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Pharmacological potential of acetazolamide in traumatic intracranial hypertension

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ABSTRACT

Traumatic brain injuries are an important cause of morbidity and mortality around the world. These types of lesions are often associated with increased intracranial pressure and cerebral edema, proper management of this can reduce tissue damage of the brain and improve brain perfusion. The use of acetazolamide is not indicated in guidelines for the management of intracranial hypertension, which is used to a great extent for the management of idiopathic intracranial hypertension. However, it is not yet known in the management of traumatic intracranial hypertension.

1. Introduction

Brain trauma represents an important source of morbidity and mortality in the world. About 10 million people in the world die or are hospitalized as a result of this. Its etiology is varied and depends on variables such as age, place of residence, sex, socioeconomic stratum, among others; For example, in young people, the most

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common causes are car accidents and assaults. Subsequent to a traumatic injury, the risk of developing intracranial hypertension and cerebral ischemia increases[1,2].

Acetazolamide is a drug that helps to reduce cerebrospinal fluid secretion. However, it is not recommended for this type of lesions, but in idiopathic intracranial hypertension. (3-6) This article aims to describe the pathophysiology of traumatic intracranial hypertension and the mechanism of action of acetazolamide, aiming to show its possible use cases of traumatic intracranial hypertension.

2. Pathophysiology

Intracranial pressure (PIC), is the pressure exerted by the brain, blood and cerebrospinal fluid (CSF) in the vault of the skull. This varies with age, normal values in adults are <10-15 mmHg, in children between 9 and 11 years is 3 to 7 mmHg and in infants is 1.5-6.0 mmHg. When ICP is between 20 and 25 mmHg, treatment is required in most circumstances and values greater than 40 mmHg indicate severity, which threatens the patient's life[3].

A closed cranial trauma is composed of two related pathological processes: the primary lesion, which has a mass effect associated with neurological dysfunction and secondary cerebral edema, and consequently the increase of ICP. Secondary lesion occurs when cerebral edema and dysregulation of blood flow result in increased ICP and cerebral ischemia. According to the Monroe-Kellie hypothesis, the intracranial space has a fixed volume given by brain tissue, blood, and CSF, so when the brain compensation mechanisms are overwhelmed due to the mass effect produced by intracranial hemorrhage and Dysfunctional edema lead to an increase in ICP[2-4]. Initially, cell death occurring at the site of injury releases excitatory amino acids such as aspartate and glutamate. This together with the activation of voltage-dependent channels of Ca^{2+} and Na^{2+} lead to apoptosis, thus causing oxidative stress, hypoperfusion, and vasospasm, leading to cerebral ischemia and edema[2].

3. Mechanism of action of acetazolamide

Acetazolamide AZ is a potent inhibitor of the enzyme carbonic anhydrase[3,5,6,7-10] known to lower extracellular pH in the brain by inhibiting the reversible hydration of CO_2 to bicarbonate ions and catalyzed protons by the same enzyme[7,10], this occurs after the alkalization of the interior of the cells[9], in addition, it reduces the production of CSF and is used in the treatment of hydrocephalus, high altitude disease[3,11-13] and Benign or idiopathic intracranial hypertension[3,5,6,11]. However, it has other uses such as increased activity dependent on alkaline transients, decreases the power of oscillatory wave θ in REM sleep, is anticonvulsive[7,10,13], impairs spatial learning and can also eliminate depolarizations mediated by HCO_3-dependent GABAA in rats. In addition, it has been reported that it can increase the number of triggered action potentials and depolarize the neurons, affecting brain neuronal excitability[10]. Cerebral blood flow may also vary depending on the dose of AZ used by the decrease in extracellular pH in the brain generating acid vasodilation that does not depend on AZ but from the general systemic reaction to the decrease in pH[10,14].

AZ is the drug most commonly used to reduce ICP, mainly in idiopathic intracranial hypertension[3,5,6,11]. This exerts an inhibitory action on the choroid plexus, where the active transport of Na^+ ions in the cerebral ventricles by Na^+ / K^+ ATPase is the main driving force for CSF secretion[11].

Among the adverse effects of AZ are electrolytic disorders, hepatic enzyme alteration, renal lithiasis[15] metabolic acidosis[8,9,13,15], renal failure, anorexia, vomiting, increased diuresis, Central nervous system[9], hypokalemia[8,13], numbness of the extremities [8,11,13], headache, tinnitus and gastrointestinal disorders[8,13].

4. Management of traumatic intracranial hypertension

After the initial stabilization of the patient, the hemodynamic, respiratory and nutritional aspects of the patient should be optimized. For this reason, fluid administration, mechanical ventilation, and enteral feeding are necessary for this type of injury[1,4,11].

In order to manage the increase of ICP in cases of cerebral trauma, the main objective is to identify the underlying cause and treat it by adding the necessary measures to reduce ICP[3]. Initially, the state in which air life, breathing, and circulation are to be evaluated and treated. Then, $PaCO_2$ can be reduced to a range between 30 and 35 mmHg, which is effective in reducing ICP. In the pharmacological treatment, hypertonic fluids, osmotic diuretics, barbiturates, among others[1,4,11] are used.

At the time of a brain trauma, the PIC can be elevated by the deregulation of the compensatory mechanisms of the brain. The priority in these cases is to stabilize the patient in a timely and effective manner. AZ is one of the drugs most used in the treatment of patients with idiopathic cranial hypertension. Further studies are needed to determine the potential use of this drug for the management of traumatic cranial hypertension.

Conflict of interest statement

We declare that we have no conflict of interest.

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