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Clinical Pharmacology and Drug Therapy in the Burned Patient

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TRAUMA IS THE FOURTH leading cause of death in the United States and the leading cause of death in persons under the age of 38.¹ Burn trauma alone occurs in over two million Americans every year. Irrespective of type—electrical, chemical, scald, or flame—burns that exceed 10–15% of the total body surface area give rise to a cascade of systemic and localized physiologic responses.^{2,3} Pathophysiologic changes accompanying burn trauma, which can alter the disposition of administered drugs, include cardiovascular changes,^{3–5} alterations in renal and hepatic function,^{6,7} and fluctuations in plasma protein concentrations.^{8–10} This review summarizes current knowledge of the altered pharmacology of the burned patient.

Pathophysiologic Changes Affecting Drug Kinetics

CARDIOVASCULAR FACTORS

The clinical course of the burned patient is marked by two distinct metabolic phases. In the acute (or resuscitative) phase, immediately after injury, blood flow to the organs and tissues is decreased.^{3,4} Multiple factors, including hypovolemia, depressed myocardial function, increased blood viscosity, and the release of vasoactive substances, contribute to this decreased blood flow.^{3–5,11–13} Therefore, during this period drugs administered by the enteral, subcutaneous, or intramuscular route will have delayed absorption with decreased peak concentrations and/or decreased bioavailability. If high dosages have been administered to overcome poor absorption, restoration of perfusion may lead to unexpectedly rapid uptake of medications from these sites, resulting in toxic effects.

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Thus, small, repetitive doses of intravenous drugs generally are more effective during this initial phase.

The second phase of burn injury, the so-called hypermetabolic or recovery phase, is associated with increased blood flow to organs and tissues.^{3–7} This phase begins at about 48 h after injury, provided that adequate resuscitation has been instituted. In the geriatric patient, this response is usually delayed or not present. Although total body and hepatic oxygen consumption as well as glucose and protein turnover by the liver are increased,⁶ whether or not drug metabolism increases accordingly is unclear from the few clinical studies that have been performed. From a theoretic standpoint, these alterations in blood flow should affect the kinetics of flow-sensitive drugs.

PROTEIN-BINDING FACTORS

Plasma protein concentrations may be altered in both the resuscitative and recovery phases of burn injury.¹⁰ Of note from a pharmacologic perspective, the albumin concentration is decreased, but the concentration of the acute phase reactant, α_1 -acid glycoprotein is increased.⁸ Thus, the plasma binding of predominantly albumin-bound drugs, such as benzodiazepenes and antiepileptics, is decreased (increased free fraction),^{8,14} while the binding of some other drugs, such as tricyclic antidepressants and neuromuscular relaxants, is increased (decreased free fraction).^{8,9} Changes in drug binding due to these burn-induced changes in plasma protein concentrations can affect kinetics as well as plasma concentration–response curves.^{8,9,14–18} The changes in protein binding may also result in alterations in the volume of distribution and clearance.^{15,16} Increased binding will generally lead to a decreased volume of distribution while decreased binding will have opposite effects.^{14–16} Relative to drug elimination, changes in protein binding affect only the clearance of low-extraction drugs. In the kidney, for example, increased binding will result in decreased elimination of glomerulus-filtered drugs, because only the free fraction is filtered, whereas decreased binding will lead to enhanced elimination. Similar directional changes can occur in the liver with respect to the clearance of low-extraction (binding-sensitive) drugs.^{16,17} For example, burn-induced decreased plasma binding of phenytoin resulted not only in a larger distribution volume of drug but also more

rapid clearance.¹⁴ Changes in plasma binding of drugs also complicate the interpretation of drug concentrations reported by the laboratory. Because most laboratories report total drug (free + bound) concentrations, it is difficult to know whether the reported concentration is therapeutic, subtherapeutic, or toxic.^{8,15,18} In these situations reported total plasma concentrations of highly bound drugs should be interpreted with caution, and whenever possible, methodology for measuring free concentrations should be used.¹⁸

OTHER FACTORS

Sepsis, drugs that induce¹⁹ or inhibit²⁰ drug metabolism; hepatotoxic or nephrotoxic drugs²¹; malnutrition²²; parenteral nutrition²³; preexisting systemic disease; and endogenous burn-induced substances^{11-13,24,25} are factors that can complicate drug disposition and response. The onset and presence of hepatic, renal, and pulmonary dysfunction may confound matters even further. Yet the contribution of each of these factors to the altered pharmacology in the burned patient remains to be characterized.

Pharmacologic Studies in Burn Patients

ANTIBIOTICS—SYSTEMIC

Sepsis remains a common complication and cause of death in the burn patient, and antibiotics, singly or in combination, play an important role in therapy.^{3,21} It is well established that generally higher than normal doses of certain antibiotics are required in burned patients to maintain adequate therapeutic levels.^{21,26} The major reasons for the increased requirement include: 1) enhanced elimination of drugs *via* the kidney, resulting from burn-induced increases in the glomerular filtration rate^{21,24-27}; and 2) drug loss through the burn wound.²⁸ For drugs that have minimal plasma-protein binding, the creatinine clearance may give an indirect estimate of the capacity of the burned patient to excrete antibiotic drugs by glomerular filtration. The elimination of half-life of tobramycin, which is directly correlated with creatinine clearance, exemplifies this hypothesis.²⁷

Loss of drug through the burn wound may be more significant in the infant and child than the adolescent or adult because of their relatively high surface-area to body-weight ratio. Thus, intuitively, one would expect to find a direct correlation between burn body surface area and antibiotic clearance; however, no such relationship has been shown. Although loss of antibiotic through burn wound is significant, clinical experience in patients with renal failure suggests that this is not an important route of elimination, and antibiotic therapy has to be modified

in the presence of renal failure just as it has to be in non-burned patients.^{26,29}

Clearly, systemic antibiotic administration in the burned patient is complex and deserves special consideration, including close monitoring of plasma drug concentrations. Because most antimicrobial agents bind little to plasma,³⁰ measured total drug concentrations will not be affected by alterations in protein concentrations.

ANTIBIOTICS—TOPICAL

The capacity of normal, intact skin to absorb therapeutic concentrations of drugs has been exploited extensively in the administration of drugs such as nitroglycerin. When the skin is destroyed, the capacity for topically applied drugs to be absorbed through the wound is often increased and can cause several adverse effects. For example, systemic effects on acid-base balance and ventilatory patterns of burned patients have been observed following the topical administration of mafenide acetate.³¹ Peak blood levels of mafenide and its metabolite, p-carboxybenzidine sulfonamide, occur within 2 to 4 h of application.³ Similarly, high serum concentrations of iodine have been observed following the topical application of povidone-iodine, and the amount of iodine absorbed has been shown to be directly related to the size of the burn.³² Although there have been no reports of altered thyroid function following absorption of high levels of iodine, with impaired renal function plasma iodine concentrations may become toxic. The presence of unconjugated sulfonamide in blood, as well as leukopenia, has also been observed following the application of silver sulfadiazine.³³ Topical applications of silver nitrate can result in the absorption of large volumes of free water from dressings and loss of potassium, sodium, and calcium from the body, resulting in plasma fluid derangements.^{34,35} Rarely, in the presence of aerobactercloacae, nitrate may be broken down to nitrite, which when absorbed into the blood stream leads to methemoglobinemia.³ The blood in these instances appears cyanotic, but measured PaO₂ (not saturation) values will be normal because plasma oxygen tension is not affected. Methemoglobinemia is easily corrected by the administration of methylene blue 1-2 mg/kg iv.

ANTACIDS

Curling noted at post mortem the high incidence of stress ulcers in burned patients.³⁶ Acute erosions of the stomach and duodenum have been demonstrated in 86% of patients with major burns within 72 h after burn injury.³⁷ More than 40% of all patients with major burns have occult gastrointestinal bleeding in their gut, and some suffer life-threatening hemorrhage.^{37,38} The mainstay of therapy for control of increased gastric acidity and bleeding includes early external feeding and the adminis-

tration of antacids and H₂-receptor antagonists.³³ Instituting early enteral feeding and oral antacids may be difficult in some patients because of intestinal ileus or perioperative fasting. Thus, parenterally administered antisecretory drugs, such as cimetidine, may be useful.

The efficacy of cimetidine in burned patients has been evaluated in several studies.³⁸⁻⁴² In adults given cimetidine in the first 18 h after burn, the number of oral antacid (Mylanta®) doses required to maintain gastric pH above 6 was significantly reduced. Between 18 and 42 h after burn, however, cimetidine was less effective.³⁹ Subsequent pharmacokinetic studies explained the reason for this phenomenon. During the early resuscitative phase of burn injury, urinary excretion was decreased and total cimetidine clearance was comparable with that in normal patients.⁴² Thus, therapeutic concentrations were maintained normal. In the hyperdynamic phase of burn injury, total and renal cimetidine clearance were increased in direct proportion to the burn size, resulting in subtherapeutic plasma cimetidine levels.⁴⁰ Therefore, the usual adult dose of 5-6 mg/kg q 6 h should suffice for the first 24 h after burn. In the period that follows, however, to compensate for enhanced clearance, both the dosage and frequency of administration may have to be increased. As long as cimetidine concentrations are greater than 0.5 µg/ml, gastric pH is likely to be greater than 4.0.⁴⁰ That is, target organ sensitivity is not changed. A dose of 400 mg q 4 h, or twice the normal 24-h dose, seems appropriate.⁴¹

The incidence of acute stress ulceration in children is approximately twice that of adults.⁴³ Although normal children tolerate and indeed require greater daily dosages of many drugs, including cimetidine, to achieve the same serum concentration or effect,⁴⁴ administration of higher dosages of cimetidine alone was not sufficient to maintain the gastric pH above 4.0 in a significant number of children.³⁸ Our preliminary studies have indicated that clearance rates of cimetidine in burned children are even higher than in burned adults.

The kinetic and dynamic behavior of ranitidine, a newer H₂-receptor blocker, has not been documented in burned patients.

ANXIOLYTICS

Anxiolytics and sedatives are commonly administered to burned patients. When diazepam is administered (usually intravenously), the therapeutic efficacy is short-lived due to the rapid decline of drug concentration in the plasma. This rapid decline in concentration following a single dose is due to the high lipid solubility of the drug and rapid uptake by the tissues.⁴⁵ Thus, although the elimination half-life of diazepam is long (36 h in normal patients, 72 h in burned patients),⁴⁶ the duration of action

of a single dose may be quite short.⁴⁵ This behavior is somewhat similar to the kinetics and dynamics of thiopental, where the elimination half-life is prolonged but the hypnotic effect is brief because of redistribution of drug in the tissues.⁴⁷ With repeated administrations of diazepam (or thiopental), however, the tissues can become saturated, and the termination of effect depends more on biotransformation by the hepatic enzymes, which can be quite depressed in the burned patient.⁴⁶

Thus, it is not surprising that weaning patients from a respirator can be difficult if the patient has been sedated for long periods with repeated doses of diazepam or chlordiazepoxide (Librium®), another drug with prolonged half-life and high lipid solubility.⁴⁵ The metabolites of diazepam and chlordiazepoxide are also pharmacologically active and can prolong and potentiate the sedative effects of the parent compound. The impaired mental status observed in many burned patients long after the termination of these drugs may be related to these factors. We have observed high levels of the parent compound (after repeated diazepam administration) in patients as much as 2 weeks after the drug has been terminated. The active metabolites persisted for even longer periods.

The mechanism of the reduced hepatic clearance of diazepam following burns has not been established in humans. Diazepam metabolism, which occurs in the cytochrome p450 mixed oxidases, is said to be an oxidative metabolic (or phase I) reaction. Numerous structural and functional abnormalities occur with burn injury.^{48,49} Inflammatory, neoplastic, infectious, and toxic diseases with hepatic or functional abnormalities, as well as the co-administration of other drugs, affect phase I reactions more than phase II (conjugation) reactions.^{45,50} Thus, impaired diazepam metabolism may be due to a nonspecific impairment of the drug-metabolizing capacity of the liver, as has been shown for other disease states^{45,50} and in several animal studies following burns.^{51,52} Alternatively, it may be attributable to concomitant administration of other medications. Of particular importance is cimetidine, a known inhibitor of diazepam clearance.²⁰

A newer benzodiazepene, lorazepam, possesses three important features that distinguish it from diazepam. First, lorazepam is metabolized by conjugation (a cytochrome p450-independent pathway) to a pharmacologically inactive glucuronide metabolite.⁴⁵ Second, the clearance of lorazepam is: 1) faster than that of diazepam⁴⁵; 2) unimpaired in the burned population⁵³; and 3) unaffected by concomitant cimetidine administration.⁵⁴ Third, the unbound volume of distribution of lorazepam is much less than that of diazepam, with clinically effective blood concentration persisting for many hours after the dose, resulting in profound, long-lasting sedation.⁴⁵ (In certain situations, this could be considered a disadvantage.) In summary, there is some theoretic basis for preferring lor-

azepam to diazepam, particularly when repeated doses are administered or when cimetidine therapy is required. These theoretic considerations need to be validated in clinical studies, particularly with reference to the pharmacodynamics.

Evidence from nonburned patients suggests that ranitidine does not affect the metabolism of either diazepam or lorazepam.⁵⁵ However, interaction of ranitidine with another benzodiazepene, midazolam, increases the soporific effects of the latter.⁵⁶

ANALGESICS

Despite the need for pain control, a major problem with burns, pain assessment and relief, have received scant attention.^{57,58} The elimination of pain, particularly in those patients unable to communicate because they are too young to speak or who are being mechanically ventilated is difficult to assess. Concern about possible addiction or the inability of burned patients to eliminate administered drugs has led to undermedication.^{59,60} Yet a nationwide survey of 151 burn centers and more than 10,000 hospitalized patients indicated no single case of iatrogenic addiction.⁵⁸ Inhalation of methoxyflurane (self-administered or otherwise), popular in the 1970s,⁶¹ has been largely discontinued in burn centers because of the potential for nephrotoxicity due to the release of fluoride ions.⁶²

Nitrous oxide-oxygen mixtures have been used for analgesia for quite some time, and the usefulness of the mixtures for hydrotherapy and debridement procedures has been tested.^{63,64} These studies have documented that self-administered analgesic mixture of 50% nitrous oxide with oxygen (Dolonox[®], Entonox[®]) is useful when combined with analgesics. This preparation produces analgesia approximately 20 s after the onset of inhalation and peaks at about 40 s to 2 min. Nitrous oxide is advantageous because it can be self administered, has minimal cardiovascular effects, and the duration of being NPO is decreased.⁶⁴

Side effects of nitrous oxide that warrant consideration include excitability, particularly at higher concentrations, drowsiness, and inhibition of cell proliferation in bone marrow and neurologic disease.^{65,66} Megaloblastic anemia and leukopenia can occur following exposure to nitrous oxide for 2–6 h.⁶⁷ Whether shorter duration but daily exposure to nitrous oxide during dressing changes and tubbing, especially in a burned patient who already has hematologic and immunologic abnormalities,⁶⁸ will potentiate these abnormalities sooner is unknown. Similarly, whether intermittent but frequent exposure of burned patients to nitrous oxide will worsen the already present neuromuscular disease⁶⁹ is subject to speculation. Finally, environmental contamination with N₂O, may be of some

importance to pregnant employees because of the possible association between exposure to anesthetics and miscarriage.⁷⁰

The use of narcotics, such as morphine, meperidine, and, more recently, fentanyl—administered intramuscularly or intravenously with or without sedatives—is the most common form of analgesic therapy for burned patients.⁵⁸ Although it has been known for some time that narcotic requirements are increased in burned patients,^{58,59} whether this is due to pharmacokinetic or pharmacodynamic factors has not been completely characterized. In addition, activation of endogenous opioid pathways occurs during stress-induced analgesia in animals and humans and could alter responses to exogenous opioids.^{57,71} One of the many reasons given for the reluctance to prescribe high dosages of narcotics for burned patients is the fear that these patients may be unable to handle the drugs safely because of their altered metabolic state. This concern has been addressed by Perry and Inturrisi, who found that the pharmacokinetics of morphine in burned patients were not significantly altered in comparison with normal controls.⁷² The results of this study should be regarded as preliminary, since Perry and Inturrisi used a radioimmunoassay (RIA) that did not distinguish between the parent compound and its major, inactive metabolite, morphine glucuronide.⁷³ Additionally, this investigation used historical controls from a study performed 5 yr earlier at another institution.

Meperidine and other newer synthetic narcotics, such as fentanyl, have also been used extensively.⁵⁸ Dosages, comparative efficacies, and side effects in burned patients remain to be documented. The most undesirable side effect of the narcotics, especially the newer synthetic preparations, is the skeletal muscle rigidity they may produce.⁷⁴ Many studies in nonburned patients have recently assessed the value of self-administered or patient-controlled intravenous analgesic therapy,^{73,75} which consists of self administration of small intravenous doses of narcotics by means of a triggered, programmable infusion pump to control pain. In order to avoid overdosage, the device only allows a maximum dose in a given time period. In these studies the authors found wide variability in dose requirements and kinetics. However, it was also noted that compared with conventional methods (intermittent iv, im or po), patient-controlled analgesia provided superior analgesic control. Because of large patient-to-patient variability in the pharmacokinetics and pharmacodynamics of drugs in burned patients, individualized (patient-controlled) dosage regimens may be preferable when treating pain. In view of the positive results observed in postoperative patients, the application of this technique in burned patients clearly deserves further study.

Recently, efforts have been made to understand the physiologic significance of the hypermetabolic (stress) re-

sponse to trauma and techniques to modify this response has been suggested.^{76,77} The afferent responses to increased metabolism can be accentuated by the brain, particularly in the presence of pain and anxiety.^{2,78} In this context, high-dose morphine and beta blockers have been shown to decrease the hypermetabolic response to trauma.^{78,79} However, study in one patient indicates that single-dose spinal blockade does not alter energy metabolism.⁸⁰ In a preliminary study Demling reported that patients with persistently high levels of endorphins (and possibly catecholamines) developed sepsis. The question has been raised whether these substances might decrease oxygen delivery and cause the sepsis.⁷⁷ He further demonstrated that sedatives and opiate administration decreased endogenous opiate levels, and these patients did quite well. Although more studies are necessary, it appears that the administration of exogenous opiates is not harmful to burned patients.

ANESTHETICS

Although the clinical pharmacology of anesthetic drugs in the burned patient has received some attention, few data characterizing uptake, distribution, and elimination of these drugs are available.

The most extensively used intravenous anesthetic is ketamine.⁸¹⁻⁸⁵ The advantages of ketamine include: 1) its cardiovascular-stimulating properties, particularly useful in critically ill patients; 2) its intense postoperative analgesic effect; and 3) the ability to administer it intramuscularly.⁸⁴ Low-dose ketamine (1.5-2.0 mg/kg im) produces adequate amnesia and analgesia, with rapid reestablishment of activities such as eating.^{84,85} Ketamine, 4-5 mg/kg im, can produce good operative conditions for eschar excisions.⁸⁵ The prolonged awakening associated with high doses of ketamine may be an advantage in the acutely burned patient, as it gives the nursing staff extra time to position and provide care for the freshly grafted wound areas before the patient awakens. Despite the cardiovascular-stimulating properties of ketamine, hypotension may occur in some critically ill patients. This is probably due to the inability of the already stimulated sympathetic nervous system to counterbalance the direct myocardial depressant and vasodilatory effects of ketamine.⁸⁶ The repeated use of ketamine results in tolerance^{86,87}; thus, the dose should be titrated according to need.

Halothane continues to be the anesthetic of choice for burn patients in many burn units. In a review of 408 patients who received 1,770 halothane anesthetics, Gronert *et al.* reported that repeated administrations of halothane to burned patients involved no additional risk.⁸⁸ Our experience at the Shriners Burns Institute, with over 10,000 repeat anesthetics during the last 15 yr, confirms this. If

hepatitis attributable to halothane is mediated *via* an allergic response,⁸⁹ the anergic state of the burn patient⁹⁰ may perhaps be the reason for the absence of halothane-related hepatitis in this population. Of course, with the multiple complicating and confounding factors affecting the burn patient, it will always be difficult to pinpoint halothane or any other agent as *the* cause of hepatitis.

Although free fluoride ion is increased following enflurane anesthesia, the potential for toxicity is minor because, at least in normal patients, peak concentrations of fluoride never attain toxic levels.⁶² The pharmacokinetic and pharmacodynamic advantages of isoflurane over other inhalational agents^{91,92} remain to be confirmed in burned patients.

ADRENERGIC AGONISTS

Cardiovascular instability can occur in the acute phase of thermal injury and with sepsis.^{3,5} Restoration of adequate hemodynamics, without producing volume overload, is the major goal of fluid (volume) resuscitation. In some instances, volume replacement alone is inadequate, and the use of adrenergic agonists has been advocated both during resuscitation and when complications such as sepsis occur. Aikawa *et al.* provided equivocal evidence for the efficacy of dopamine in treating decreased cardiac output in the early phase of thermal injury.⁴ In a prospective study during burn resuscitation, dopamine 5-10 $\mu\text{g} \cdot \text{kg} \cdot \text{min}^{-1}$ produced no change in hemodynamic parameters.⁹³ In another study, dopamine (3-9 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was used to correct right ventricular dysfunction occurring in the later phase of burn injury.⁹⁴ No significant improvement of right ventricular end-diastolic volume index, right ventricular ejection fraction, or systemic hemodynamics was observed; however, significant elevation in mean pulmonary artery pressures was noted, particularly in patients with mean pulmonary artery pressures elevated prior to infusion.⁹⁵ The ineffectiveness of dopamine in doses as high as 24 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (α effects) to improve systemic hemodynamics in sepsis has also received attention.⁹⁴ Thus, the clinical studies in burn trauma reported to date do not substantiate any useful α - or β -adrenergic effects of dopamine. These findings are in contrast to studies performed in other surgical patients in whom infusions of dopamine produced significant improvement in cardiovascular dynamics.⁹⁶

Burned patients normally have high levels of circulating catecholamines.^{79,97} These levels are higher than those observed in other stress states⁹⁸ and, in the normal patient, result in significant changes in cardiovascular parameters.^{98,99} Up to ten-fold higher than normal plasma concentrations of catecholamines have been observed in burned patients following topical applications of epinephrine to decrease bleeding during excision and grafting

procedures.¹⁰⁰ Although the authors drew attention to the potential for epinephrine to interact with halothane to cause arrhythmias, none were reported. In other studies, although plasma catecholamines were not measured, the absence of arrhythmias and minimal changes in cardiovascular parameters were noted following application of topical epinephrine during burn surgery.^{101,102} This lack of responsiveness to β -receptor agonists may be related to the already present, burn-induced, high and continuous level of catecholamine stimulation,^{79,97,100} leading to alterations in both receptor affinity and number (down regulation).¹⁰³

Although numerous laboratory studies have documented advantages of such diverse agents as adrenergic agonists, verapamil, reserpine, nitroprusside, and digoxin to improve cardiovascular function,¹⁰⁴⁻¹⁰⁶ systematic evaluation of these drugs at the bedside have not been performed. Vasodilator therapy with hydralazine may have some beneficial effects in patients in the early phase of burn injury.¹⁰⁷ A clinical study indicates that larger than normal doses of β -receptor antagonists may be required to completely block adrenergic responses.⁷⁹ This may be related to both high levels of circulating catecholamines and to increased plasma binding of propranolol following trauma and inflammation.^{8,108,109}

ACETYLCHOLINE-RECEPTOR AGONISTS AND ANTAGONISTS

The response of the nicotinic acetylcholine receptors (neuromuscular junction) to agonist and antagonist drugs is altered as a consequence of burn trauma.¹¹⁰⁻¹¹⁷ This subject has been reviewed recently.¹¹⁸ Administration of succinylcholine, a depolarizing muscle relaxant that is structurally similar to acetylcholine, can induce a massive potassium release from the muscle cell that may result in a lethal hyperkalemia.¹¹⁰ This hyperkalemic response is related to the dose of succinylcholine, time elapsed since injury, and severity of the burn injury.¹¹¹ In normal muscle, depolarization with succinylcholine (or acetylcholine) causes an increase in membrane permeability at discrete endplate junctions and the release of potassium from the cell. It is speculated that after burn injury, a denervation-like phenomenon occurs with a spreading of acetylcholine receptors throughout the muscle membrane.¹¹⁰ Thus, the administration of succinylcholine causes potassium release from the entire muscle membrane rather than from discrete endplate junctions. Although catecholamines and the adrenergic nervous system play an important role in potassium homeostasis,¹¹⁹ the importance of this system in the hyperkalemic response to succinylcholine has not been elucidated.¹²⁰ Indirect evidence suggests that the hyperkalemic response may last as long as 2 yr after the

burn occurs.¹¹² If the drug is administered inadvertently and cardiac arrest develops, calcium chloride should be administered in incremental doses until the peaked T-waves on the electrocardiogram return to normal. Although one might anticipate the hyperkalemia to reverse fairly rapidly with redistribution and tissue uptake of potassium, lethal hyperkalemia lasting more than 20 min has been reported.¹²¹ Other therapeutic maneuvers include bicarbonate, glucose, and insulin. During this time, cardiopulmonary resuscitation should be instituted.

Numerous recent studies of nondepolarizing muscle relaxants show that burned patients have a decreased sensitivity to *d*-tubocurarine, metocurine, pancuronium, and atracurium.¹¹²⁻¹¹⁷ To achieve a given level of paralysis, both the dose administered and serum concentration required in these patients are increased two- to three-fold. Altered pharmacokinetics and increased plasma protein binding of muscle relaxants contribute little and do not completely account for the augmented dose requirement.^{9,122} However, an increase in acetylcholine receptor number just described may have occurred,^{110,123} explaining the altered response to both agonist (succinylcholine)^{110,111} and antagonist (curare-like) drugs.¹¹²⁻¹¹⁷ Important factors contributing to changes in receptor number and response include immobilization and disuse atrophy.^{125,124}

Conclusions

Multiple factors, including alterations in blood flow, plasma protein binding, and organ function can affect the pharmacokinetics of drugs administered after burn injury. This situation is confounded by the co-administration of drugs that can induce or inhibit the metabolism and excretion of other drugs. The pharmacology of this population is further complicated by changes in target-organ sensitivity induced by multiple endogenous substances released in response to, or as a consequence of, the burn injury, as well as from malnutrition, physical immobilization, and various iatrogenic factors. There is some evidence to indicate that the patient with minor burns (<15% body surface area) responds differently to a drug than the patient with major burns (>30%).^{98,114,115} Although a number of studies have been conducted on the antibiotics and muscle relaxants, the mechanisms underlying the altered pharmacokinetics and pharmacodynamics of these agents in association with burn injury require more complete characterization. Further studies are needed to examine the relationship between particular drugs and the 1) type of burn injury (*e.g.*, scald *vs.* electrical *vs.* flame); 2) time elapsed since injury when the drug is administered, and 3) magnitude of the burn. Although additional research using animal models will undoubtedly

assist in defining the mechanisms responsible for these altered responses, clinical research in humans is urgently required.

If we are to improve the care of patients with burn and other traumatic injury, we must begin to conduct definitive clinical studies in these patients. Nutritional status and the effects of malnutrition appear to have important implications for the pharmacologic action and metabolism of drugs,^{22,23} yet very little information is available concerning the combined effects of malnutrition, parenteral nutrition, and critical illness on the disposition and pharmacologic effect of drugs. With the current move to centralize trauma and burn care in many centers across the country, these studies should be forthcoming. Their need cannot be overemphasized.

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