Clinical Pharmacokinetics in Burn Patients

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Introduction
Burn victims are a special group of patients who need immediate care and treatment. The pathophysiological changes and complications such as sepsis that burn patients go through significantly alter the pharmacokinetic parameters. Recommendations are done for proper dosing & administering the proper drug at the proper time to avoid serious consequences as acute renal failure. The aim of this paper is to provide a brief review on the pathophysiological changes and their effect on the pharmacokinetic parameters of the most drugs that are used in this situation.

Pathophysiology

The pathological changes can be divided into two phases, first the acute phase of the injury lasting for approximately 48hrs. The second phase is the hypermetabolic phase beyond 48 hrs after the thermal injury. Thermal injury cause both local and systemic response, resulting in both local burn tissue damage and systemic effects e.g (cardiovascular, renal & gastrointestinal systems). Thermal injury initiates systemic inflammatory reactions producing burn toxins and oxygen radicals and finally leads to peroxidation.

Cardiovascular Response
The acute phase is characterized by hypovolemia, which is first due to the direct heat effect on the body leading to decreased blood flow to tissues and organs. Secondly, to liberation of vasoactive materials, from the injured area which increase the permeability and promotes fluid and protein loss into extravascular compartment within minutes. The cardiac output falls leading to increase in the peripheral vascular resistance. The cardiac output decrease is in proportion to burn size.

The hypermetabolic phase
Is characterized by edema due to increase in blood flow to the tissues and organs, increased internal core temperature, hypoproteinememia and increase in the water permeability of the interstitial space. The hypermetabolic state is associated with catecholamine production and an increase in the end diastolic volume while right ventricular ejection fraction decreases.

Renal Responses
During the acute phase of burn injury, renal blood flow and glomerular filtration rate (GFR), as measured by creatinine clearance, decrease. In the hypermetabolic phase, creatinine clearance is increased; the tubular function is impaired despite the increase renal perfusion. The incidence of acute renal failure (ARF) in severely burned patients ranges from 1.3 to 38%. The pathophysiologic mechanism may be related to filtration failure or tubular dysfunction. Two different forms of
acute renal failure have been described in burned patients, differing in terms of their time of onset. The first occurs during the first few days after the injury and is related to hypovolemia with low cardiac output and systemic vasoconstriction which damages the tubular cells. Elevated levels of stress hormones like catecholamines, angiotensin, aldosterone and vasopressin have been reported to be implicated in the pathogenesis of this form of ARF.

The other form of ARF develops later and has a more complex pathogenesis. This form has been reported to be related to sepsis and multiorgan failure and is most often fatal.

In addition to these mechanisms that support the pathogenesis, the kidney damage induced by burn injury is dependent upon the formation of oxygen radicals, as evidenced by increased lipid and protein oxidation with a concomitant decrease in renal antioxidant (glutathione) levels.

**Gastrointestinal Response**

Gastric dilation, delay in gastric emptying, with a decrease of mesenteric blood flow are among the effects of thermal injury on the gastrointestinal system.

The stomach has been found to secrete excess protons which will eventually lead to ulcers in the majority of patients. In the small intestine decreased nutrient (glucose, calcium and amino acids) absorption and DNA synthesis occurs and enhanced intestinal permeability has been observed. Intestinal ischemia resulting from decreased splanchnic blood flow may activate the neutrophils and tissue-bound enzymes such as xanthine oxidase and these factors destroy the gut mucosal barrier and result in bacterial translocation.

Intestinal and colonic motility in the rat were decreased following burn injury accompanied by a delay in gastric emptying.

Liver blood flow is significantly increased during the hypermetabolic phase.

Hepatic metabolism is also affected: there is an acute depression in microsomal activity (phase I), but conjugative metabolic activity (phase II) is unaffected and may possibly increase. Other liver functions, such as protein synthesis, are also impaired.

The changes associated with the hypermetabolic phase evolve over several days, and their intensity will vary with time.

Burn injury also causes hepatic damage and considerable changes in plasma protein levels. In general, patients exhibit decreased albumin and increased α-acid glycoprotein levels.

**Percutaneous Absorption:**

Percutaneous absorption, the process of diffusive penetration through the skin, may be substantially increased through burned tissue. Normally, a drug must diffuse into the stratum corneum and pilosebaceous gland ducts. Further movement transcending the epidermal strata is required before the drug becomes available to the systemic circulation. Burn injury can destroy these normal barriers. And depending on the degree of burn and surface area involved, the systemic absorption of topical medications may be clinically significantly enhanced if the local vasculature remains intact.
Table 1 Systemic Response to Burn Injury

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<th>Pharmacokinetics Parameters</th>
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<td><strong>Studying the pathological changes in burn patients leads to a better understanding of the potential alteration in the pharmacokinetic parameters such as bioavailability, protein binding, volume of distribution (Vd) and clearance.</strong> The extent of these alterations depends on the drug, the type and extent of injury and the time that elapsed between injury and drug administration. <strong>Bioavailability:</strong> bioavailability of large and hydrophilic molecules may be increased because of enhanced intestinal permeability; Hyperchlorhydria may affect the dissolution and disintegration of orally administered drugs in tablet form, as well as the partitioning of the neutral un-ionized species between the stomach and bloodstream. <strong>Protein binding:</strong> The free fraction of a drug in plasma can be increased or decreased. Plasma albumin level rapidly decreases immediately after injury and remain depressed for 60 days post-burn. Thus, the protein binding of acidic and neutral drugs will decrease and higher amounts of free fraction will be available at the biophase. On the other hand, alpha 1-acid glycoprotein increases in concentration and remains elevated at least 20 days post-burn. Basic drugs exhibit increased protein binding and will most probably need an increased dosage to achieve the appropriate pharmacological effect. <strong>Volume of distribution (Vd):</strong> may change as a consequence of altered protein binding or an enlarged extracellular fluid volume. <strong>Clearance:</strong> Alterations in clearance may be due to changes in glomerular filtration, tubular secretion, hepatic blood flow, drug-metabolizing activity, protein binding and to the presence of additional elimination pathways depending which phase the patient is in. <strong>Elimination half-life:</strong> changes when Vd and/or clearance are affected following burn injury.</td>
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to those in the hypermetabolic phase (when sepsis predominantly occurs), other studies have combined pediatric and adults ignoring the actual physiological differences in both groups. Finally, studies undertaken during the prophylactic use of antibiotics may yield different results from those performed when antibiotics are used to treat infection, as sepsis is known to alter drug pharmacokinetics. The results of these studies are of limited values. This may explain why some studies find an increased dosage requirement whilst others do not. Standardization of all the variables is not necessary, and probably impossible. Certain parameters, such as conducting the study either in the acute or the hypermetabolic phase, ensuring that enough patients with high creatinine clearance are included and separating children from adults, need to be predefined, as their influence on studies may be critical. It is important to recognize that burns patients are an extremely heterogeneous group with significant inter- and intrapatient variation with regards to drug handling. The danger with any study lies with the possibility that it will not be truly representative of the whole population. This is particularly so with small studies.

Drug used in Burn Patients:

Burn patients administer a variety of drugs such as:
Antibacterial, anti-ulcer drugs, analgesics, muscle relaxants, anxiolytics, phenytoin and cyclosporine.

Antibiotics:
The challenge has been to achieve therapeutic levels rapidly, as this improves outcomes from sepsis. The rapid clearance of antibiotics in the burn population means that some patients may be exposed to subtherapeutic levels. Any reduction in antibiotic concentrations is likely to be more significant in burn patients as they are immunocompromized and often infected with Gram-negative pathogens such as *P. aeruginosa* or *Acinetobacter* spp., which have higher MICs compared with other Gram-negative species.

Aminoglycosides:
Aminoglycosides are indicated for the treatment of burn patients either as part of empirical therapy or for established Gram-negative sepsis. Conventional aminoglycoside dosing, by trial and error, resulted in an unacceptable delay in achieving adequate levels. An alternative way of dosing burn patients was required.

The alternative was to measure the pharmacokinetics in each patient this can be achieved in burn patients using fist dose (FD) pharmacokinetics. Judicious use of larger initial doses of aminoglycoside (1.0–1.7 mg/kg and 3 mg/kg of gentamicin) might attain therapeutic concentrations even more rapidly.

Tobramycin:
Is eliminated primarily by the kidney unchanged. In study by Loirat et al there where no differences in the volume of distribution between burn and nonburn patients but a significance difference in the mean serum half-life (0.85hr) in burn patients and (1.13hr) in nonburn patients and this decrease in the half-life was attributed to the increase clearance in these patients. Higher doses of tobramycin are recommended.

Gentamicin:
Glew et al, in their study of 18 burned children, they summarized that the increased dosage requirements resulted from either loss of drug across burn
wounds or increased renal excretion larger doses at more frequent intervals than normally utilized were often necessary.

Zaske et al concluded that to maintain peak serum gentamicin levels in the range of 7-8 µg/ml, the average dose required in the adult group was 7.2 mg/kg/day. And in the children group 12.8mg/kg/day. For patients with relatively short half-life, it was necessary to decrease the dosing interval to 4 hours to prevent prolonged periods of subtherapeutic serum concentration. These authors strongly recommended individualization of gentamicin dosing regimens for burned patients with life threatening infections, in another study the authors individualized gentamicin therapy using daily doses (15-30mg/kg) that were three to six times those recommended. A patient who received lower doses did not survive. No nephrotoxic or ototoxic reactions where noted in any of the patients.

Glycopeptides

They are indicated in the treatment of other severe Gram-positive infections (e.g. S. pyogenes and methicillin-sensitive S. aureus) if β-lactams are contraindicated owing to allergy and in methicillin-resistant Staphylococcus aureus (MRSA).

Vancomycin

Creatinine clearance and vancomycin clearance were significantly elevated in burns patients. The increased clearance appeared to be due to both raised glomerular filtration and increased tubular secretion. The traditional method of vancomycin administration has been challenged in both non-burn and burn patients. Conventional practice is to give vancomycin by short infusion, two to four times per day, and to measure peak and trough levels. The vancomycin bacterial killing is not concentration dependent, but is a function of time. In theory, administration of vancomycin by continuous infusion (CI) might better match the drug's characteristics, resulting in cidal activity being maintained throughout the dosing interval. With conventional dosing (CD), the high peaks confer no extra bactericidal activity, but when the serum concentrations fall below 4x MIC, cidal activity is lost.

Concil et al looked at CI of vancomycin in 18 burn patients with a mean burn surface area of 40%. Their average age and weight were 44 years and 63.4 kg, respectively. was administered at an initial dose of 35 mg/kg and the target vancomycin concentration was ≥15 mg/L, but measurement of vancomycin concentrations on day 3 showed 80% of cases to be below this value. The only patients with adequate levels were those >58 years of age. Eleven patients required an increase in dose to at least 40 mg/kg/day to achieve the target value. In only two cases was the vancomycin dose reduced. Continuous infusion of vancomycin was tolerated well and there was no evidence of an adverse effect on renal function. As vancomycin levels are routinely measured, the necessity for administering larger doses to burns patients should be apparent. The outstanding questions are whether CI is the preferred method of administration and, if so, what is the target serum concentration.

Teicoplanin

The median concentration of teicoplanin in fluid from the burn wound was 60% of the serum antibiotic concentration. A single IV dose of 12 mg/kg of teicoplanin was sufficient to produce therapeutic serum concentrations in burn patients for 24 hr. but monitoring of antibiotic levels in serum may be
advisable in those with high total clearance, especially children. A target minimum trough serum concentration of 15 mg/L is recommended.

**β-Lactams**
The indications for using this group of agents is the same as that for using any broad-spectrum agent active against Gram-negative bacteria.

**Ticarcillin/clavulanate**
The volume of distribution and elimination half-life of both components were increased, but was much greater for clavulanate. The total clearance was also significantly increased for both components, despite the increased terminal half-lives of ticarcillin and clavulanate, there is no evidence of accumulation and in view of the serious nature of infection in burn patients it is recommended to administer the highest dosage of the drug.

**Piperacillin (PPR)/Tazobactam (TZB)**
Bourget et al reported a marked increase in apparent volumes of distribution and prolonged elimination half-lives of the combination i.e., 1.8 (0.3) versus 1.5 (0.3) hr for PPR in burn patients and healthy subjects, respectively, and 1.7 (0.3) versus 1.4 (0.3) hr for TZB. These findings indicate the possibility of nonrenal translesional diffusion of PPR-TZB in burn patients. The polarity of the association would further support this hypothesis. It has been shown here that the recommended dosage regimen for administration of PPR-TZB must be high in major-burn patients, i.e., 4 g/0.5 g every 6 h. The data obtained provides valuable information, which is suitable for immediate application in everyday clinical practice.

**Ceftazidime**
The pharmacokinetics of ceftazidime (CL & Vd) were significantly different compared with other patient groups although much interpatient variation was noted. The ceftazidime clearance could be explained by the relative decrease in ceftazidime elimination in relation to the burn area, and the higher ceftazidime volume of distribution in the presence of interstitial edema, which could act as a reservoir from which ceftazidime returns slowly to the circulation. Apparent volume of distribution was substantially increased, as was the elimination half-life. These changes will have consequences for the ceftazidime dosing regimen. Continuous infusion of 6 g/day ceftazidime may be most advantageous to treat serious infections in burn patients.

**Carbapenems**
It is indicated to treat Acinetobacter spp.

**Imipenem**
The pharmacokinetic parameter was not significantly different from previously reported parameters in non-burn. However, substantial interpatient variability has been noted. For example, the terminal half-life in non burn was 0.93 ± 0.09 h, whilst for burns patients it was 1.12 ± 0.44 h. Imipenem clearance is significantly related to creatinine clearance. Adjustment in dosage or dose interval might be considered in those patients with burns who have an abnormally high or low creatinine clearance.

**Meropenem**
Clinical experience with meropenem in burns is limited, but a study in non-burn
patients suggests that the pharmacokinetics are very similar to imipenem².

Quinolones

Ciprofloxacin.

A prospective study on eight burn patients each patients has received 400mg IV every 8hr. Clearance was higher and t1/2 was shorter than noted in previous studies of acutely ill, hospitalized patients. A good correlation was noted between creatinine clearance (CLCR) and both total ciprofloxacin CL (r = 0.85) and CLR (r = 0.84). A moderate inverse correlation was noted between percent body surface area burned and total ciprofloxacin CL (r = 0.55). An AUC/MIC ratio above 125 SIT-1 (where SIT is serum inhibitory titer), which has been strongly correlated with clinical response and time to bacterial eradication, was achieved in five of eight patients (63%) with a MIC of 0.25 microgram/ml. At a ciprofloxacin dosage of 400 mg i.v. every 12 hr, an AUC/MIC ratio above 125 SIT-1 would have been achieved in only two of eight patients (25%). The authors conclude that ciprofloxacin CL is highly variable, but generally increased, in burn patients compared with that in acutely ill, general medical and surgical patients. Because of an increase in CL, a ciprofloxacin dosage of 400 mg IV. every 8 hr (1200mg/day) is more likely to produce the desired response in burn patients than the same dose given every 12 hr ¹¹.

Fluconazole

Pharmacokinetics in burn patients appear to differ from those in healthy volunteers or other patient populations. Estimates of fluconazole’s t1/2 were 13% shorter and its CL was 30% greater than the most extreme values previously published ³. Thus, moderate and aggressive daily doses of fluconazole in the prophylaxis and treatment, respectively, of fungal infections in burn patients are recommended.

Phenytoin

Low serum concentration was observed in epileptic burned patients maintained on the normal regimen. This finding was related to the decrease of plasma protein binding of the drug; which was 25.8% unbound (normal~10%) serum albumin levels was decreased (2.68 vs. 3.5 g/dl in normal) leading to a conclusion that the free fraction of phenytoin is inversely proportional to albumin concentration ⁸.

Valproic Acid:

A fivefold increase in free fraction of valproic acid in plasma, with only 50% decrease in the albumin ⁸.

Topical Drug

In full-thickness burns, the epidermal layer is destroyed. Topical drugs have less of a barrier to cross and, consequently, less drug is needed to achieve effectiveness. Topical application of mafenide acetate, providone iodine, and gentamicin to burn wounds has resulted in varying amounts of systemic absorption. Various systemic toxicities have been attributed to these topical therapies, especially in patients with compromised renal function. The extent and area of the burn, degree of hydration, and the amount of drug applied are factors influencing transcutaneous absorption. Sulphonamide derivatives are excreted in the urine subsequent to the application of silver sulphadiazine

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cream, but silver ions appear to be localized on surface tissue and are thus unavailable to the subeschar space. Lidocaine absorption from the jelly form in patients with thermal injury showed a high degree of absorption so caution should be taken when using the jelly form.

Summary

The pathophysiology associated with thermal injury is complex leading to changes in the pharmacokinetics behavior of drugs. These pharmacokinetics alteration require therapeutic drug monitoring and dosage adjustment to ensure rational and well tolerated drug therapy in patients with burns. Individualization is warranted to avoid subtherapeutic drug concentration levels.

Burns patients with a normal or elevated creatinine clearance should be given at least the maximum recommended dose. Future studies should focus on the impact of specific patient variables such as conducting the study either in the acute or the hypermetabolic phase, ensuring that enough patients with high creatinine clearance are included and separating children from adults, need to be predefined, as their influence on studies may be critical and on the extent of pharmacokinetic alterations.

References:

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