Anesthesia for the 21st century

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Anesthesiology is on the verge of a major evolution that will involve newer, more specific, and better anesthetic agents and newer, safer, and simpler techniques to deliver these agents. Why we need new drugs is the first question. We need them because the drugs we have today can cause damage and even death if given incorrectly. We need better and safer anesthetics. Our patients should be demanding such agents.

So what will anesthetics of the future be like? One possibility is a collection of what we call "magic bullets" (1, 2). These agents are very specific for certain receptors and/or neurotransmitters in the body (3–6). They may, in fact, use the body's own proteins and peptides (7, 8). We are entering into an era within which doctors can create or mimic the proteins and peptides that our bodies make. At least some of these agents will be endogenous substances that have high safety margins. It is possible that we may be administering agents that are chemicals using physical forces (energies) that stimulate the body's own neurotransmitters nonchemically and/or receptors noninvasively.

POTENT RECEPTOR-SPECIFIC DRUGS

One reason for the development of receptor-specific drugs is to create substances that have higher safety margins, higher differences between the median lethal dose and the median effective dose. Classically, anesthesiologists have used drugs that have low therapeutic indices, which simply means that the lethal and/or dangerous dose or concentration is close to the effective analgesic or anesthetic dose. Pentothal and meperidine are examples of drugs with low therapeutic indices. But some of the new ones—for example, fentanyl, sufentanil, alfentanil, and ketamine—have therapeutic indices that are measured in the hundreds or thousands. Of the available opioids, fentanyl has a higher therapeutic index than morphine (400 vs 70), and remifentanil has the highest therapeutic index of any opioid or anesthetic (33,000).

Remifentanil is the most recent potent synthetic opioid. It is "20 to 30 times more potent (milligram for milligram)" than alfentanil, the last potent opioid approved by the US Food and Drug Administration (FDA) (9). Remifentanil is really not very different from some of the other fentanyl-like drugs, but it has a very high therapeutic index (33,000) and an extremely short half-life (7½ minutes vs the 90 minutes of alfentanil, the shortest lasting opioid we currently have). This means the drug needs to be given as a continuous infusion or perhaps as a single large bolus followed by a continuous infusion. Its potency is somewhere between that of fentanyl and sufentanil. But this is just the beginning. There are many more potent opioids, some of them 400, 500, or 1000 times more potent than morphine with therapeutic indices as high as or higher than that of remifentanil.

Sufentanil is the most potent opioid available today and is perhaps closer to the future than any of the other drugs available to clinicians. It is more than twice as lipid soluble as fentanyl. However, its properties, along with its high degree of plasma protein binding (98%) and lower volume of distribution, are the probable explanation for sufentanil's shorter elimination half-life and duration of effect compared with fentanyl. Sufentanil also has a high affinity for the mu receptor (10), higher than that of any other opioid.

In a study in volunteers that evaluated equipotent doses of sufentanil and fentanyl to determine any differences in analgesia and respiratory effects, we found that at peak effect (approximately 5 minutes after administration) both drugs produced an equal degree of analgesia (11). Analgesia was raised to about 50% of baseline. We then evaluated analgesia over 180 minutes. The sufentanil dose produced a longer lasting analgesia than did the fentanyl. Looking at respiratory depression in the same volunteers, respiration was depressed to about 30% of baseline 5 to 6 minutes after injection of sufentanil or fentanyl. While those who received sufentanil had longer lasting analgesia, their respiratory depression returned to baseline much more quickly. If this really is true and if additional compounds are produced that are even more specific for the mu receptor or for the analgesic component of the mu receptor, we will begin to see, as the potency continues to increase, further and further separation of the analgesic effects of opioids from their respiratory depressant effects.

Anesthesiology of the future will also have drugs that manipulate the endogenous central nervous system transmitters. Some of these are likely to be peptides. Clearly, these drugs can produce profound analgesia and sleeplike states that mimic hibernation. In hibernating animals, body temperatures are close to freezing, oxygen use is 2% to 3% of normal, heart rates are

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reduced from hundreds of beats per minute to a couple of beats per minute, and respiratory rates are reduced to 1 or 2 breaths an hour instead of 30 or 40 breaths per minute. These profound changes can be artificially induced by taking the plasma of hibernating rodents and injecting it into active animals (12). Within an hour or two, the temperature of the injected animal is reduced 8° to 10°. Heart rate and respiratory rate are reduced, and the animal does not eat for a week. All of this is immediately reversible with naloxone, but during this state the animal's stress hormones are also dramatically reduced and the whole state of anesthesia is less "stressful." We are hearing a lot about "stress-free" anesthesia these days. Hibernation is a natural phenomenon of the mu receptor and the endogenous peptides that stimulate the mu and, perhaps, the delta and kappa receptors as well. It may be that anesthesia of the future will mimic animal hibernation.

The Boston Children's group published a study of high doses of sufentanil administered not only during surgery but also postoperatively to minimize hemodynamic changes and the responses of the so-called stress-responding hormones (13). The mortality and morbidity with this approach were dramatically less than those with more standard postanesthetic approaches. We are going to see more postoperative administration with the new drugs of the future.

The new drugs are also going to focus on other things that are fascinating to us, not only as anesthesiologists but as human beings. Drugs will be given to patients to slow or even reverse their biological clocks, to prevent aging or to turn it around. At the age of 30, the production of human growth hormones begins to decline in 1 of 3 ways. In the first, we produce slightly less than normal levels of human growth hormone and stay lean and vigorous. In the second, one third of us have dramatically less human growth hormone and gain weight and become less physically active. A final third of us have no growth hormone, and we get very old and very frail rapidly. The new drugs are going to prevent this.

A number of studies are in progress or have just been completed in which men, aged 60 to 80 years, have been receiving one of these drugs for a year or so, and their aging has been dramatically reduced, and, in fact, they have stopped aging. The idea is that these drugs will temporarily awaken those sleeping genes that had been keeping us young. It is estimated that by the year 2000, the average life expectancy of the American population will be 85 years, by the year 2010 it will be 115 years, and by the year 2030, 200 years.

NEW DRUGS, NEW ROUTES, AND NEW DELIVERY SYSTEMS

Unfortunately, these new drugs are expensive. A few years ago, it took about 10 years for the average drug to be approved in the USA at an average cost of $125 million. By 1992, the cost of a new drug had increased to $231 million, and it took an average of 12 years for FDA approval. Today the average new drug takes 12 to 13 years from discovery to approval and costs $280 million. This is too costly and too long for all but the drugs that will generate billions of dollars of revenue. These facts also suggest that we may begin to see older drugs given by new routes and delivery systems. These approaches should increase the efficiency of drug delivery, decrease the cost of drugs and drug delivery, improve safety, improve convenience and compliance, and optimize the pharmacokinetic characteristics of the older drugs. The traditional routes may be with us for a little while longer, but their limitations, side effects, costs, pain of administration, and inefficiency in terms of bioavailability and patient compliance will be among the reasons they are eliminated.

Anesthetic delivery has not appreciably changed in the past 150 years. We still give drugs using needles. We still ask patients to breathe the vapors of very potent volatile liquids—drugs that could take the paint off a car. We still ask patients to swallow pills and solutions, some of which actually produce the desired effect some of the time. Much of the time there is very little effect, and some of the time there is an overdose, even though the dose administered is that recommended in the package insert.

The new routes and delivery systems promise improved convenience, improved safety, increased effectiveness, increased bioavailability, continuous delivery with fewer peaks and valleys, decreased side effects, decreased dosage and frequency of administration, and decreased cost. The pharmaceutical companies are interested in drug delivery because it provides new uses for old drugs, new patents for old drugs, and decreased FDA approval time for old drugs.

Some of these new drug delivery systems have become clinically available in the past decade. Patient-controlled analgesia (PCA), epidurally as well as intravenously, is available at some institutions. PCA is an example of precision drug delivery. In it patients control the administration of an analgesic until they achieve a plasma concentration resulting in analgesia (pain relief). PCA results in less overdosing, less underdosing, and more optimal drug delivery. It is popular because analgesia is achieved faster, and as a result patients are mobilized and out of the hospital sooner. In some studies, patients go home a day to a day and a half sooner than after standard postoperative analgesic regimens. Oral slow-release drug systems, patches, iontophoretic techniques, and transmucosal delivery are also available. These drug systems are more efficient and safer than intramuscular or intravenous drug delivery.

Intravenous anesthesia is also evolving. The trend is toward a continuous drug infusion rather than an intermittent bolus approach. The obvious advantages of continuous drug infusion are less total drug given, faster recovery, more optimal hemodynamic control, and more appropriate depth of anesthesia. Prevention of less-than-threshold blood concentrations and concentrations over toxic levels is, of course, the objective of continuous drug delivery. Ideally, this keeps the plasma drug levels within the therapeutic window. Care has to be taken, however, not to strive for a constant plasma concentration, because even though a drug may be within the therapeutic window, increases and decreases may be needed as the surgical stimulus changes. Intravenous anesthetic or automated drug infusion machines are being developed and are undergoing early clinical testing. These studies will focus on the use of propofol, opioids, and other drugs that can be given intravenously as slow continuous infusions. The computer is going to have a great impact in future intravenous anesthesia by helping to adjust intravenous infusions according to precalculated dosing schemas.

We need to be able to instantaneously measure the depth of anesthesia and to rapidly and accurately measure plasma concen-

trations of the agents we use. One technology being pursued is reverse diffusion through the mucosa of the mouth. This technique can allow rapid assessment of plasma concentrations of drugs (anesthetics) in the vessels immediately below the mucosa of the mouth. It is still in early development, but if it is successful it may be a method that enables rapid determination of the plasma concentrations of the agents we infuse intravenously.

NONINVASIVE DRUG ADMINISTRATION

Another important concept is noninvasive drug delivery. Controlled release systems offer the advantages of decreasing dosage frequency, increasing convenience, and maintaining blood levels with fewer fluctuations. Transdermal drug delivery is an example of noninvasive drug administration. A number of transdermal patches are now available for nitroglycerin, fentanyl, scopolamine, nicotine, clonidine (14), and other drugs. These patches decrease hepatic first pass metabolism, improve or maintain relatively stable blood drug concentrations, improve patient comfort because of the continuous noninvasive delivery of drugs, and, because of patient comfort, increase patient compliance.

Clearly, these devices are able to maintain relatively constant plasma concentrations of agents such as fentanyl. One can maintain plasma concentration and reduce the frequency with which patients with cancer pain have to take other drugs to get pain relief. The fentanyl patch comes in 4 sizes, delivering 25, 50, 75, or 100 μg/hour. Although many studies have been reported in patients in the postoperative period and in patients with cancer pain, only the use for cancer pain has been approved by the FDA (15–17).

Respiratory depression and misuse by applying >1 patch are risks associated with these techniques. Perhaps the most serious problem of the transdermal systems is the fact that they are good for chronic problems but not for acute problems. It takes 6 to 8 hours to achieve a sufficient plasma concentration with today's patches, and patients may not be willing to wait that long. Another problem is that once a patch is removed, much drug remains in the skin and thus delivery can continue for a day or more. Plasma concentrations are not easily changed, either up or down, with current patches. In addition, 20% of patients have dermatologic reactions to the patch.

In an attempt to make drug delivery faster with transdermal patches, iontophoresis is being evaluated. Iontophoresis is a technique in which an electric current helps drive a drug from a patch through the skin (18–20). The devices use direct current, 40 microamperes to 10 milliamperes. Iontophoresis is generally painless, and a number of drugs are being evaluated for this approach.

One of the important delivery systems in the near future is transmucosal drug delivery—nasal, buccal, ocular, rectal, and mucosal. These techniques provide most of the advantages of the patch. In addition, because mucosal membranes are thinner and more highly vascularized, there is the potential of giving large molecules, like peptides and proteins. Because their drug delivery is much faster, the transmucosal systems also allow the possibility of titrating drugs and thus provide enhanced flexibility.

The easiest mucosal technology is the transnasal mucosal approach (21–25). For example, dipping a cotton swab tip into sufentanil and applying it to the nasal mucosa of the ferret produces an effect within seconds. For a more potent drug, like carfentanil, the effect is more immediate and can be achieved with less drug. The reason why these systems work so well is that there is an enormous surface area, 180 cm^2, and an enormous blood supply in the mucosa, almost the same blood supply as the brain receives.

A variety of drugs are being evaluated for transnasal drug delivery. Nasal sufentanil has been used in pediatric populations to ease separation from parents, decrease coughing, decrease inhalation anesthetic requirements, and provide faster and smoother recoveries (22). Nasal midazolam in doses of 0.2 or 0.3 mg/kg has been used to provide sedation in 5 to 10 minutes and to ease separation. Midazolam is a little bitter and sufentanil can cause rigidity if too much is administered too fast, but the plasma concentrations are not much lower than what occurs when the same dose is given intravenously. Nasal ketamine has also been tried, 1.5 to 3.0 mg/kg, and is effective. Transnasal buprenorphine (26), Stadol, and other opioids are also being considered.

Clearly, clinicians have an interest in the transnasal application of drugs. However, there are issues that need to be studied. How does a cold or an atmospheric condition like the humidity affect the speed of the mucosal flow and absorption? What is the ideal drug concentration? What is the ideal pH of drugs for transnasal approaches? To my knowledge, much of this work remains to be done.

Oral or buccal transmucosal delivery is another potentially important transmucosal technique. The buccal cavity is also highly vascularized and moist; the epithelium is very thin, and there is an enormous surface area for drug absorption. Many drugs are approved by the FDA for buccal or sublingual absorption. Not many of them are anesthetics, and not many of them find use in the operating room. Obviously, nitroglycerin does have a potential use in the operating room. One company is working on buprenorphine as a transbuccal patch, and there are now patches that will stick on wet surfaces and transmit their drug through the mucosa of the mouth.

We at the University of Utah have been studying oral transmucosal fentanyl citrate (OTFC or fentanyl Oralet) (27–29). The drug is incorporated in a dissolvable matrix on a stick (Oralet). As patients suck on the fentanyl Oralet, fentanyl dissolves in saliva and can be absorbed through the mucosal membranes of the oropharynx. Increases in plasma fentanyl and onset of clinical effect are more rapid (5–10 minutes) after OTFC than after swallowed solutions of fentanyl. Drug bioavailability is also greater for OTFC than swallowed fentanyl. In addition, no mucosal depot of fentanyl occurs after OTFC administration. An advantage of OTFC is that drug delivery can be stopped at any time by removing the Oralet from the mouth. This can allow titration to a sedative or analgesic endpoint. Initial studies with OTFC in volunteers and children have shown this system to produce reliable sedation and anxiolysis when used as a premedication (27, 28). This system offers a new route of premedication (30–32) and of providing acute postoperative analgesia and chronic pain therapy (33) in various clinical settings. At present, it appears that its greatest use will be in patients with cancer, because the drug can be titrated, particularly in patients with breakthrough or incident pain.

The side effects are classical opioid side effects: nausea, vomiting, pruritus. The potential for respiratory depression and aspiration also exists, because consuming a unit of the drug will increase secretions in the stomach. As with any opioid, employing appropriate doses and antiemetics and reducing ambulation when significant drug action is present will reduce and minimize side effects.

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