurement of S100B constitutes a step forward in meeting this goal. Seventy-four patients with angiographically proven aneurysmal SAH were treated in a neurointensive care unit with a standardized care protocol. The World Federation of Neurological Surgeons score, patient age, aneurysm location and size, and the magnitude of hemorrhage (Fisher score) were recorded on admission. Blood S100B concentrations were measured on a daily basis for 8 days. Patients underwent either aneurysm clipping (28%) or coiling (72%). Vasospasm was defined according to clinical criteria and confirmed by transcranial Doppler and angiography. At both neurointensive care unit discharge and at 6 months after hemorrhage, neurologic outcome was measured using the Glasgow Outcome Scale score.

Patients with worse initial World Federation of Neurological Surgeons or Fisher scores or middle cerebral artery aneurysms had greater admission blood S100B concentrations than those patients with less initial neurologic morbidity, smaller hemorrhage size, or aneurysms at other locations. This is consistent with other studies that have associated the magnitude of brain injury with S100B concentration. S100B concentration was also greater in patients subjected to clipping *versus* coiling. Although this would seem to be consistent with the decreased morbidity previously reported for coiling,⁴ absence of randomization to treatment condition or control for surgical manipulation in the current study precludes drawing any conclusions regarding superiority of either technique. S100B did not detect onset of cerebral vasospasm for the entire population, within which initial S100B concentrations varied widely. However, in patients with low initial S100B concentrations, a significant increase in S100B was observed at spasm onset. This likely indicates that the background signal from already damaged brain reduces sensitivity of the assay to detect change and demonstrates potential limits in using repeated analysis of a neurochemical marker to screen for vasospasm.

A quantitative association between S100B values and 6-month outcome was established, *i.e.*, blood values greater than 0.4 $\mu\text{g/ml}$ significantly predicted a poor outcome. Outcome was associated with both initial and

mean daily S100B values. The World Federation of Neurological Surgeons score and patient age similarly predicted outcome. Although this indicates an independent prognostic value for S100B, evidence was not provided that prognostic accuracy is increased by measurement of S100B over readily obtained neurologic scores or demographics.

Weiss *et al.*¹ identified an inexpensive neurochemical marker of post-SAH injury that is predictive of long-term outcome. To some extent, we already have this prognostic capacity in the initial standardized neurologic examination, although factors such as examination complexity and intraobserver and interobserver variability limit its utility.¹⁰ The step forward in this investigation was definition of a quantitative and objective assessment that has potential to be used as a simple short-term surrogate to accelerate screening of therapeutic efforts aimed at reducing SAH-associated long-term morbidity. The next step is to definitively determine whether reduction of S100B concentrations caused by an intervention in the acute phase can be associated with improved long-term outcome, as has been suggested in pilot studies investigating S100B during treatment with simvastatin.¹¹ Then, a surrogate neurochemical marker with clinical value will be in hand.

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Sugammadex: A Revolutionary Approach to Neuromuscular Antagonism

IN 1975, an editorial in this journal asked the question, "Does clinical anesthesia need new neuromuscular blocking agents?"¹ The reply was in the affirmative, *if* these new drugs "provide the practitioner with additional clinical options that broaden the scope of services he can safely provide the patient and surgeon." Ten years later, atracurium and vecuronium met those criteria, and their introduction into clinical practice produced major alterations in the way we administer nondepolarizing relaxants. In this issue of ANESTHESIOLOGY, articles by de Boer *et al.*² and Sorgenfrei *et al.*³ provide preliminary animal and human data on sugammadex (Org 25969), a new compound that has the potential to produce an even greater change in the way we think about and administer neuromuscular blocking agents. It seems that we may have, for the first time, the ability to rapidly and completely reverse profound nondepolarizing neuromuscular block.

Early reports suggested that residual muscle weakness in postanesthesia care units was much less common after atracurium and vecuronium than after a long-acting drug such as pancuronium.⁴ However, it has become clear that drugs of intermediate duration are not as trouble free as initially suggested. Reports of postoperative residual curarization continue to appear.⁵ In part, this is a function of a change in our understanding of what constitutes adequate neuromuscular recovery. For multiple reasons,⁶⁻⁹ there is now general agreement that return to a train-of-four (TOF) ratio of 0.90 or greater at the end of surgery should be our goal after the administration of nondepolarizing relaxants. Unfortunately, there is a limit to the magnitude of block, which can be completely antagonized by anticholinesterases.¹⁰ There is abundant evidence that with the tools available to us at present, prompt recovery to a TOF ratio of 0.90 or greater at the end of anesthesia is often an unrealistic goal.^{11,12} If we wish to achieve that target on a routine basis, a new paradigm is called for.

This Editorial View accompanies the following two articles: Sorgenfrei IF, Norrild K, Larsen PB, Stensballe J, Østergaard D, Prins ME, Viby-Mogensen J: Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex: A dose-finding and safety study. ANESTHESIOLOGY 2006; 104:667-74; and de Boer HD, van Egmond J, van de Pol F, Bom A, Booi LHDJ: Reversal of profound rocuronium neuromuscular blockade by sugammadex in anesthetized rhesus monkeys. ANESTHESIOLOGY 2006; 104:718-23.

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Sugammadex administration represents an entirely new approach to the reversal of nondepolarizing neuromuscular block. This compound is a modified γ -cyclodextrin and forms very tight 1:1 complexes with aminosteroid-based relaxants. It functions as an irreversible chelating agent for neuromuscular blocking agents such as rocuronium, pancuronium, and vecuronium. When administered in adequate dosage, it very rapidly decreases the concentration of free or unbound neuromuscular blocking agents to values below the threshold necessary to achieve significant receptor occupancy.

Although the data of Sorgenfrei *et al.*³ are based on a relatively small number of subjects, their observations are nonetheless striking. After 0.60 mg/kg rocuronium, they administered varying doses of sugammadex when the TOF count had returned to two detectable responses. At sugammadex doses of 2.0 mg/kg and greater, the TOF ratio recovered to values of 0.90 and greater in less than 2 min. (In contrast, Kopman *et al.*,¹³ reversing rocuronium at a similar degree of block, found that 5 of 30 patients did not reach a TOF ratio of 0.90 within 30 min of neostigmine [0.50 mg/kg] administration.) Even more impressive is a preliminary report by Boer *et al.*¹⁴ These investigators attempted reversal 5 min after a 1.2-mg/kg dose of rocuronium. By increasing the dose of sugammadex to 12 mg/kg they were also able to achieve TOF ratios of 0.90 within 2 min of drug administration.

Several clinical implications logically follow from the above. When sugammadex becomes commercially available, anesthesiologists will be much less reluctant to give incremental doses of relaxant as the end of surgery approaches. A TOF count of 1 during skin closure will no longer be a source of concern. In addition, high-dose rocuronium for rapid-sequence intubation becomes a much more attractive proposition, especially for cases of short duration. Finally, the clinician will be able to rapidly terminate rocuronium's effects if faced with a "cannot intubate, cannot ventilate" situation. However, questions remain regarding the potential impact of sugammadex on the day-to-day practice of anesthesia.

Will Sugammadex Replace Anticholinesterase Antagonists?

Sugammadex has no ability to reverse the neuromuscular effects of benzylisoquinolinium-based relaxants such as cisatracurium. Ergo, the availability of neostigmine will still be required when drugs of this class are administered. However, based on currently available evidence, a strong case can be made for abandoning the use of anticholinest-

erases for the reversal of aminosteroid-based neuromuscular blockers. Sugammadex is simply a more efficacious antagonist of rocuronium- or vecuronium-induced block than neostigmine. Its side effects seem to be minimal, and no concomitant muscarinic blocking agents need to be added to the reversal mixture.

The extent to which sugammadex will actually supplant neostigmine for the routine reversal of aminosteroid relaxants will probably depend at least in part on economic considerations. The cost of administering neostigmine (plus a muscarinic blocking agent) amounts to only a few pennies. We still have no knowledge of how sugammadex will be packaged or what the acquisition cost will be. The balance that will be struck between drug efficacy and pharmacoeconomics will undoubtedly vary from institution to institution.

In the Future, Will There Still Be a Role for Benzylisoquinolinium-based Blockers?

Sugammadex seems to be entirely dependant on renal elimination. When rocuronium is bound to the molecule, hepatic pathways of elimination are no longer available. Although sugammadex-induced reversal is likely to be sustained in patients with renal disease,¹⁵ the fate of the sugammadex-rocuronium complex in these patients is unclear. Until more information is available, atracurium or cisatracurium represents a more conservative choice for patients with impaired kidney function.

Even if aminosteroid relaxants come to dominate the market, benzylisoquinolinium-based drugs will serve a useful backup role. After sugammadex administration, it may be difficult to reestablish block with rocuronium or vecuronium. Certainly, the required dose these agents will be unpredictable. Benzylisoquinolinium-based agents will retain their expected potency in this situation.

Will Pancuronium Become a Viable Option for Cases of Short Duration?

Sugammadex does not have an equal affinity with all aminosteroids. Reversal of pancuronium (a bis-quaternary) seems to require larger doses of sugammadex than are needed to antagonize rocuronium. Therefore, the lower initial cost of pancuronium compared with rocuronium may be offset by a higher acquisition price for sugammadex. Will routine monitoring of neuromuscular function still be required?

A recent editorial in this journal opined that it was time to introduce objective neuromuscular monitoring in all operating rooms and that quantitative monitoring should be used whenever a nondepolarizing neuromuscular blocking agent is administered.¹⁶ Will the introduction of sugammadex modify this recommendation? Perhaps.

It is the opinion of this author that no drug is “user-proof.” Attempts to reverse profound block with inadequate doses of sugammadex will result in incomplete reversal. Therefore, it will still be important to know the extent of neuromuscular block before sugammadex administration. However, knowledge of the TOF count or the posttitanic count may be sufficient information on which to base sugammadex dosage. Objective measurement of the TOF ratio may be most helpful when determining whether antagonism of residual block is actually required.

Does Clinical Anesthesia Still Need New Neuromuscular Tools in Addition to Sugammadex?

Although rocuronium at a dose of 1.0 mg/kg or greater followed shortly thereafter by high-dose sugammadex can be made to mimic (or even improve upon) the onset-offset profile of succinylcholine, it is doubtful that this protocol will be adopted on a routine basis. The sequence is likely to be somewhat cumbersome and, of greater importance, probably prohibitively expensive. Therefore, there is still a gap in our armamentarium: a nondepolarizing replacement for succinylcholine. Progress in this direction continues.¹⁷

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Succinylcholine

New Insights into Mechanisms of Action of an Old Drug

EVEN 50 yr after its introduction, succinylcholine continues to be used, because it still has the fastest onset of effect of the clinically available muscle relaxants.¹ After the initial description of the neuromuscular blocking properties of succinylcholine by Daniel Bovet,² S. Thesleff³ at the Karolinska Institute in Stockholm was one of the pioneers who introduced the drug into clinical practice to induce neuromuscular paralysis in humans. (Bovet was awarded the Nobel Prize for Physiology and Medicine in 1957 for his discovery of synthetic compounds that act on the vascular system and skeletal muscle.) Despite half a century of use, several pharmacologic properties of succinylcholine remained essentially unexplained. These include the lack of fade with single-dose treatment, the development of phase II block with larger doses of the drug, and cardiovascular side effects, particularly the bradycardia and cardiac arrest commonly observed after second or third injections of succinylcholine.^{4,5} Because of the chemical nature of succinylcholine, it was assumed that the cardiovascular side effects were related to the nonneuromuscular actions of succinylcholine on other acetylcholine receptors (AChRs), including the heart, autonomic ganglia, and adrenal medulla. In this issue of *ANESTHESIOLOGY*, a report by Jonsson *et al.*, also from the Karolinska Institute, provides biophysical insight into some of the mechanisms of action and side effects of succinylcholine.⁶

To date, 17 nicotinic AChR subunits have been cloned and consist of $\alpha 1$ - $\alpha 10$, $\beta 1$ - $\beta 4$, δ , γ , and ϵ .⁷ The mature AChR in muscle is composed of five subunit proteins, including two $\alpha 1$ and one each of $\beta 1$, ϵ , and δ . The

prejunctional nicotinic AChR is purported to consist of $\alpha 3\beta 2$,⁸ and the AChRs in the ganglion are mainly composed of $\alpha 3\beta 4$.⁹ Jonsson *et al.* use up-to-date methodology to study the interaction of the AChR subtypes with succinylcholine. In essence, they create a simplified version of the AChRs expressed at the neuromuscular junction, presynaptic nerve terminal, and autonomic ganglia by artificially expressing these AChRs in oocytes of the toad *Xenopus laevis*. These oocytes are convenient "protein factories" and are frequently used to study receptor properties. Using this model, they found that (1) succinylcholine caused an initial activation of the muscle AChR followed by desensitization; (2) at clinically relevant concentrations, succinylcholine had no stimulatory or inhibitory interaction with $\alpha 3\beta 2$ (presynaptic) or $\alpha 3\beta 4$ (ganglionic) AChRs; and (3) high doses of succinylcholine caused inhibition of both $\alpha 3\beta 2$ and $\alpha 3\beta 4$ receptor.

When acetylcholine binds to the AChR on muscle, the channel opening is of a very short duration because of the rapid transmitter degradation by acetylcholinesterase in the perijunctional area. In contrast, the depolarizing relaxants decamethonium and succinylcholine have a biphasic action—an initial contraction followed by relaxation. This is because both drugs are not susceptible to hydrolysis by acetylcholinesterase and are therefore not eliminated from the junctional cleft easily. Depolarization of the endplate by the relaxant causes the adjacent voltage-gated sodium channels to open, causing a wave of depolarization to sweep along the muscle. If the depolarizing relaxant is not removed from the cleft, the sodium channels adjacent to the endplate remain in the inactivated state, resulting in muscle paralysis or relaxation.¹⁰ Jonsson *et al.* now demonstrate that in addition to this sodium channel-dependent mechanism, the receptor itself, after initial depolarization, becomes desensitized to further depolarization. This observation is consistent with *in vivo* studies and clinical observations: Even long after complete recovery of twitch and train-of-four from succinylcholine-induced paralysis, the neuromuscular junction can often behave in a more sensitive (desensitized) fashion when depolarizing or nondepolarizing relaxant is subsequently administered.⁵

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The finding that high doses of succinylcholine inhibited presynaptic $\alpha 3\beta 2$ AChRs (*i.e.*, the compound behaved like a nondepolarizing relaxant) may help to explain how high or repeated doses of succinylcholine result in a nondepolarizing type of block (phase II block) characterized by fade and posttetanic potentiation. However, the study did not include direct comparisons of the effects of nondepolarizing compounds on $\alpha 3\beta 2$. Therefore, it is not possible to make conclusive statements as to the similarity between effects of succinylcholine and nondepolarizing muscle relaxants on these presynaptic receptors.

Finally, the lack of effect of succinylcholine on ganglionic receptors ($\alpha 3\beta 4$) suggests that tachyarrhythmias occasionally seen with succinylcholine are unrelated to this interaction. Therefore, this study puts to rest previous hypotheses that such tachyarrhythmias are related to stimulatory effects on the autonomic ganglia or release of catecholamines from the adrenal medulla by succinylcholine. We are still left without a conclusive mechanism of the (more common) succinylcholine-induced bradycardia, which is usually attributed to agonist actions on the muscarinic AChRs of the heart.⁵ The authors did note, however, that succinylcholine dose-dependently inhibited ganglionic AChRs. Can the inhibition of the autonomic ganglia and the continued agonist action of succinylcholine on the muscarinic (vagus) receptor explain the bradycardia seen with repetitive doses of succinylcholine? If this is correct, how does the previous administration of d-tubocurarine prevent the bradycardia?

In using models as far removed from clinical reality as the *Xenopus* oocyte expression model, a number of assumptions have to be made. Two most important questions are whether the receptors expressed in the oocyte truly duplicate all those present at the site that is modeled, and whether the RNAs injected are actually expressed and in the appropriate stoichiometry. The second question is addressed by the authors in the article, but the first one requires some comment. Responses to acetylcholine can be seen even when the critical α subunit is omitted from the RNA mixture used for oocyte injection, suggesting the presence of an endogenous oocyte α subunit (with possibly different responses to succinylcholine).¹¹ It is therefore possible that other receptor subtypes may be present in the model and that the investigators are studying a mixture of receptor subtypes. Furthermore, the exact nature and composition of presynaptic nicotinic and muscarinic AChRs at the nerve terminal are not fully characterized.^{8,12} Based on monoclonal antibody studies, nicotinic $\alpha 3$ receptors are

known to be expressed at the nerve terminal,¹³ but what other subunits are involved is not known with certainty, except that presynaptic AChRs do exist.¹²⁻¹⁴ Therefore, did the investigators choose the correct subunit mixture of $\alpha 3\beta 2$? Complementary studies to document that a nondepolarizing relaxant inhibits these purported presynaptic receptors would have been supportive evidence.

Despite these caveats—unavoidable in a study of this nature—Jonsson *et al.*, with their elegant and detailed experiments, provide a splendid example of how modern molecular techniques can be used to address old (but important) questions in anesthetic pharmacology.

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