Anesthesiology 2009; 111:229–30

Is Anesthesiology Going Soft?

Trends in Fragile Pharmacology

IS anesthesiology going soft? If the study by Cotten *et al.* in this issue of ANESTHESIOLOGY can be viewed as a lead indicator, the answer is clearly yes.[1] The "soft drug" approach, a strategy wherein novel active compounds are specifically designed to be vulnerable to rapid biotransformation into inactive metabolites, can be employed to develop drugs that meet the unique demands of anesthesia practice.[2] In essence, a soft drug is metabolically fragile and thus rapidly eliminated,[3,4] enabling anesthesiologists to manipulate the drug concentration up and down as needed.

Cotten *et al.* describe a soft drug development effort aimed at producing a short-acting etomidate-like molecule, methoxycarbonyl-etomidate (MOC-etomidate). A key goal of this effort was to preserve etomidate's desirable hemodynamic profile but eliminate the well-documented suppression of adrenal corticosteroid synthesis associated with etomidate administration.[5] In summary, using a variety of sophisticated *in vitro* and *in vivo* methods, Cotten *et al.* were able to demonstrate that MOC-etomidate is active at the γ-aminobutyric acid-A receptor, that it is rapidly metabolized by nonspecific esterase activity, that it has an etomidate-like hemodynamic profile, and that it is indeed devoid of adrenal corticosteroid suppressive effects. Although this body of work must be regarded as preliminary in that it represents only the preclinical beginning of what is typically a long, expensive, and scientifically challenging development pathway that is vulnerable to failure at many points along the way, the results reported by Cotten *et al.* are intriguing and have exciting, albeit unproven, clinical potential in man.

Although the terminology is new, soft drug success stories in anesthesiology date back many years. Perhaps the modern prototype example is the short-acting opioid remifentanil.[6,7] Approved by the US Food and Drug Administration in 1996, remifentanil has emerged as a useful adjunct in the provision of general anesthesia, especially when total intravenous anesthesia techniques are used.[8] Looking back, the historical soft drug prototype is succinylcholine, a short-acting muscle relaxant metabolized in the plasma by butyrylcholinesterase. An older drug to which the newer soft drug label obviously applies, succinylcholine has been a work horse in the production of neuromuscular blockade for decades despite the pharmacogenetic issues that complicate its use.[9] Other soft drugs commonly used in anesthesia practice include esmolol, a short-acting β-adrenergic blocker that shares the metabolic pathway of remifentanil.[10]

MOC-etomidate is the latest example of a novel soft drug under investigation within anesthesiology and is only part of a larger, noticeable trend. Other recently published soft drug development programs include THRX-918661, a rapidly acting, putative propranadid relative,[11] and CNS-7557, an esterase metabolized, short-acting benzodiazepine.[12,13] As Cotten *et al.* point out, a common theme observed within this series of soft drug molecules is the ester structure, although the ester structure alone is not enough to confer reliably a short-acting pharmacokinetic profile; the ester must also be "sterically" available for rapid hydrolysis.[1]

Why has drug development in anesthesiology gravitated toward soft drugs? The answer is obvious. The pharmacology of anesthesia practice is unique compared to other disciplines within medicine. Most settings in clinical medicine do not require immediate onset and rapid offset of pharmacologic effect. When an internist prescribes an antihypertensive, for example, the fact that a few days may be required for establishment of a therapeutic effect is of little consequence. Similarly, when terminating therapy, the necessity to wait a few days to achieve complete dissipation of drug effect is usually of no clinical importance.

Anesthesiologists, in contrast, must respond to the dynamic needs of patients under anesthesia where the optimal degree of central nervous system depression may widely and frequently fluctuate, requiring continuous adjustment of drug concentrations. In addition, the anesthesiologist must respond to the practical realities of modern medical practice in terms of operating room efficiency and the outpatient revolution, meaning that the anesthesiologist must rapidly anesthetize the patient and then quickly reanimate the patient when the surgeons have finished their work, enabling the patient to transition quickly through the recovery process in preparation for going home.

As a result, the profound physiologic alterations of the anesthetized state (and their reversal) must be produced on demand. To achieve this degree of pharmacologic control, anesthesiologists increasingly rely on drugs with rapid onset and predictable offset of effect to ensure

This Editorial View accompanies the following article: Cotten JF, Husain SS, Forman SA, Miller KW, Kelly EW, Nguyen HH, Raines DE: Methoxycarbonyl-etomidate: A novel rapidly metabolized and ultra-short acting etomidate analogue that does not produce prolonged adrenocortical suppression. ANESTHESIOLOGY 2009; 111:240–9.

Accepted for publication May 11, 2009. Dr. Egan received research support and scientific advisory board consulting fees from Theravance, South San Francisco, California, to study THRX-918661, an investigational drug mentioned in this editorial. Dr. Egan also receives research support from Organon, Roseland, New Jersey, to study sugammadex, another drug mentioned in this editorial.

maintenance of an anesthetic state intraoperatively with return of responsiveness, spontaneous ventilation, and other vital functions at the appropriate time. Insoluble inhaled agents such as desflurane and sevoflurane and soft drugs like remifentanil have revolutionized our ability to achieve our goals. The trend toward rapid-onset, rapid-offset drugs in anesthesia pharmacology is firmly entrenched. Sugammadex, the cyclodextrin-based neuromuscular blockade reversal agent, although not a soft drug, can be viewed as another example of a drug development program aimed at improving the second-to-second control of anesthesia.[14] As a rapidly acting antagonist, sugammadex makes rocuronium behave as if it were a soft drug, reversing neuromuscular blockade on demand.

Perhaps in part because of these advances in anesthesia pharmacology, sometimes our surgical colleagues appear to view the delivery of anesthesia as a fanciful switch on the operating room wall; anesthesiologists magically turn the state of anesthesia on, and we turn the magic switch off when the surgeons have completed the operation. The advent of soft drugs (and other rapid-on, rapid-off approaches such as insoluble vapors and sugammadex) has made it increasingly possible for us to fulfill the magic switch fantasy. Although there are limits to how much can be achieved by the soft drug strategy, the concept certainly makes more precise and accurate titration of anesthetic effect possible. With the soft drug trend clearly established, it can indeed be said that anesthesia is going soft, and it's a good thing.

Talmage D. Egan, M.D., Department of Anesthesiology, University of Utah School of Medicine, Salt Lake City, Utah. talmage.egan@hsc.utah.edu

References

1. Cotten JF, Husain SS, Forman SA, Miller KW, Kelly EW, Nguyen HH, Raines DE: Methoxycarbonyl-etomidate: A novel rapidly metabolized and ultra-short acting etomidate analogue that does not produce prolonged adrenocortical suppression. ANESTHESIOLOGY 2009; 111:240–9

2. Kilpatrick GJ, Tilbrook GS: Drug development in anaesthesia: Industrial perspective. Curr Opin Anaesthesiol 2006; 19:385–9

3. Bodor N, Buchwald P: Soft drug design: General principles and recent applications. Med Res Rev 2000; 20:58–101

4. Bodor N, Buchwald P: Designing safer (soft) drugs by avoiding the formation of toxic and oxidative metabolites. Mol Biotechnol 2004; 26:123–32

5. Wagner RL, White PF, Kan PB, Rosenthal MH, Feldman D: Inhibition of adrenal steroidogenesis by the anesthetic etomidate. N Engl J Med 1984; 310: 1415–21

6. Feldman PL, James MK, Brackeen MF, Bilotta JM, Schuster SV, Lahey AP, Lutz MW, Johnson MR, Leighton HJ: Design, synthesis, and pharmacological evaluation of ultrashort- to long-acting opioid analgetics. J Med Chem 1991; 34:2202–8

7. Egan TD, Lemmens HJ, Fiset P, Hermann DJ, Muir KT, Stanski DR, Shafer SL: The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. ANESTHESIOLOGY 1993; 79:881–92

8. Scott LJ, Perry CM: Remifentanil: A review of its use during the induction and maintenance of general anaesthesia. Drugs 2005; 65:1793–823

9. Lockridge O: Genetic variants of human serum cholinesterase influence metabolism of the muscle relaxant succinylcholine. Pharmacol Ther 1990; 47: 35–60

10. Haidar SH, Moreton JE, Liang Z, Hoke JF, Muir KT, Eddington ND: Evaluating a possible pharmacokinetic interaction between remifentanil and esmolol in the rat. J Pharm Sci 1997; 86:1278–82

11. Sneyd JR: Recent advances in intravenous anaesthesia. Br J Anaesth 2004; 93:725–36

12. Kilpatrick GJ, McIntyre MS, Cox RF, Stafford JA, Pacofsky GJ, Lovell GG, Wiard RP, Feldman PL, Collins H, Waszczak BL, Tilbrook GS: CNS 7056: A novel ultra-short-acting Benzodiazepine. ANESTHESIOLOGY 2007; 107:60–6

13. Stafford JA, Pacofsky GJ, Cox RF, Cowan JR, Dorsey GF Gonzales SS, Jung DK, Koszalka GW, McIntyre MS, Tidwell JH, Wiard RP, Feldman PL: Identification and structure-activity studies of novel ultrashort-acting benzodiazepine receptor agonists. Bioorg Med Chem Lett 2002; 12:3215–8

14. Jones RK, Caldwell JE, Brull SJ, Soto RG: Reversal of profound rocuronium-induced blockade with sugammadex: A randomized comparison with neostigmine. ANESTHESIOLOGY 2008; 109:816–24