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Case report

Burns and epilepsy – review and case report

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ABSTRACT

Decompensation of epilepsy in burned patients may be caused by several factors. Burn is a classic etiology of systemic inflammatory response syndrome, and evolves into two physiological phases. The first 48 h after injury corresponds to the first phase involving severe hypovolemic shock. The second phase corresponds to the hypermetabolic response to burns. Altered pharmacokinetics of anticonvulsant drugs is observed. Albumin and other plasma proteins are reduced, leading to increased free fraction of phenytoin, resulting in greater clearance and a lower total drug concentration. Associated with metabolic changes of burned patient, this fact predisposes to seizures in epileptic burned patients. The authors present the case of an epileptic 36-year-old-woman who developed recurrent seizures after a thermal injury, despite using the same medications and doses of anticonvulsant drugs of last 12 years, with controlled epilepsy.

1. Introduction

The prevalence of epilepsy around the world is estimated at 10/1000 people [1], being the most serious noninfectious chronic neurological condition in the world. Brazilian studies have shown lifetime prevalence of 11.9 to 21/1000 [2]. These patients are at increased risk for burns [3] and other events [4]. Burns as a result of a seizure represent 1.6–10% of admissions to burns units [5–9] and 3.7–15.9% of adult epileptics have been burned due to seizures [10,11].

Several factors may contribute to decompensation of epilepsy that occurs in burned patients as pain, fever [12], hypovolemia and metabolic changes after burns [13]. The main factors that reduce the seizure threshold is fever, sleep deprivation, abrupt withdrawal of anticonvulsant medication, hyperventilation, intake of alcoholic beverages or stimulants, use of euphoric drugs, use of drugs with convulsant action (e.g. isoniazid), physical or psychological stress, hormonal disorders, flashing lights, repetitive sounds, flashing lights, repetitive sounds, hypoglycemia.

2. Burns and pharmacokinetics changes of drugs

Burn is a classic etiology of systemic inflammatory response syndrome (SIRS), which can lead to multiple organ dysfunction

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syndrome (MODS) [14,15]. The skin lesion leads to the induction of a local inflammatory process through activation of coagulation, kallikrein–bradykinin cascades, complement and arachidonic acid. These paths lead to the release of different compounds that induce increased local microvascular permeability, vasodilation and generalized cellular edema by cell membrane dysfunction [16].

Thus, disturbance in the homeostasis occurs locally and systemically, which explains the severe hemodynamic alterations observed in major burn [17].

Based on physiological approach, burns evolve into two phases. The first 48 h after injury corresponds to the first phase involving severe hypovolemic shock. The inflammatory process begins in the burned patient rapidly after tissue injury to the skin resulting in local vasodilation, increase of vascular permeability and destruction of the extracellular matrix. These changes induce a rapid flow of albumin from the vascular to the interstitial space, leading a twofold increase in the interstitial volume within the initial hours after injury. In uninjured tissue, edema formation is delayed by several hours (24–36 h) and it is related to the systemic effects of inflammation in combination with a low oncotic pressure (hypoalbuminemia) [17,18].

The fluids leaking from the vascular space induces circulatory failure with low cardiac output and low glomerular filtration rate (GFR), leading to the low urine output and increased systemic vascular resistance in unburned tissues. Circulatory failure may induce organ damage, especially in acute kidney injury when the resuscitation fails. Fluid administration during resuscitation restores blood volume but increases the formation of edema. These physiological changes are temporary and the rate of edema formation decreases after the first 36–48 h. During this phase, the pharmacokinetics is mainly modified by a slower rate of delivery of drugs and decreased renal clearance [17,18].

The second phase (more than 48 h after injury) corresponds to the hypermetabolic response to burns, which is related to the systemic effects of inflammation and oxidative stress. At this stage, after adequate fluid administration, the hemodynamic status of a patient is hyperactive with increased cardiac contractility, high cardiac output and low systemic vascular resistance, as a septic shock state. Regional blood flow is increased, especially in the liver and kidneys, leading to an increased glomerular filtration rate and creatinine clearance (Crcl). The non-renal clearance is also increased by the leakage of exudate in burned areas, but its role in the elimination of drugs remains controversial [17,18].

The hypermetabolic phase is also characterized by the production of acute phase proteins, especially in the liver, wherein the synthesis of constitutive protein (albumin, prealbumin, transferrin, etc.) is shifted for synthesis of acute phase proteins (alpha 1-acid glycoprotein acid, haptoglobin, fibrinogen, alpha 2-macroglobulin, etc.) to help immune response, coagulation and wound healing function. Therefore, the serum albumin level is severely decreased due to decreases hepatic production and leakage during formation of edema and exudate loss [17,18]. Several studies have demonstrated that during this phase, plasma drug delivery is severely changed [18–20].

Regarding the liver, burn may induce hepatic dysfunction [21,22], with decreases in cytochrome P-450 and all activity related to oxidation, reduction and hydroxylation reactions involved in the drug metabolism. Other routes of metabolism, such as conjugation, are not changed [23].

The hypermetabolic phase may develop and persist over several days or weeks. The pharmacokinetic parameters of drugs are affected differently (volume of distribution, protein binding, hepatic clearance, half-life) depending on the time elapsed since the beginning of the lesion. Obviously, some other important factors related to the burned patient may affect the pharmacokinetics, as preexisting comorbidities, age, fluid replacement and presence of sepsis. Clearly, such changes have a large interindividual variability in drug pharmacokinetics [17,18,24].

Bowdle et al. [25] showed altered pharmacokinetics of phenytoin in burned rats. The main changes were increased clearance and volume of distribution, attributed to a greater free fraction compared with control mice (33.4% vs. 27.1%). The decline in plasma protein binding was directly associated with a lower concentration of albumin. The increase in the free fraction and its inverse correlation with the level of albumin were also observed in burned patients, in whom the free fraction was about 2.5 times higher than in healthy individuals. Results showed greater clearance and a lower total drug concentration, while the average concentration of free drug is not altered [25].

Phenytoin is highly bound to plasma proteins (90%), thus the changes in the unbound fraction are of clinical significance [26,27]. The drug has a moderately large volume of distribution. Clinically important displacement can be caused by bilirubin and several drugs particularly sodium valproate, which is often combined with phenytoin. Displacement will lower the total serum concentration but will little affect the free drug concentration. The metabolism of phenytoin to the major metabolite, 5-(p-hydroxyphenyl)-5-(phenylhydantoin, is saturable, giving rise to a nonlinear dose–serum concentration relationship. Therefore, the dose range compatible with a therapeutic serum concentration is narrow within subjects, and monitoring serum concentrations is of particular value in dosage tailoring. In renal failure, the binding of phenytoin to plasma proteins is reduced and therefore a lower range of serum drug concentrations is compatible with therapeutic control. In liver disease, protein binding may also be impaired but delayed metabolism may occur in addition. During pregnancy the serum concentration may fall progressively as pregnancy advances, probably due to an increased rate of metabolism [26,28].

3. Case report

Female, 36 years-old, litter collector, admitted to the Emergency Room (ER) of São Paulo Hospital on 08/18/2009, brought by a rescue unit, with a history of having fired into the body with alcohol and flame. Such information was referred by people at the incident scene to the professional who performed the rescue. There, the patient was found with the fire extinguished and generalized tonic-clonic seizure,