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REVIEW
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The role of acetazolamide in critical care and emergency medicine

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ABSTRACT

Acetazolamide is the commonly prescribed oral and intravenous carbonic anhydrase inhibitor; over the years, its use in clinical practice has decreased in favor of more recent drugs. However, it is a rather handy drug, which can be useful in several clinical settings when managing critically ill patients. The objective of this review is the evaluation of the most recent evidence on the use of acetazolamide in emergency medicine and critical care medicine. Furthermore, the safety profile of this drug has been evaluated. This is a narrative review on the use of acetazolamide in the main contexts in which this drug can be useful in emergency situations for patients with potential critical issues. For the timeline 1999–2024, a search was conducted on the main scientific platforms; resources of greatest relevance for the use of acetazolamide in critical care and emergency medicine were selected. The most common emergency situations in which a critically ill patient could benefit from acetazolamide therapy are acute heart failure, acute mountain sickness, post hypercapnic metabolic alkalosis, idiopathic intracranial hypertension and acute angle-closure glaucoma. In a few cases, however, randomized controlled clinical trials have been conducted. There are also other less solid indications based mostly on experience or retrospective data. Acetazolamide seems to be an overall safe drug; serious side effects are rare and can be avoided by carefully selecting the patients to be treated. Acetazolamide represents a precious resource for emergency physicians and intensivists; critical patients with different conditions can in fact benefit from it; furthermore, acetazolamide is a safe drug if administered to correctly selected patients.

Carbonic anhydrase inhibitors (CAIs) are sulfonamide derivatives; the observation that some bacteriostatic sulfonamides induced alkaline diuresis led to the use of these molecules as diuretics. The first generation of CAIs is represented by acetazolamide which is the commonly prescribed oral and intravenous CAI; other less used CAIs are diclofenamide, dorzolamide and brinzolamide.[1,2]

CAIs act blocking predominantly carbonic anhydrases-type II and IV (or carbonate dehydratases – EC 4.2.1.1) that are metalloenzymes containing zinc and play a crucial role for the interconversion between CO_2 and H_2O and the dissociated ions of carbonic acid (i.e., HCO_3^- and H^+). In the kidney at the proximal tubule, by blocking carbonic anhydrase, CAIs determine an increase in the renal elimination of bicarbonate, sodium, potassium and water; urinary excretion of sodium bicarbonate induces a decrease in plasma bicarbonate, causing metabolic acidosis with consequent reduction in bicarbonate filtered at the glomerular level.[3,4]

The critical unsubstituted sulfonamide moiety of these drugs is linked to various aliphatic, aromatic or heterocyclic groups, thus implicating their differing pharmacologic characteristics. In humans, several isoforms of

carbonic anhydrase exist; these are widely distributed and their main functions are maintaining acid–base homeostasis, regulating pH, fluid balance and hemoglobin function via the Bohr effect. The ciliary body of the eye secretes HCO_3^- from the blood into the aqueous humor; furthermore, the choroid plexuses produce cerebrospinal fluid by secreting bicarbonates; these processes are inhibited by CAIs.[1]

The most commonly used CAI is acetazolamide which is a sulfonamide derivative with high protein bound and elimination by the kidney; oral administration ranged from 250 mg to 4000 mg; the most commonly prescribed dosage is 250-500 mg/day; taken orally, it is rapidly absorbed from the gastrointestinal tract; maximum plasma levels are obtained within two hours of oral administration. The total half-life is 8 hours but the real clinical effects is longer than half life time. Acetazolamide enter the cerebrospinal fluid and the placenta, and transfers into breast milk.[5]

The main clinical indications for acetazolamide in critical care medicine and emergency medicine are: (1) acute heart failure; (2) acute mountain sickness; (3) metabolic alkalosis; (4) idiopathic intracranial hypertension; (5) acute angle-closure glaucoma.

Acetazolamide is also used to treat epilepsy, periodic paralysis, Meniere's disease, gastric and duodenal ulcers, osteoporosis, sleep disordered breathing, primary hypoventilation syndromes and when urine alkalinization is needed.[6] In addition, acetazolamide and other CAIs have an emerging role in fields such as neuropathic pain, cerebral ischemia, rheumatoid arthritis, oxidative stress and Alzheimer's disease and cancer.[7,8]

The scope of this review is to describe the most common uses and indications of acetazolamide in critical care medicine and emergency medicine (Figure 1).

METHODS

We conducted a narrative review on the use of acetazolamide in the main contexts in which this drug can be useful in emergency situations for patients with potential critical issues. For the timeline January 1999 – January 2024, a search was conducted on the main scientific platforms: Pubmed, Scopus, Medline, Embase, Google scholar. We used MeSH terms, matching "acetazolamide or carbonic anhydrase inhibitors" separately with each MeSH term: "heart failure", "edema, cardiac", "altitude sickness", "alkalosis", "ventilator weaning", "pseudotumor cerebri", "glaucoma, angle-closure", "Meniere's disease", "epilepsy", "cerebrospinal fluid leak", "contrast media/toxicity" "methotrexate/toxicity". We then selected the resources of greatest relevance for the use of acetazolamide in critical care and emergency medicine.

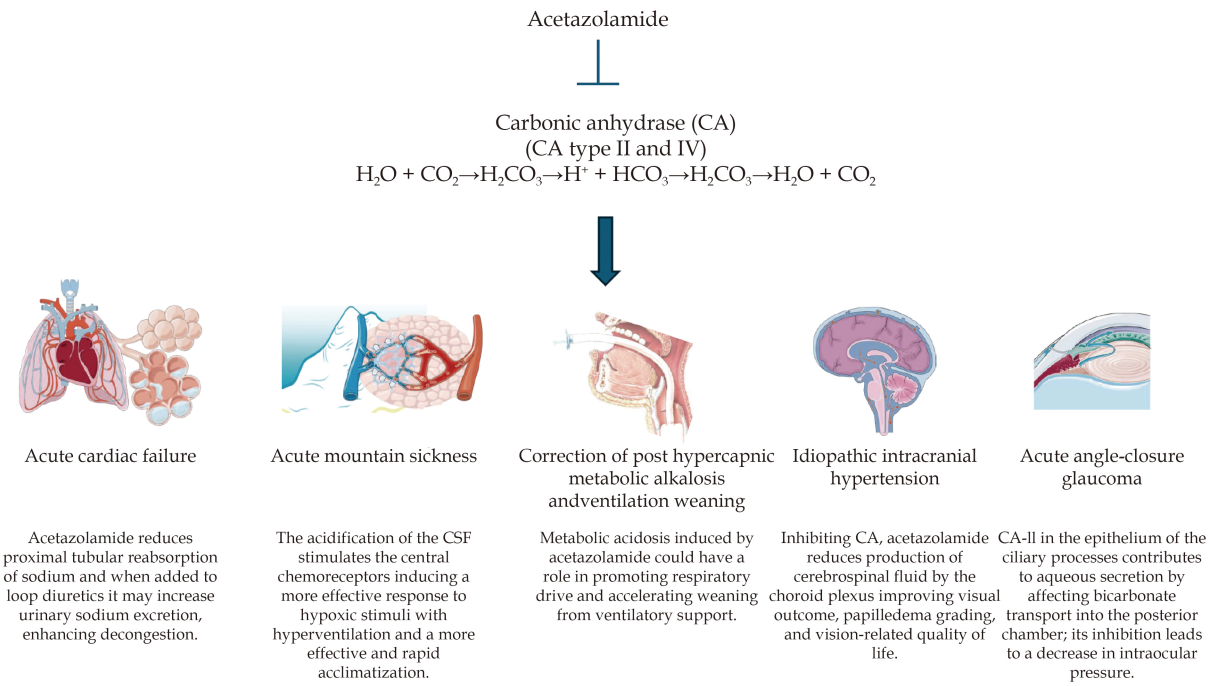

Figure 1 Clinical pharmacology of acetazolamide.

RESULTS

The most common emergency situations in which a critically ill patient could benefit from acetazolamide therapy are acute heart failure, acute mountain sickness, metabolic alkalosis (especially post hypercapnic metabolic alkalosis in ventilator weaning), idiopathic intracranial hypertension (also known as pseudotumor cerebri) and acute angle-closure glaucoma. Most common indications and dosage of acetazolamide in emergency medicine and critical care medicine are reported in Table 1.

Principal Clinical Uses

Acute cardiac failure

Loop diuretics are the cornerstone of acute heart failure therapy. However, stepped pharmacologic-therapy algorithms are emerging as effective strategies to achieve better decongestion.[9] Acetazolamide has been used for years as an anti-edema drug. Indeed, acetazolamide reduces proximal tubular reabsorption of sodium and when added to loop diuretics it may increase urinary sodium excretion, enhancing decongestion. Nonetheless, only a few trials have studied the use of acetazolamide in heart failure (Table 2).[10]

The role of acetazolamide in improving symptoms of fluid overload was studied in a 2022 trial. The Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial demonstrated that the addition of acetazolamide to standardized intravenous loop-diuretic therapy may improve the incidence of successful decongestion among patients with acute decompensated heart failure. The primary end point was successful decongestion itself, defined by a congestion score that took into account the presence of pleural effusion, ascites and edema at 3 days after randomization. Patients undergoing treatment with intravenous bolus of acetazolamide (500 mg once daily) in addition to loop diuretic at double the oral maintenance dose achieved the primary outcome in 42.2% of cases *vs.* 30.5% in the placebo group. Furthermore, in this trial acetazolamide demonstrated a good safety profile; less treatment benefit was reported among patients receiving a higher oral maintenance dose of loop-diuretics. Although the acetazolamide group had a shorter hospitalization, death from any cause or rehospitalization for heart failure during 3 months of follow-up were similar in the two groups.[11]

In the ADVOR trial, more than 80% of patients had chronic kidney disease; thus, a pre-specified analysis of

Table 1 Most common indications and dosage of acetazolamide in emergency medicine and critical care medicine.

Indication	Dosage
Acute heart failure	500 mg once daily
Acute mountain sickness prevention	125–250 mg twice daily
Acute mountain sickness treatment	250 mg twice daily
Metabolic alkalosis complicating respiratory failure	500 mg daily up to 250-500 mg every 6 to 8 h
Idiopathic intracranial hypertension	1000 mg to 2000 mg, up to 4000 mg daily
Acute angle-closure glaucoma	500 mg daily

Table 2 Trials of acetazolamide in heart failure.

	ADVOR trial	DIURESIS-CHF trial	Acetazolamide as Add-on Diuretic Therapy
Publication year and Author	Mullens, *et al.*, 2022[11]	Verbrugge *et al.*, 2019[14]	Imiela T & Budaj A., 2017[15]
Sample size	519 (256 acetazolamide and 259 placebo)	34 (16 loop diuretic alone and 18 loop diuretic with acetazolamide	20 (10 acetazolamide and 10 no treatment as add-on diuretic therapy)
Acetazolamide dosage	500 mg after randomization and during the next 2 days or until complete decongestion	250–500 mg daily in addition to low-dose loop diuretics	< 75 kg, 250 mg; 75–100 kg, 375 mg; > 100 kg, 500 mg for four days
Primary outcomes	Successful decongestion	Natriuresis	Diuresis, natriuresis, fluid balance, and symptoms
Main results	Greater incidence of successful decongestion in acetazolamide group	Loop diuretic efficiency increases with the addition of acetazolamide	The addition of acetazolamide produced an additional diuretic effect and alleviation of dyspnea.

the trial showed that the positive effects of acetazolamide on decongestion were consistent across the entire renal function spectrum; moreover, effects on diuresis were better in patients with a worse baseline renal function. Patients treated with acetazolamide had a higher risk of worsening renal function, but this was not associated with worse outcome if decongestion was achieved.[12] Of note, SGLT2i-treated patients were excluded in ADVOR trial.

Another sub analysis of the ADVOR trial sought to investigate the effect of acetazolamide on natriuresis; the Authors found that acetazolamide was the strongest independent predictor of a greater natriuretic response, which was associated with faster and more effective decongestion and with a lower risk of death or HF readmissions.[13]

In addition to the ADVOR trial, two other small trials have studied the use of acetazolamide in patients with heart failure. In the DIURESIS-CHF trial, patients were randomized to a loop diuretic alone or a loop diuretic with acetazolamide; one of the main conclusions of this trial was that loop diuretic efficiency increased with the addition of acetazolamide.[14] In a trial conducted in Poland, the addition of acetazolamide to other diuretics produced an additional diuretic effect with improvement of symptoms in patients with chronic heart failure exacerbation.[15] However, these trials enrolled only 34 and 20 patients respectively.

Acute mountain sickness

High-altitude illnesses (HAI) are a group of syndromes that may occur in unacclimatized individuals ascending to an altitude of over 2000/2500 m. Among these, acute mountain sickness (AMS) and high altitude cerebral edema (HACE) appear to be a continuum of severity, sharing the same pathogenetic process.[16] AMS is the most frequent form of HAI, headache being the almost always present symptom; other non-specific symptoms, such as nausea, dizziness, fatigue, insomnia may also be reported. Several mechanisms appear to be involved in the pathogenesis: hypoxemia implies an increase in cerebral blood flow and vascular permeability, with the consequent formation of edema, for which a physiological predisposition also seems to be implicated.[17]

The role of acetazolamide is better clarified in the prevention rather than in the treatment of acute mountain sickness. In fact, regarding the prevention of AMS, acetazolamide is the agent of choice: following inhibition of carbonic anhydrase, acetazolamide induces metabolic acidosis with a reduction of bicarbonate in the cerebrospinal fluid; the acidification of the CSF stimulates the central chemoreceptors inducing a more effective response to hypoxic stimuli with hyperventilation. This would result in a more effective and rapid acclimatisation.

Several clinical trials have been carried out on the topic; a 2021 systematic review and meta-analysis concluded that acetazolamide significantly reduces the incidence of AMS and severe AMS compared to placebo; in this meta-analysis, increasing doses of acetazolamide did not demonstrate significant impacts on outcomes; therefore, the lower dosage (125 mg twice daily) would represent the minimum effective dose.[18] The dosage of 62.5 twice daily mg has also been studied, with mixed conclusions which currently cannot recommend its use.[19,20] Anyway, prophylactic therapy is generally started the night before the ascent and continued until the descent begins or for 2–3 days of staying at the target altitude. The indication to administrate prophylactic therapy for high altitude-related pathologies is based on the target altitude to be reached, the speed of the ascent and the medical history of previous episodes of AMS.[21]

As regards the treatment of AMS, the main initiatives to be undertaken are interrupting the ascent and starting the descent;[22] however, in more severe cases, acetazolamide may play a role; the dosage indicated in this case is 250 mg twice daily.[21,23,24] However, the evidence supporting the clinical use of acetazolamide in this setting is rather scarce.[25]

Correction of post hypercapnic metabolic alkalosis and ventilation weaning

Metabolic alkalosis is a frequent disorder in critically ill patients: it is observed in patients with hypokalemia (by a shift of hydrogen ions into the cells), loss of gastric secretions (vomiting or nasogastric suction), diarrhea and urinary hydrogen ion losses.[26]

In particular, patients with chronic obstructive pulmonary disease (COPD) and chronic respiratory acidosis are characterized by an increase in renal reabsorption of bicarbonate, in order to compensate for the acidic pH caused by the respiratory disorder. When a patient with an exacerbation of COPD is treated with mechanical ventilation, the blood pressure of carbon dioxide is reduced, while the bicarbonate level may remain elevated, resulting in a condition known as post hypercapnic

metabolic alkalosis; the alkalemia that thus arises could suppress respiratory drive, resulting in a further worsening of ventilation with a delayed weaning from artificial ventilation.[27]

In fact, in patients with COPD subjected to mechanical ventilation, it is common to face a mixed disturbance of the acid-base balance, with the coexistence of respiratory acidosis and metabolic alkalosis. In this context, protective ventilation and permissive hypercapnia protocols may further trigger a state of alkalosis. Acetazolamide inhibits the renal reabsorption of bicarbonates and leads to alkalinization of the urine; it was therefore hypothesized that the state of metabolic acidosis induced by acetazolamide could have a role in promoting respiratory drive and accelerating weaning from ventilatory support.[28–30]

A recent systematic review and meta-analysis of randomized controlled trials analyzed the role of acetazolamide in patients with chronic hypercapnia and acute respiratory failure; three studies comparing acetazolamide vs placebo were included; in these studies, acetazolamide dosage varied from 250 mg two or three times a day to 500-1000 mg twice daily. The meta-analysis did not show benefits in terms of mortality, need for initiation of ventilatory support, duration of ventilatory support, duration of ventilatory weaning, length of intensive care admission or length of hospitalization. Nonetheless, the Authors stated that certainty of evidence was low and larger trials are required.[31] Evidence is even more limited regarding the role of acetazolamide in patients who develop post hypercapnic metabolic alkalosis when subjected to non-invasive ventilation.[32]

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension is a condition characterized by increased intracranial pressure in the absence of other causes of increased intracranial pressure highlighted by neuroimaging; obese young women of childbearing age are primarily affected. Idiopathic intracranial hypertension manifests mainly with headache and papilledema and can also lead to permanent blindness; in fact, it is essential to identify patients at greater risk of permanent ophthalmological damage early.[33] Transient visual obscurations, diplopia due to sixth nerve palsy, loss in visual field or loss of visual acuity may occur. Papilledema is almost always present.

The pathogenesis is poorly understood, however, it seems that the mechanisms of dynamic regulation of the cerebrospinal fluid, such as overproduction and outflow obstruction are implicated. In addition, increased venous pressure in the venous sinuses should be implicated.[33]

Patients with severe papilledema and those with vision loss at presentation appear to be at greatest risk for severe and permanent visual disturbances.[34] A minority of patients may present with a fulminant form of idiopathic intracranial hypertension, with early, severe, and rapidly worsening visual loss.[35]

Acetazolamide represents the cornerstone of pharmacological therapy for idiopathic intracranial hypertension.[36] Inhibiting carbonic anhydrase, acetazolamide reduces production of cerebrospinal fluid by the choroid plexus. The multicenter, double-blind, randomized, controlled clinical trial "Idiopathic Intracranial Hypertension Treatment Trial" showed that acetazolamide (at the maximally tolerated dosage, up to 4000 mg a day) improves visual outcome, papilledema grading, and vision-related quality of life. In this trial, however, only patients with mild visual loss were enrolled.[37] As regards fulminant idiopathic intracranial hypertension (of greatest interest for emergency medicine), on the basis of the results obtained in the less severe forms, expert opinions suggest administering acetazolamide 2000 to 4000 mg a day while awaiting surgical intervention, even if patients of a case series of fulminant idiopathic intracranial hypertension were treated with acetazolamide at a dosage of 1000 to 2000 mg/day.[35,38]

Acute angle-closure glaucoma

Acute angle-closure glaucoma is an ophthalmological emergency characterized by an increase in intraocular pressure; the increase in intraocular pressure is due to the outflow obstruction of aqueous humor. The aqueous humor is produced by the ciliary body, passes through the pupil and exits the eye draining through the trabecular meshwork. In case of obstruction of this mechanism, the increase in intraocular pressure can cause damage to the optic nerve with possible serious consequences, up to blindness.[39]

Patients with a presentation suggestive of acute angle-closure glaucoma should be referred for urgent ophthalmological evaluation;[40,41] however, it is essential to promptly start medical therapy: in addition to the administration of pressure-lowering eye drops, systemically administered acetazolamide (either orally or intravenously) also plays a role in this field. In fact, carbonic

anhydrase II localized in the epithelium of the ciliary processes contributes to aqueous secretion by affecting bicarbonate transport into the posterior chamber; the inhibition of this enzyme therefore leads to a decrease in intraocular pressure. The dose of acetazolamide in emergent cases of high intra-ocular pressure is 500 mg, keeping in mind that intravenous administration has a more rapid onset of action.[42,43] However, it should be noted that no randomized controlled clinical trials on the medical therapy of acute angle-closure glaucoma have been conducted so far and the indication for the use of acetazolamide is based on clinical experience.

It should be noted that sulfa drugs, in particular topiramate, are among the drugs capable of causing drug-induced angle-closure glaucoma; this is believed to happen by inducing ciliary body edema, which causes relaxation of the zonules and thickening of the lens; paradoxically, anecdotal cases of glaucoma induced by acetazolamide are reported.[44,45] Nonetheless, acetazolamide remains one of the only systemic pharmacological alternatives in patients with acute angle-closure glaucoma and should probably be avoided only in patients with angle-closure due to topiramate therapy.

Other Uses of Acetazolamide

Meniere's disease

Dizziness is a common presenting symptom in the emergency department, accounting for 4% of all visits.[46] The differential diagnosis includes Meniere's disease, characterized by vertigo, tinnitus, and hearing loss. Diuretics have been used in Meniere's disease, since they may have a role in reducing hydrops of the endolymph, that is believed to be the main pathogenic mechanism. However, in clinical practice diuretics have a limited role in acute attacks, although some Authors in the past have indicated a tapering regimen starting from 1250 mg on the first day, with maintenance regimens of 250-500 mg daily. Anyway, no randomized controlled trials on the use of acetazolamide in this field is available.[47]

Epilepsy

Neurons, glial cells, and choroid plexus cells, express carbonic anhydrases where they regulate cerebrospinal fluid production, metabolism and pH.[48] Acetazolamide, by inhibiting carbonic anhydrase, induces pH reduction with effects on acid - sensing ion channels essential for its anti-epileptic properties. Changes in extracellular pH in the brain can regulate neuronal excitability: in particular, H^+ inhibits NMDA receptors and voltage-gated calcium channels, so that a reduction or increase in extracellular pH can inhibit or increase neuronal excitability, respectively.[49] A magnetic resonance spectroscopy study in humans showed that in the interictal state, the brain region involved in the seizure was more alkaline than the contralateral side.[50] Acetazolamide is rarely prescribed and there is weak evidence with no randomized controlled trials on its use in epilepsy. Shukralla, *et al*.[51] conducted a review of twelve observational studies on the use of acetazolamide in the treatment of epilepsy; out of a total of 767 patients, 48% had more than a 50% reduction in seizure frequency and a total of 122 out of 607 patients were seizure-free, with an average seizure-free rate of 20%. As the Authors pointed out, however, the studies were extremely heterogeneous especially about the age of the patients, type of epilepsy, acetazolamide dosage and concomitant anti-seizure medications, and none of the studies included randomized patients selection. Further studies are required to determine which patients would best benefit from acetazolamide.

Cerebrospinal fluid leak

Cerebrospinal fluid (CSF) leaks consist of the passage of cerebrospinal fluid, through the dural membrane at one or multiple sites, connecting the subarachnoid space with the epidural space and sometimes the skin. CSF leaks may occur spontaneously or as a result of lumbar puncture or spinal anesthesia, traumatic skull base injuries or iatrogenic penetration during neurosurgical procedures.[52] Spontaneous CSF leaks occur as a result of direct invasion or erosion of bone due to CSF pulsations in the presence of a chronic increase in intracranial pressure and in about 70% of cases is related to idiopathic intracranial hypertension. Other cause of spontaneous CSF leaks includes intracranial tumors, osteophyte or calcified disk herniation, meningeal diverticula, CSF–venous fistulas. Cranial CSF leaks may present with watery rhinorrhea or otorrhea, headaches, tinnitus, or meningitis. Spinal CSF leaks typically present with postural headaches and/or other symptoms from intracranial hypotension such as vestibulocochlear symptoms, nausea and emesis, disequilibrium, posterior neck pain, cognitive impairment, fatigue.[53–56] Management and treatment of CSF leaks by surgery or conservative measures depends on the underlying causes, severity of the symptoms, location and size of the tear. Since acetazolamide reduces

CSF production by inhibiting carbonic anhydrase in the choroid plexus,[57] it has also been used as a medical management of CSF leakage to reduce CSF production and intracranial pressure after surgical repair of spontaneous CSF leaks, or in some cases as an alternative to surgery[58] enabling the resolution of dural tear. In a retrospective study that included 39 patients with established CSF rhinorrhea, 19 were cases of atraumatic CSF leaks. In all cases of spontaneous post-operative CSF leaks, a tablet of acetazolamide was administered at a dosage of 500 mg twice daily for the first week, followed by a lower dosage of 250 mg twice daily for the second week, registering a 100% success rate in closing the primary defect in spontaneous CSF leak with control of intracranial pressure in the immediate post-operative period. However, one patient experienced a recurrence at a new site after a period of 8 months.[59] An OPEL label randomised controlled trial assessed the role of early acetazolamide administration in reducing the risk of CSF leakage in 57 patients with skull-base fractures with presence of rhinorrhea or otorrhea, pneumatocele and/or evidence of severe skull-base fracture on imaging. In 28 patients randomly assigned to the experimental group, 25 mg/kg per day of acetazolamide therapy was started within the first 48 h after admission, whereas in the control group it was administered after 48 h. CSF leakage resolved in all of the patients in the experimental group less than 14 days after the first day of admission, while 6 out of 27 patients (22%) in control group continued to exhibit CSF leakage after 14 days of admission. No significant difference was found in the duration of hospitalization, frequency of meningitis and number of patients who needed surgical intervention for the termination of CSF leak.[60]

These studies suggest the use of acetazolamide for conservative management of post-operative CSF leak and intracranial hypertension and for preventing CSF leak after severe and symptomatic skull-base fracture. Nonetheless, the small number of cases underlines the need to recruit a larger patient population to make data more meaningful.

Contrast-induced Nephropathy

Contrast-induced nephropathy (CIN) is the sudden deterioration of renal function related to intravenous or intra-arterial contrast agent administration. The mechanisms underlying CIN are not yet fully understood. Two major theories are renal vasoconstriction resulting in medullary hypoxemia and the direct cytotoxic effects of contrast on tubular epithelial cells.[61] Acetazolamide has been proposed to be beneficial in the prevention of CIN by inducing renal vasodilation and increasing renal blood flow. A randomized double-blind trial evaluated the effectiveness of the preventive use of bicarbonate infusion versus 0.9% sodium chloride injection alone or 0.9% sodium chloride injection with acetazolamide in 288 patients undergoing coronary angiography or percutaneous coronary intervention. In the 0.9% sodium chloride injection and acetazolamide group, oral acetazolamide 250 mg was given 2 hours before and 6 hours after contrast administration. The risk of CIN was significantly higher in the 0.9% sodium chloride injection group compared to bicarbonate infusion or 0.9% sodium chloride injection plus acetazolamide group. Even though acetazolamide may enhance the protective effects of 0.9% sodium chloride injection, no benefit over bicarbonate infusion was found for the prevention of CIN.[62] Another study evaluated 96 children with chronic renal insufficiency, randomly assigned to receive either a 154 mEq/L infusion of sodium bicarbonate (HCO^{-}_{3}) (n = 46) or 0.9% sodium chloride plus oral acetazolamide (n = 50). The mean serum creatinine concentration 48 hours after receiving contrast was lower in the group treated with acetazolamide plus 0.9% sodium chloride injection than in the group treated with bicarbonate.[63] These studies suggest that the use of acetazolamide in combination with 0.9% sodium chloride infusion may be considered for patients at risk of CIN although stronger evidence is needed to support the beneficial effects.

Urine alkalinization

Acetazolamide alkalinizes urine by the inhibition of tubular-cell carbonic anhydrase, leading to a lack of reabsorption of tubular bicarbonate through the prevention of hydrogen ion synthesis in tubular cells.[64] This inhibitor has occasionally been added to sodium bicarbonate regimens along with hyperhydration to assist in urinary alkalinization during high dose methotrexate (MTX) administration as in treatment protocols of osteosarcoma, acute lymphoblastic leukemia, primary central nervous system lymphoma, and Burkitt's lymphoma.[65–67] Indeed, increasing the urine pH from 6 to 7 increases the solubility of methotrexate five to eightfold,[68–69] thus preventing renal toxicity secondary to precipitation of methotrexate in the renal tubule and crystalluria. Truong HH *et al.* conducted a systematic review

and meta-analysis including six observational study in order to provide a summary of existing evidence on the efficacy and safety of acetazolamide in the prevention and treatment of renal toxicity associated with high-dose MTX compared to standard therapy.[70] The study revealed that acetazolamide, co-administered with other alkalization treatments (sodium bicarbonate, sodium chloride, etc) or alone, was not inferior in preventing the toxicities related to high-dose MTX, including acute kidney injury, hepatotoxicity, and delayed methotrexate clearance although there was great heterogeneity among studies such as underlying diseases, malignant stages, doses, and the measurements of adverse events.

SIDE EFFECTS AND SAFETY CONSIDERATIONS

According to a recent meta-analysis, the most frequent side effect of acetazolamide is paresthesia; other frequent side effects are dysgeusia, polyuria, fatigue, nausea and dizziness; these side effects appear to be dose-dependent.[71] Acetazolamide is an overall safe drug; serious side effects are rare and can be avoided by carefully selecting the patients to be treated: hypokalemia appears to be limited to patients treated with other drugs that induce hypokalemia.[1,71] Acetazolamide has also been associated with metabolic acidosis: patients with other predisposing factors to acidosis should be closely monitored when treated with acetazolamide.[72,73] Acetazolamide is contraindicated in cases of cirrhosis or significant alteration of liver function; furthermore, the use of acetazolamide should be avoided in case of adrenal insufficiency.[25] Although the use of acetazolamide has traditionally been discouraged in cases of renal failure, the recent findings connected to the ADVOR trial could open up new scenarios in patients with renal failure and acute heart failure.[11,12] Since one of the most established indications for the use of acetazolamide is the prevention of HAI and in particular AMS, the concern that it may have a negative effect on maximum exercise capacity and respiratory muscle work should be considered.[74,75] However, the observed effects are poorly relevant from a practical point of view and, therefore, these considerations should not be viewed as a reason to avoid acetazolamide in AMS prevention or treatment.[75]

A common concern with the use of acetazolamide is cross-reactivity in patients with allergy to sulfonamides and other sulfonamide derivatives, usually sulfonamide antibiotics. Nevertheless, while antimicrobial sulfonamides are associated with Stevens-Johnson syndrome and toxic epidermal necrolysis, cutaneous adverse reactions due to acetazolamide are rare.[76] Moreover, a large retrospective cohort study stated that, even though an association between hypersensitivity after the receipt of sulfonamide antibiotics and a subsequent allergic reaction after the receipt of a sulfonamide nonantibiotic exists, this association is probably due to a predisposition to allergic reactions rather than to cross-reactivity with sulfonamide-based drugs.[77] In fact, current evidence does not support the actual existence of a cross-reactivity between sulfonamide antimicrobials and sulfonamide non-antimicrobials.[78,79] Nonetheless, a careful risk-benefit assessment is recommended before administering acetazolamide to a patient with a history of a sulfa allergy.[79]

CONCLUSIONS

Acetazolamide is nowadays a little used drug; however, its safety profile, low cost and usefulness in various clinical contexts could lead to a rediscovery. In acute heart failure the recommended dosage is 500 mg once daily in combination loop diuretics; for AMS prevention, the recommended dosage varies from 125 twice daily to 250 mg twice daily; for AMS treatment, 250 mg twice daily. For the treatment of alkalosis complicating respiratory failure in patients in intensive care units, the usual dosage vary from 500 mg daily to 250 or 500 mg every 6 to 8 h. In idiopathic intracranial hypertension, daily doses of 1000 mg to 2000 mg up to 4000 mg are used. In acute angle closure glaucoma, a dose of 500 mg of acetazolamide is generally administered. Although the intravenous injection form is not available in some Countries, emergency physicians and critical care physicians must be aware of the potential uses of acetazolamide in these fields, carefully selecting patients who could benefit from it, according to the rather limited high quality evidence.

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