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Magic Bullets, Science, and Medicine

EVERYONE INVOLVED with therapeutic agents—patient, physician, medicinal chemist—wants a "magic bullet," a drug that does exactly what it is expected of it and does nothing else. Although we frequently have been led to think perfection has been achieved, wise physicians learned long ago that the goal has been as unobtainable as the Holy Grail. Every drug has several actions; some are useful, some are innocuous, some cause adverse effects, trivial or serious.

As they perfect their science, the medicinal chemists are coming closer to the goal and are making drugs that are more specific. In comparison with older medicinals, today's drugs are stronger in producing beneficial results and weaker in causing deleterious effects. However, just as the medicinal chemists are getting better, so are some of their brethren, the analytic chemists, and they are pushing the rewards farther away by finding that even well-designed drugs may be transformed by the patient's body into new and sometimes dangerous metabolites. Rather than "detoxifying" drugs, the body sometimes turns an innocuous compound into a potential poison.

So with atracurium. The chemists produced a compound that was more specific than its predecessors in blocking neuromuscular transmission. They went farther and, by incorporating groups that are sensitive to spontaneous degradation via a Hoffman elimination, they made a product, the destruction of which is independent of body processes. As a final touch, they made a molecule that destroyed itself rapidly so the drug's effect would be short lived, whether it was administered as a single injection or given by infusion. How seemingly close to the ideal? They made a drug with few potential adverse effects and whose duration of action would be exactly the same in all patients. The liver could be good or bad, kidneys could be present or absent, the patient could be young or old, sick or healthy, no matter, the Hoffman elimination would assure destruction of the compound inexorably and at a constant rate, letting the neuromuscular blockade end at a predictable time.

It is an unusual and very good drug—or is it? An alert scientist noted that while the Hoffman elimination broke up the atracurium molecule and so ended activity at the neuromuscular junction, it produced a product, laudanosine, that might not be innocuous. Laudanosine is hardly a familiar word among physicians and pharmacologists, but bottles of it have been gathering dust on chemical supply shelves for a century. From time to time an inquisitive soul would check the material for biologic activity and, after finding enough to justify a publication but not enough to warrant clinical exploitation, would return the bottle to the shelf. So it was recorded that laudanosine is a modest stimulant of the central nervous system that may sometimes cause seizures. Moreover, it is a rugged molecule; most of the compound stays in the body until eliminated by the kidneys.

Anesthesiologists were put on an alert; atracurium might be transformed in the body into a new compound, laudanosine, that could be a particular danger for those subjected to long infusions and whose kidneys were absent or deficient. Thus alerted, anesthesiologists did what all good scientists do: they tested the hypothesis experimentally. Two articles in this issue report the results.[1,2] The approaches and methods are different, but the results are complementary and they help put laudanosine into a clinical perspective.

Lanier *et al.*[1] used an elaborate set of protocols to compare atracurium and pancuronium in their effects on anesthetic requirement, the electroencephalogram and various physiologic and biochemical parameters of brain function. Each drug was given as a single dose in a rapid, short infusion. They observed the animals clinically and dealt with the possibility that neuromuscular blockade might obscure peripheral manifestations of a central nervous system (CNS) action by reversing the block with neostigmine and glycopyrrolate. They found that atracurium, but not pancuronium, caused a shift in the EEG toward an "arousal" pattern in lightly anesthetized but not in more fully anesthetized dogs. Seizures, or seizure activity in the EEG, were never seen. They did not measure laudanosine directly, but after careful consideration of the delay between administration of atracurium and the appearance of the "arousal" pattern in the EEG and of alternative explanations of their data, they concluded that the best explanation of their results is that laudanosine produced from atracurium caused stimulation of the CNS.

Shi *et al.*[2] took a different approach. They bypassed the use of atracurium by infusing laudanosine into rabbits and measuring the blood concentrations of the compound in comparison with the amount of halothane required to achieve MAC. They found that laudanosine causes a concentration-dependent increase in anesthetic requirement.

Although neither study is complete within itself, taken together they afford convincing evidence in favor of the

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hypothesis that atracurium is degraded into the CNS stimulant, laudanosine, and that the laudanosine can cause arousal or, conversely, an increase in the amount of inhaled anesthetic needed to maintain anesthesia. The papers go further, however, in putting this effect into perspective for the practitioner.

Most importantly, neither group of investigators saw frank seizures, not even when the first group clanged cymbals at the ears of the anesthetized dogs. Shi *et al.* saw some uncoordinated muscle activity and high-frequency EEG activity shortly after the rapid administration of high doses of laudanosine, but the effects were short-lived and not seen under other circumstances; indeed these authors postulate that laudanosine may have a ceiling on its effects that cannot be penetrated in the clinical situation in which inhaled anesthetics are simultaneously present to depress the CNS. These experimental observations fit with the clinical experience; to my knowledge, there has not been a report of seizures produced by atracurium in human beings.

Of almost equal importance, both reports point out that the administration of atracurium may lighten the anesthetic, and an anesthetist should be prepared to increase the amount of inhaled anesthetic, particularly if a prolonged infusion of atracurium is used. Shi *et al.* additionally note that there still are no data to predict the experience of patients in the recovery room who received very prolonged infusions of atracurium during surgery and who have rid themselves of the inhaled anesthetic before they cleared laudanosine because of poor or absent renal function. Although it is not likely that such set of circumstances will occur, it is not possible to rule out the possibility of abnormal motor activity or even a seizure if such a patient were encountered.

Most of all, however, the articles point out the importance of having alert anesthesiologists. As always, we need them in the operating room to adjust anesthesia to the needs of an individual patient, but it is equally important to have them in the laboratory. It was no mean intellectual or technical feat to recognize a subtle potential hazard in the use of a new drug and explore that hazard experimentally so soon after the drug was available. In this case the experiments suggest that atracurium is not likely to be a significant clinical hazard, and because nothing dramatic happened to the animals given the drugs, the articles contain largely negative results and may be perceived as unexciting. But, to perceive them that way would be to miss an important point. The really remarkable aspect of the atracurium matter is that our colleagues were alert to the potential hazard and moved quickly to investigate and define it before clinical tragedy had a chance to occur. Nobody likes negative results, except the patient who does not suffer from previously unrecognized positive ones. Prevention does not gain much attention and does not bring much fame to its practitioners, but it always is the best form of medical care.

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Continuous Positive Airway Pressure: To Breathe or Not to Breathe

CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) has been employed clinically at least since 1912.[1] Although its efficacy in the treatment of hyaline membrane disease is clearly established and accepted, application of this therapy to spontaneously breathing adults with acute restrictive lung disease (adult respiratory distress syndrome—ARDS) remains controversial. Most clinicians acknowledge that partial pressure of arterial oxygen (Pa_{O_2}) and functional residual capacity (FRC) are increased

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