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Improving Analgesic Therapy

A FREQUENT COMPLAINT of hospitalized patients is that of inadequate relief of pain, especially that occurring after surgical intervention.[1] Narcotic analgesics are the mainstay of pain relief in the postoperative period, and it is easy to recognize factors contributing to their ineffective use: 1) Concern about ventilatory depression due to an overdose of the narcotic analgesic *per se* or to an interaction with other drugs leads to the use of smaller-than-effective doses. 2) Concern about apnea and hypotension as well as a desire to prolong their action prompts the avoidance of intravenous administration and the use of intramuscular or subcutaneous injection. 3) Concern about creating drug dependency mandates limitations on dose size and frequency of administration. 4) Legislative actions by governments and accrediting agencies restrict the physician to prescribing a specific dose at a fixed interval and preclude the flexibility necessary for effective relief of pain that varies in intensity and that occurs in patients who differ in their rates of eliminating narcotic analgesic drugs. 5) The busy physician tends to write "routine" orders although patients are quite individualistic in their requirements for analgesic therapy. 6) Anxiety about inadequate pain relief builds in the patient, increases the discomfort associated with pain, and perhaps, leads to inappropriate requests for analgesics. ("I'd better ask for an injection now so I won't have to wait when the pain returns.")

These concerns could be allayed, at least partially, by a dosage regimen that would provide a fairly constant drug level within the therapeutic range while avoiding levels that may be toxic. In order to achieve this goal of greater precision in analgesic therapy, the therapeutic and toxic levels must be defined and factors contributing to variability must be identified.

Variability in the responses of patients to drugs is a fact of life. It can be of two general types: 1) *Pharmacodynamic* variability refers to differences in responses of the tissue when exposed to the same concentration of the drug. 2) *Pharmacokinetic* variability results from altered absorption, distribution, biotransformation, or excretion of the drug such that the responding tissue does not acquire the same concentration of the drug after a given dose; its sensitivity to the drug remains the same. Measurements of drug concentrations under certain conditions allow these two types of variability to be distinguished.

Meperidine (Demerol) is frequently used to control pain in the postoperative period. It is a lipophilic drug, able to penetrate biological membranes rapidly. It is expected that a correlation will exist between meperidine concentrations in plasma (or blood) and the intensity of its effects.[2] In this issue of ANESTHESIOLOGY, Austin, Stapleton and Mather[3] present data gathered from a small number of patients to show for the first time that there is a relationship between blood levels of meperidine and its effectiveness in relieving postoperative pain. This is an important first step toward the development of greater precision in the use of this narcotic analgesic.

The same investigators have taken additional steps that are reported in this issue and elsewhere. They have shown that management of postoperative pain by the intramuscular injection of meperidine at fixed intervals resulted in highly variable blood concentrations of the drug that remained above the minimum analgesic concentration for only 35 per cent of each four-hour dosing interval. Peak plasma levels varied considerably in terms of both concentration and time of occurrence after intramuscular injection. They concluded that absorption from intramuscular injection sites was the primary factor in the variability of plasma concentrations and in the analgesic effects that resulted.[4] This cause of pharmacokinetic variability could be eliminated by intravenous injection, which bypasses the absorption process entirely.

There are a number of advantages of intravenous injections of drugs: 1) rapid onset of drug action; 2) more predictable maximum concentrations and peak effects occur early; 3) drug levels decline progressively and so do the effects of most drugs after an intravenous bolus dose. These advantages can be realized in the use of meperidine: 1) A rapid onset of action produces prompt relief of pain and limits the development of the patient's anxiety. 2) The early occurrence of peak effects facilitates titration of drug dosage to meet the needs of the individual patient. 3) The tendency for drug levels to decline progressively after intravenous injection limits the time in which toxic effects are likely to occur; if careful observation of the patient during the first 5 to 10 minutes after an intravenous injection of meperidine does not reveal adverse consequences, they are unlikely to occur subsequently unless other aspects of the patient's condition also change.

However, there are two major disadvantages to intravenous bolus injections of most drugs: 1) Drug action is relatively short-lived as plasma levels of the drug decline rapidly due to its uptake by nonresponsive (storage) tissues and its elimination from the body (biotransformation and excretion).[5] 2) In order to sustain the effect for a longer time, a large dose may

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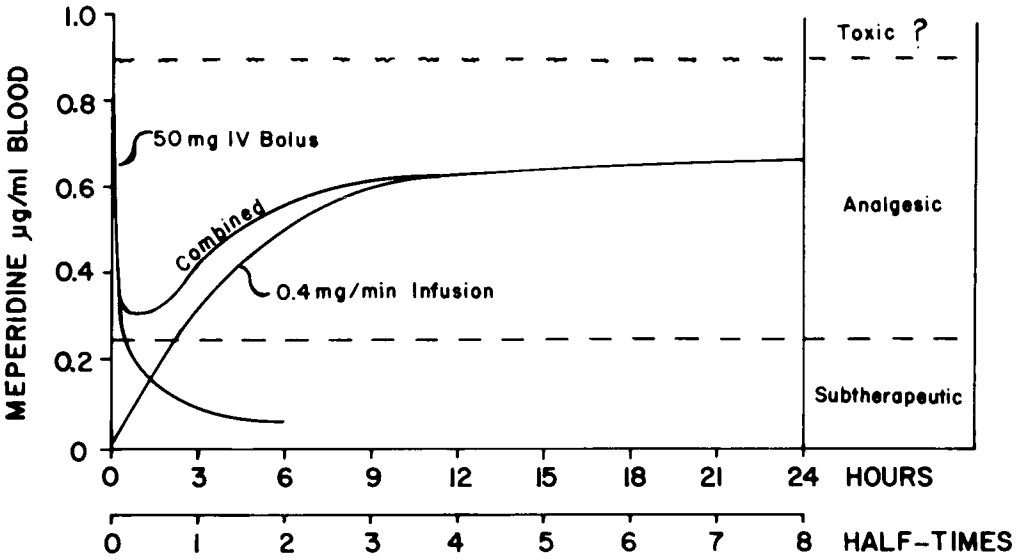

FIG. 1. Simulation of blood levels of meperidine resulting from the combination of an intravenous bolus dose of 50 mg and a continuous infusion of 0.4 mg/min begun at time zero. After the bolus dose alone, blood levels would initially be higher than necessary (near toxic?) and would fall into the subtherapeutic range after 20 to 40 minutes.[8] With the continuous infusion of 0.4 mg/min it would take slightly more than two hours to reach the lowest analgesic concentrations.[5,9] By combining the two methods of administration, blood levels of meperidine remain within the analgesic range; an additional bolus dose might be useful after about 20 minutes.[10] An even better method would involve the use of a priming infusion to limit the peak concentration and to minimize the depth of the concentration trough.[11] The toxic level of meperidine has not been defined; a concentration of 0.7 µg/ml was estimated to provide relief of pain in 95 per cent of cases,[3] and gave no evidence of clinically significant respiratory depression (or toxicity).[9]

be given initially and produce plasma concentrations that are in the toxic range. Alternatively, repeated small doses may be given, but this may become impractical because of the demands it places on nursing personnel by the frequency of injections and by the requirements for very close observation of the patient as plasma concentrations fluctuate more or less rapidly between toxic and ineffective levels. ("Demand analgesia" may offer a practical means of delivering small intravenous doses repeatedly.[6])

Another option is to provide a stable level of the drug by its continuous infusion at a rate that matches its elimination rate from plasma. Again, Mather and colleagues have provided crucial information with which to formulate such an approach for meperidine,[7,8] and they also have demonstrated the applicability of a continuous infusion for the relief of postoperative pain.[9] It is especially noteworthy that patients receiving constant intravenous infusions of meperidine had continuously satisfactory relief of their pain and at the same time "most remained alert and were able to read." Also noteworthy is the fact that recovery from meperidine occurred at the rate predicted from its elimination half-time of three hours. That is, patients requested additional analgesics between 2.5 and 10 hours after the initial analgesic administration, when approximately 50 to 90 per cent of the drug would be expected to have been eliminated from the body.

Of course, some questions remain to be answered before the use of constant intravenous infusions of narcotic analgesics can be done on a "routine" basis. What is the pharmacokinetic variability among surgical patients? What factors contribute to pharmacodynamic variability? Does the type of surgical intervention matter? Does tolerance to analgesia develop? What drug interactions are important? Do environmental factors (*e.g.*, noise, stimuli associated with nursing care) influence the concentration–response relationships? What is an appropriate dosage regimen to initiate and then to maintain therapy? How will dosage regimens differ for different narcotic analgesics that have different rates of elimination, and especially for morphine, which does not equilibrate rapidly between sites of action in the CNS and plasma? What is the maximum safe plasma concentration of these drugs in the spontaneously breathing patient? How do the above factors influence the threshold concentration for *clinically significant* respiratory depression?

Austin and his colleagues have made a start in answering some of these questions in this issue of ANESTHESIOLOGY. The number of patients is small, but the feasibility of such investigations is demonstrated. Their initial reports provide the basis for more definitive studies.

Despite the gaps in our knowledge, it is clear that constant intravenous infusion techniques should be explored as a means of remedying the clinically sig-

nicant problem of ineffective and inefficient use of narcotic analgesics for the relief of pain. There is a good example of efficient and effective drug therapy to be found in the continuous infusion of lidocaine for the control of cardiac dysrhythmias.[10] The same principles can be applied to the use of narcotic analgesics (*e.g.*, see fig. 1). Pharmacokinetic data on which to base experimental designs are now available in the literature, and the means of estimating loading and maintenance infusion rates have been suggested.[11] The principles underlying the administration of drugs by intravenous infusion are essentially the same as those on which the induction and maintenance of anesthesia with inhaled agents are based. Certainly the anesthesiologist is well prepared to make advances in conquering the acute pain of surgery, his *raison d'être*.

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Differential Nerve Block by Local Anesthetics

IN THIS ISSUE of ANESTHESIOLOGY, Gissen and colleagues[1] challenge the traditional concept of sequential nerve blocking action by local anesthetics. It has long been held that the larger the diameter of an axon, the more resistant it is to local anesthetic blockade. These beliefs may have to be modified, for Gissen *et al.* now present data suggesting that the larger the diameter of an axon, the more *susceptible* it may be to conduction block.

The classic concept of differential nerve block evolved from the work of Gasser and Erlanger,[2] who, in the 1920s, explored the electrical properties of nerves with the just-discovered cathode ray oscilloscope. The new technology enabled researchers to examine noninvasively the fiber representation of intact nerve by scanning the compound action potential for blips from axons conducting impulses at different speeds. It also proved to be an excellent tool to study blockade of nerve impulses by local anesthetics.

Gasser and Erlanger categorized nerves into three main classes. They called myelinated somatic axons *A fibers*, myelinated autonomic axons *B fibers*, and nonmyelinated axons *C fibers*. While the small-diameter B and C fibers are quite homogeneous anatomically as well as physiologically, the A fibers encompass a wide range of sizes in man (from about 2 to 20 μm in diameter) and a wide range of electrical properties (conduction velocities from about 10 to 120 m/s). For that reason, the A group was further divided into four bands—labeled A alpha through A delta—according to decreasing diameter and impulse conduction velocity.

Though that classification was based on electrophysiologic characteristics, many other neural properties such as physical (response to cooling or pressure) and pharmacologic (response to local anesthetics) also showed inter-class differences. For instance, conduction in nonmyelinated C fibers was blocked by a lower concentration of cocaine than was conduction in A fibers. Further, large-diameter A alpha fibers proved more resistant to cocaine blockade than small-diameter A delta fibers.

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