CHAPTER

21

Diuretics

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CARBONIC ANHYDRASE INHIBITORS [*SEDA-15, 643; SEDA-34, 339; SEDA-35, 387, SEDA-36, 289*]

Acetazolamide

Eyes

Therapeutic use of acetazolamide post eye surgery may cause acetazolamide-induced bilateral choroidal effusion. A case report describing this effect in a 28-year-old patient was recently published discussing the uneventful surgery for hyperopia. However, 24 hours after surgery, the patient presented with bilateral shallow anterior chamber in both eyes. Ultrasound showed choroidal thickening in both eyes, which was consistent with choroidal effusion syndrome. When the drug was stopped, the condition improved slowly and resolved completely within 1 week [1A].

Dermatology

Cutaneous adverse drug reactions (CADR) to oral acetazolamide have been previously reported in the literature; however, skin tests have rarely been studied. Jachiet and colleagues sought to retrospectively evaluate acetalozamide CADR skin tests in nine patients and 12 controls. According to the authors, "seven patients developed maculopapular exanthema and four had acute generalized exanthematous pustulosis and patch tests were positive for 8/9 patients." This small study demonstrated the importance of skin tests in patients presenting with new onset dermatological reactions after initiation of oral acetazolamide therapy [2A]. Another similar reaction was reported in a second study of acute generalized exanthematous pustulosis due to oral acetazolamide administration. The reaction was initially negative on patch testing and confirmed by delayed-reading intradermal testing [3A].

Respiratory

Shock and transient non-cardiogenic pulmonary edema was identified in one patient after receiving a single oral dose of acetazolamide after eye surgery [4A].

LOOP DIURETICS [*SEDA-15, 567, 1454; SEDA-34, 342; SEDA- 35, 390; SEDA-36, 290*]

Azosemide

Urinary System

A single center study of 11 patients with type 2 diabetic kidney disease (DKD) and diuretic-resistant edema sought to evaluate the safety and efficacy of thiazide diuretic, hydrochlorothiazide (HCTZ) in addition to loop diuretics (azosemide or furosemide) and examine the clinical parameters of blood pressure (BP) control, proteinuria, and eGFR before and after addition of HCTZ. Each of the 11 patients had an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 and were suffering from severe edema even with loop diuretics. Patients were receiving either azosemide (60–120 mg/day) or furosemide (80 mg/day). In addition, patients were receiving a 13.6 ± 3.8 mg/day dose of HCTZ. After the addition of HCTZ therapy, systolic blood pressure (SBP) and diastolic blood pressures (DBP), as well as proteinuria significantly decreased (SBP: at 12 months, $p < 0.01$, DBP: at 12 months, $p < 0.05$, proteinuria: at 12 months, $p < 0.01$). The annual change in eGFR was not significantly different before and after HCTZ therapy. These findings suggest that the combination of HCTZ and loop diuretics (specifically azosemide and furosemide) may improve SBP and

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DBP levels and decreases proteinuria even in advanced stage type 2 DKD patients with severe edema in whom previously HCTZ was thought to be less beneficial [5c].

Bumetanide

Urinary System

A retrospective single center study which analyzed 242 patient records with acute heart failure who received either continuous infusion of bumetanide or continuous infusion of furosemide alone or in combination with metolazone sought to evaluate the difference in these three regimens based on outcomes of urine output (UO) and incidence of worsening renal function. Compared to baseline, all regimens increased mean hourly urine output ($p < 0.0001$ for all). Incidence of worsening renal function was not different between regimens. The incidence of hyponatremia was higher with the combination therapy and bumetanide group versus furosemide alone [6c].

Ethacrynic Acid

Ethacrynic acid has been used in clinical practice for several decades, particularly in patients who require loop diuretics but have a true sulfa allergy as all other loop diuretics contain a sulfa moiety. This is currently the only sulfonamide-free loop diuretic. However, this agent is not a very potent diuretic and should only be reserved for those patients who cannot tolerate or have failed other diuretic therapies. Ethacrynic acid is also rarely used because of its increased incidence of ototoxicity as compared to the other loop diuretics. Amongst other expected diuretic side effects, this agent is known to cause: skin rash, Henoch–Schönlein purpura (IgA vasculitis), hematuria, agranulocytosis, severe neutropenia, thrombocytopenia, and vertigo [7S].

Electrolyte

A retrospective-cross-sectional study evaluated children (<18 years of age) who received ethacrynic acid as a continuous infusion in order to determined the mean/median effective dose as well as efficacy and safety markers. No significant differences were noted with magnesium and potassium levels. Five out of nine children (55%) developed metabolic alkalosis [8c].

Pharmacodynamics

The aim of this prospective study was to evaluate the effect of several cardiovascular agents (including ACE inhibitors, ARB's, HCTZ and ethacrynic acid) on the anticonvulsant activity of levetiracetam (LEV) in mice. The combinations of these agents with LEV were tested for adverse effects. The study found that ethacrynic acid at doses of 100 mg/kg did not affect the anticonvulsant activity of levetiracetam [9E].

Furosemide

Thrombocytopenia

Thrombocytopenia is a rare but serious concern with furosemide use because this agent is typically used on a chronic basis in the heart failure patient population.

- This is a report of an 84-year-old male with chronic symptomatic thrombocytopenia as a probable case of drug-induced side effect from long standing furosemide use. A dose-dependent change in platelet count was observed in association with the furosemide dose. The platelet count increased on discontinuation of furosemide and beginning of torsemide. Several months after discontinuation of furosemide, his platelet count increased to a 9-year high of $206 \times 10^3/\text{mm}^3$ from a low of $36 \times 10^3/\text{mm}^3$ while receiving furosemide therapy. Based on these observations, and other prior reports, clinicians should consider furosemide as a potential cause of thrombocytopenia [10A].

Urinary System

It is common knowledge among practitioner who treats patients with loop diuretics that renal function can become compromised. In this study by Triposkiadis and colleagues, the investigators sought to evaluate the effect of high-dose furosemide (20 mg/hour) in comparison to low-dose furosemide (5 mg/hour) and low-dose dopamine ($5\ \mu g\ kg^{-1}min^{-1}$) or low-dose furosemide alone (5 mg/hour) in 161 patients presenting with acute decompensated heart failure (ADHF). Amongst several outcomes, the authors wanted to evaluate dyspnea relief (based on Borg index) and renal function based on serum creatinine (Scr) in each group. Worsening renal function was higher in the high-dose furosemide arm than in low-dose furosemide plus low-dose dopamine arm and low-dose furosemide groups at day 1, respectively (24% vs. 11% vs. 7%, $p < 0.0001$) but not at Scr peak (44% vs. 38% vs. 29%, $p = 0.27$). No significant differences were observed in dyspnea relief and no other significant differences in adverse events were noted [11C].

Another study looked at similar outcomes and wanted to evaluate the safety and efficacy of continuous infusion versus bolus injection of intravenous loop diuretics for the treatment of acute decompensated heart failure by performing a systematic review and meta-analysis of available randomized controlled trials. Ten randomized controlled trials with over 500 patients were identified. Continuous infusion of diuretics were associated with a significantly greater weight loss (weighted mean difference, 0.78; 95% confidence interval, 0.03–1.54) compared

with bolus administration. Meta-analysis of the existing limited studies did not confirm any significant differences in the safety and efficacy with continuous administration of loop diuretic, compared with bolus injection in this patient population [12R].

Electrolytes

The EIDOS and DoTS descriptions of electrolyte disturbances due to loop diuretics, thiazide and thiazide-like diuretics have been described previously in [SEDA-35, 389].

Torsemide

Contrast-Induced Acute Kidney Injury

A review article on the use of torsemide for possible prevention of contrast-induced acute kidney injury (CI-AKI) was recently published. The authors speculated that based on observations and experiments of previous trials that RAAS (renin–angiotensin–aldosterone system) is potentially responsible for the development of CI-AKI through abnormalities of renal perfusion and other mechanisms and that torsemide could inhibit RAAS through its antialdosteronergic and diuretic functions. This review article provides some insight into the use of torsemide as an efficient, feasible and cost-effective strategy for the prevention of CI-AKI in combination with adequate hydration [13H].

THIAZIDE AND THIAZIDE-LIKE DIURETICS [*SEDA-15*, *3375*; *SEDA-34*, *340*; *SEDA-35*, *388*; *SEDA-36*, *292*]

Chlorothiazide

Metabolic

In a single center retrospective review of 82 patients hospitalized for heart failure, the authors sought to evaluate the safety and efficacy of oral hydrochlorothiazide (HCTZ) or intravenous chlorothiazide added to intravenous loop diuretic therapy (furosemide at total daily doses of >160 mg). After treatment, 24-hour urine output increased in both groups. Hypokalemia occurred frequently in both groups: 71.4% and 83.3% in the oral hydrochlorothiazide and intravenous chlorothiazide groups, respectively but was not statistically significantly different ($p = 0.21$) [14c]. This study suggests that both diuretic strategies are comparable but cost is a great consideration when making a decision regarding this type of therapy. Intravenous chlorothiazide costs over 50 times more than po hydrochlorothiazide in most countries.

Chlorthalidone

Hemodynamics

A retrospective self-controlled study of 40 patients who received HCTZ or chlorthalidone for blood pressure management evaluated the "within-patient clinic blood pressure readings, serum electrolyte levels, and renal function markers before and after a medication change from HCTZ to chlorthalidone." Both mean systolic and diastolic blood pressures showed statistically and clinically significant reductions after the medication change. A statistically significant decrease in sodium (−1.1 mmol/L [95% CI, 0.4–1.9], $p = 0.003$) and an increase in serum creatinine (0.06 mg/dL [95% CI, −0.09 to −0.02], $p = 0.002$) was observed after the patients were changed from HCTZ to chlorthalidone. However, it is up to the practitioner to decipher if these changed are deemed clinically significant [15c].

Hydrochlorothiazide

Electrolyte Balance—Hyponatremia

Hydrochlorothiazide (HCTZ) is frequently recommended as a first line antihypertensive agent. Some of the commonly known side effects of this agent are hypokalaemia and hyponatremia. A study involving 202 elderly patients (>65 years of age) evaluated the use of HCTZ to determine the frequency of hyponatremia as a potential side effect of this therapy. The reported incidence of hyponatremia was 24.87% (49 patients) in the whole group, and patients over the age of 75 were more likely to develop hyponatremia [16c].

Another similar study wanted to evaluate the rates of hyponatremia with the use of HCTZ versus chlorthalidone. The selected patients were over 18 years of age with a serum sodium levels of <130 mmol/L or hospitalized due to hyponatremic symptoms. Hyponatremia was more common with chlorthalidone than with hydrochlorothiazide at equal dose per day: adjusted odds ratio was 2.09 (95% confidence interval [CI], 1.13–3.88) for 12.5 mg/day and 1.72 (95% CI, 1.15–2.57) for 25 mg/day [17c].

Electrolyte Balance—Hypercalcemia

Due to its pharmacological mechanism of action, HCTZ has an effective capability to decreases urinary calcium excretion causing hypercalcemia. In this study, the authors assessed the frequency of hypercalcemia in 328 black patients who were receiving HCTZ for blood pressure control. At 3 months of therapy, the patients had higher calcium levels (0.2 mg/dL, $p < .001$) than nonhydrochlorothiazide participants, but only one participant in the hydrochlorothiazide group had hypercalcemia. These findings, although statistically significant, were not deemed to be clinically significant by the authors [18C].

Pharmacogenomics

Hyperuricaemia is a commonly observed side effect secondary to treatment with HCTZ. The authors of this study sought to identify a novel single nucleotide polymorphisms (SNPs) associated with HCTZ-induced elevations in uric acid (UA) and hyperuricaemia. Suggestive SNPs were replicated in Caucasians and African Americans patients from a prior study who were treated with HCTZ add-on therapy. The results indicated that there are at least "five unique gene regions identified in African Americans (LUC7L2, ANKRD17/COX18, FTO, PADI4 and PARD3B), and one gene region identified in Caucasians (GRIN3A)." Increases in uric acid levels of up to 1.8 mg/dL were observed following HCTZ therapy in patients who were homozygous for the above identified risk alleles [19C]. This may be a clinical concern in patients with underlying hyperuricaemia or a history of gout.

Metabolic

In a meta-analysis of 10 randomized controlled clinical trials, the investigators evaluated the metabolic profile (fasting plasma glucose and serum potassium) of low-dose thiazide diuretics. The cumulative mean change of fasting plasma glucose was +0.20 mmol/L for the diuretic arm versus +0.12 mmol/L ($p < 0.01$) for the comparator arm. The cumulative mean change of serum potassium was −0.22 mmol/L for the diuretic arm versus +0.05 mmol/L ($p < 0.01$) for the comparator arm. The change in glucose levels does not appear to place patients at a clinically significant risk of hyperglycemia. However, the observed change in potassium levels may be clinically significant especially in patients with underlying cardiovascular disease in whom maintaining an adequate potassium level is crucial [20M].

Skin

One case report of a 32-year-old male describes a subepidermal blistering disorder called bullous pemphigoid induced by losartan-HCTZ which was prescribed for hypertensive therapy in this patient. The patient presented with the typical flu-like prodromal symptoms and a nonspecific urticarial dermatitis primarily around the neck, trunk and both upper and lower extremities. The patient was transferred to a burn center where he was treated with oral steroids and successfully underwent several debridements of his lesions [21A].

Indapamide

Eyes

A case report of a 39-year-old female presenting with sudden headaches and bilateral loss of distant vision potentially due to indapamide 1.5 mg tablets which was prescribed several days prior to presentation is addressed below. Neurological exams and radiographic scans were unremarkable. After discontinuation of the offending agent (indapamide), the patient slowly regained her eye sight in both eyes. This is the third case in the available literature which describes indapamide-induced transient myopia. Currently, this side effect is not mentioned in indapamides package insert [22A].

ALDOSTERONE RECEPTOR ANTAGONISTS

Eplerenone [*SEDA-15, 1227; SEDA-34, 344; SEDA-35, 391; SEDA-36, 293*]

Electrolyte Balance

The EMPHASIS-HF study sought to evaluate the safety and efficacy of eplerenone in patients who are at a high risk for worsening renal function or high risk of hyperkalemia while receiving treatment of eplerenone for heart failure. The baseline glomerular filtration rate (eGFR) 30–60 mL/min/1.73 m^2 and serum potassium <5.0 mmol/L. Patients at high risk of hyperkalemia or worsening renal function were defined as patients >75 years of age, history of diabetes, and eGFR <60 mL/min/1.73 m^2. The results indicated that in all high-risk subgroups, patients treated with eplerenone had an increased risk of potassium >5.5 mmol/L but not of potassium >6.0 mmol/L. Eplerenone was both efficacious and safe when carefully monitored [23C].

Drug–Drug Interactions

In May of 2013, safety labeling changes approved by the U.S. Food and Drug administration indicated that there is an increased risk of hyperkalemia when eplerenone is used with other agents which may increase potassium levels (such as ACE inhibitors and ARB's). The FDA put out a warning that close monitoring of serum potassium and renal function is highly recommended. This side effect increases in patients who have baseline impaired renal function and the elderly [24S].

Spironolactone [*SEDA-15, 3176; SEDA-34, 345; SEDA-35, 392; SEDA-36, 292*]

Urinary System

The effects of spironolactone were studied in the TOPCAT trial which evaluated mineralocorticoid-receptor antagonists and their effect on the improvement of prognosis in heart failure patients. In this trial, the authors enrolled 3445 patients with symptomatic heart failure who received either spironolactone (15–45 mg) or placebo in addition to optimal heart failure therapy. Of the

multiple components in the primary outcomes, the only one that proved to be statistically significant was the incidence of hospitalization rates which were decreased in the spironolactone arm versus the placebo arm ($p=0.04$). However, treatment with spironolactone was associated with increased serum creatinine and doubling of the rate of hyperkalemia. The authors concluded that with frequent monitoring, there was no significant difference in the incidence of serious adverse events [25C].

Gynecomastia

It is well known that gynecomastia is a potential side effect in patients being treated with spironolactone. In a small 12-week randomized, placebo-controlled trial of 82 dialysis patients with refractory hypertension this side effect was observed. Several adverse events led four patients to discontinue therapy with spironolactone. Gynecomastia was observed in one patient in the spironolactone arm who discontinued therapy. Two patients discontinued therapy due to hyperkalemia and one due to severe nausea [26C].

Gynecological Cancers

Investigators of the following study sought to evaluate the risk of gynecological and other cancers in a large Danish cohort population of female patient's ages >20-years old on spironolactone therapy. Based on a prescription drug registry, they were able to identify 2.3 million women who received spironolactone for at least 1 year of continuous therapy. Among these women, the risk of breast, uterus, ovary, and cervical cancers were generally increased about 10–30%. In the first year of drug exposure, incidences were increased, especially for ovarian cancers. With respect to breast, uterus, and cervical cancer, there was no evidence of increased risk with spironolactone use. Considering the nature of this study, it is difficult to decipher if the use of sprinolocatone alone lead to the increased risk of ovarian cancers or were there other underlying risk factors. However, prescribers need to be cognizant of this potentially dangerous side effect of spironolactone, especially in young patients who may be on this therapy for a prolonged period of time [27M].

OSMOTIC DIURETICS

Mannitol [*SEDA-15, 2203; SEDA-34, 346; SEDA-35, 393; SEDA-36, 294*]

Urinary System

In a retrospective study of 153 adult patients presenting with intracranial hemorrhage (ICH) receiving mannitol infusions, the investigators evaluated the impact of mannitol on the incidence of acute kidney injury (AKI) from the use of this agent. The overall incidence of AKI among the study participants was 10.5% ($n=16$). The incidence also seemed to correlate with the dose of mannitol (infusion rates $\geq$1.34 g/kg/day), patient age $\geq$70 years, diastolic blood pressure (DBP) $\geq$110 mmHg, and an established renal dysfunction before starting mannitol therapy were associated with development of AKI (GFR < 60 mL/min/1.73 m^2). Knowing these risk factors, it is important to weight the risk versus benefit when initiating this agent at higher doses [28c].

Respiratory System

Inhaled mannitol is approved to be used in the European Union as a mucolytic agent in adult patients with cystic fibrosis which can be a life-threatening genetic disease characterized by the accumulation of viscous secretions in the airways, making it extremely difficult for patients to adequately breathe. Several studies have evaluated this agent in its inhaled form for the use in cystic fibrosis patients. The clinical results were primarily positive however, inhaled mannitol increased the risk of bronchospasm and haemoptysis. The authors concluded that due to these adverse effects, it is probably best to avoid inhaled mannitol in patients with cystic fibrosis [29c]. Another similar trial was performed in patients with non-cystic fibrosis bronchiectasis and the use of inhaled dry powder mannitol. This study showed that there was no difference between inhaled mannitol and inhaled placebo when it came to reported side effects. Both placebo and mannitol were well tolerated and similar proportion of patients reported side effects at rates of 80.4% versus 82.0%, respectively [30C].

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