HST-151 Clinical Pharmacology in the Operating Room

During the first few sessions in the course you will be introduced to the principles of pharmacokinetics, and you will have had an overview of cholinergic pharmacology. Both of these topics have immediate relevance for the day-to-day practice of anesthesiology.

As students, you are all welcome to join us in the operating suite. There will be 10-15 of you in each section, so we ask for your cooperation to keep the confusion to a minimum. My colleagues and I in the Department of Anesthesia and Critical Care at Massachusetts General Hospital will do our best to help you learn about each of the teaching points outlined in this handout. The overall plan is as follows:

- Each group will meet 10 minutes prior to the scheduled start.
  We will escort you from there to the surgical locker rooms where you will don scrub suits, masks, caps, and shoe covers. We will issue you guest lockers (2-3 students per locker), but we suggest that you do not leave wallets, purses and other valuables in the locker rooms. Each of you will have a temporary identification badge.
- We will divide you into groups of 3 or 4 students, each group will be assigned to a staff preceptor. Some preceptors will emphasize muscle relaxant/cholinergic pharmacology while others will handle pharmacokinetics. Please bring this handout with you.
- During your 3 hour session, we plan that you will visit 2 or 3 different operating rooms and see portions of several anesthetics. There should be ample time to accomplish all of the learning goals without rushing.

Please remember that we will be observing normal clinical care in a very busy and often confusing environment. The teaching locations and the specific cases are completely dependent upon the vagaries of the operating room schedule. In order to be flexible and to minimize O.R. disruption, we need to make sure that you stick with your designated clinical supervisor. Finally, please remember that you will be encountering real patients with real medical problems and real stresses. Some may not wish to be observed, and we must respect their wish for privacy.

The Clinical Scenario: A Typical General Endotracheal Anesthetic

The goals of general anesthesia are threefold: the patient should remain asleep, the responses to painful stimuli should be blunted, and the surgical field should be immobile. In many general anesthetics breathing is depressed, and paralytic agents are given, so the lungs must be ventilated through an endotracheal tube. Each anesthetic is tailored to the particular patient and operation, and each anesthesiologist has his or her own preferences for drugs and doses. Nevertheless, we can consider the following description a reasonable example of current clinical practice:
The patient has an intravenous line, and standard monitors (ECG, automated blood pressure cuff, pulse oximeter) are applied prior to the start of anesthesia. There may be premedications given (a sedative/hypnotic like midazolam, possibly a short-acting opioid like fentanyl). The patient inhales oxygen through a mask, then sleep is induced with a rapid acting drug like propofol or thiopental. A depolarizing muscle relaxant (succinylcholine) or a non-depolarizing relaxant (e.g. pancuronium, cis-atracurium) is given to facilitate intubation. The lungs are ventilated mechanically, and additional drugs are added to maintain anesthesia. The most common drugs for this purpose are opioids (fentanyl, morphine), hypnotics (propofol, thiopental), inhaled anesthetics (nitrous oxide, isoflurane), and more muscle relaxants. The anesthetic agents are tapered and discontinued in anticipation of the end of surgery, and if there is any residual muscle relaxant effect, it is reversed with an anticholinesterase (neostigmine) combined with an antimuscarinic (atropine, glycopyrrolate). The endotracheal tube is removed after the patient has regained consciousness, cardiovascular and respiratory stability, and skeletal muscle strength.

Pharmacokinetics and Pharmacodynamics of Intravenous Propofol

Propofol is a rapid-acting intravenous hypnotic that is widely used for induction of anesthesia. The pharmacology is summarized briefly in Golan, p. 220-1. Like thiopental, propofol is extremely lipophilic—in fact, it is administered in a lipid emulsion. It has a steady-state volume of distribution of 400-700 liters (how is this possible?), and a very high total clearance of 2000 ml/min. The decline in drug concentration is best described by a multicompartment pharmacokinetic model, and this was incorporated in the simulations presented during class. This exercise is intended to reinforce and demonstrate several of the points made during class:

1. After a bolus dose of 1-2 mg/kg, the effect of propofol occurs after a very brief delay.
2. The rate of onset is a function of the dose given. In clinical practice, a relatively large dose is injected in order to produce a very rapid effect. The price to pay for such rapidity is a very large overshoot of the propofol concentration in blood. Since propofol is a vasodilator and a direct myocardial depressant, large doses often produce large decreases in blood pressure. This is especially true in patients with cardiovascular disease, in those with decreased intravascular volume, and in those given other depressant anesthetic agents simultaneously.
3. The offset of effect is due to the rapid redistribution of propofol out of the brain. The initial distribution half-life is only 2-8 minutes. Since the initial dose may only last

from 5-10 min, more propofol or some other anesthetic agent must usually be added for maintenance of the anesthetized state.

4. There is tremendous individual variability in both the pharmacokinetics and pharmacodynamics of propofol. The nominal dose for induction is 2.5 mg/kg, but the initial hypnotic dose may be anywhere from 50-350 mg in an adult. This will depend upon a host of factors (age, debility, other medications, cardiac output, history of alcohol use, etc.)

Protocol

Oberve the use of propofol for anesthetic induction in one or more patients. In addition to the normal physiological monitors, you will have the following tools:

- Pharmacokinetic measurements--since we have no capacity for real-time measurement of propofol concentrations, we will utilize the simulation program you saw in class to model the drug as it is given. This, of course, assumes that the patient has average propofol pharmacokinetics!
- Pharmacodynamic measurements—we will measure the hypnotic effect of propofol with a processed electroencephalographic monitor. This device uses both power spectral and bispectral analysis to come up with a dimensionless number from 0 to 100 called the Bispectral Index (BIS). In general, a higher number = more awake, and BIS<60 indicates a very high likelihood that the patient is asleep. Although this monitor lags behind the patient by 5 or 10 seconds, it gives a pretty good continuous picture of hypnotic drug effect. I will be happy to discuss the theoretical basis for this monitor with anyone who is interested.

You should pay particular attention to the following:

1. What premedication/s were given? Was there an obvious effect from this?
2. What dose of propofol did the anesthesiologist select? What was his/her reasoning?
3. How long did it take for the drug to produce loss of response to voice? (Remember, it takes a few seconds before the drug is through the intravenous tubing and actually in the patient.)
4. Did the BIS go down? How long did it take before it began to rise again?
5. We will attempt to model the "effect" of this dose with the computer program (remember, it incorporates an estimate of <u>effect-site</u> concentration). Does the predicted duration of effect match what you saw clinically? If not, what do you think accounts for the discrepancy?
6. What other effects did propofol produce? What happened to blood pressure? Respiration? Did the patient complain of pain when the drug was injected? Were any of these effects a real problem (ask the anesthesiologist)? If so, how could they have been prevented?

Uptake of Inhaled Isoflurane

The pharmacology of the inhaled anesthetics is summarized on pp 205-224 in Golan. Pay particular attention to the pharmacokinetics section on pp. 207-215. The volatile anesthetics are like the intravenous agents in that they obey multicompartment kinetics;

i.e., they are distributed according to tissue solubility and regional blood flow. Unlike the i.v. agents, the lungs are both the route of uptake and the primary route of excretion. Isoflurane is almost completely exhaled, and very little undergoes metabolic clearance. Isoflurane is given by continous flow through a specially calibrated vaporizer. The carrier gases are usually oxygen and nitrous oxide, and these are adjusted by flowmeters on the anesthesia machine.

Protocol

Observe the use of isoflurane for maintenance of anesthesia (following induction with propofol) in one or more patients. (If the anesthesiologist has chosen to use desflurane or sevoflurane, the exercise is still valid.) In addition to the usual monitors, you will have access to a monitor that measures isoflurane concentration in the breathing circuit. These monitors generally display the inspired and expired ("end-tidal") concentrations simultaneously. The end-tidal concentration reflects the alveolar concentration, which is in fairly rapid equilibration with both arterial blood and the tissues of highly perfused organs. "Expired" concentration on the monitor therefore becomes a surrogate for "brain partial pressure," which is really the subject of interest.

You should pay particular attention to the following:

1. When the anesthesiologist turns on isoflurane (say, 1%) what does the "inspired" concentration reading on the monitor say? How about "expired?" Are they all the same? If not, what is the reason?
2. How long does it take for the expired isoflurane concentration to approach inspired? What can you infer about the pharmacokinetics of isoflurane? (HINT: isn't this just an <u>infusion</u> given via the lungs?)
3. If the concentration needs to be adjusted up or down, how long does it take for the drug concentration to reach its new plateau? How can the anesthesiologist influence the rate at which this change takes place?

Pharmacodynamics of Muscle Relaxants (Neuromuscular Blockers)

You have heard about some basic cholinergic pharmacology and the two broad classes of muscle relaxants. Golan (p.102) has a very brief section on this. Katzung (pp. 446-457, on reserve) has a better overview of the subject.

Protocol
Observe the use of succinylcholine or a non-depolarizing relaxant for endotracheal intubation and for maintenance of paralysis. The long-acting relaxants like pancuronium or curare have become much less popular, and many clinicians will prefer to use shorter-acting relaxants like cis-atracurium, vecuronium, and mivacurium. In addition to the usual monitors, you will have a peripheral nerve stimulator which can deliver a single or tetanic stimulus, as well as a series of four stimuli at 2 Hz (the so-called "train-of-four"). The stimulus is most commonly applied using surface electrodes over the ulnar nerve at the wrist. During stimulation, contraction of the adductor pollicis muscle is assessed by palpation. In general, we are looking for decreased or absent muscle twitch. Tetanic stimulation and train-of-four are ways to assess fade of the twitch response. For research purposes we sometimes make the measurements more precisely by using a force transducer and displaying the force of thumb contraction on a computer or strip chart output.

You should pay particular attention to the following:
1. What happens when succinylcholine is administered? Are fasciculations visible? Does heart rate increase (from ganglionic stimulation)? What happens to the train of four? Does it decrease? Does it show fade? How long does it take for the twitch to return? Could we reverse this block with neostigmine?
2. Which non-depolarizing relaxant was selected? What is the reason for the choice? Were there any cardiovascular effects after administration? Can you quantitate the intensity of effect with the train-of-four? What happens with a tetanic stimulation? Can you demonstrate post-tetanic potentiation? Why does this occur?
3. Is reversal of the relaxant required? How is this determined? Why do we give an anticholinesterase? An antimuscarinic?

While You Are Here…

Assuming you have been able to accomplish the goals for each part of this exercise, feel free to explore other aspects of pharmacology or physiology. Autonomic pharmacology, in particular, is well demonstrated in most anesthetized patients (vagal responses, beta blockade, alpha agonists). Enjoy!