Safety and Tolerability of Acetazolamide in the Idiopathic Intracranial Hypertension Treatment Trial

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Objective: To examine the tolerability and adverse events reported in the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT).

Methods: Randomized, double-masked, placebo-controlled clinical trial. Trial participants (n = 165) with mild visual loss concurrently receiving low-sodium weight-reduction diet plus the maximally tolerated dosage of acetazolamide (up to 4 g/d) or placebo for 6 months. Main outcomes measures: adverse events (AEs), assessment of clinical and laboratory findings at study visits.

Results: Thirty-eight of 86 participants randomized to the acetazolamide group (44.1%) tolerated the maximum allowed dosage of 4 g/d. The average time to achieve maximum study dosage in the acetazolamide group was 13 weeks (median 12 weeks; range 10–24 weeks). A total of 676 AEs (acetazolamide, n = 480; placebo, n = 196) and 9 serious AEs (acetazolamide, n = 6; placebo, n = 3) were reported. Notably, the percentages of participants reporting at least 1 AE in the nervous, gastrointestinal, metabolic, and renal organ systems were significantly higher in the acetazolamide group ($P < 0.05$). The odds of paresthesia (OR 9.82; 95% CI 3.87–27.82), dysgeusia (OR ∞; 95% CI 3.99–∞), vomiting and diarrhea (OR 4.11; 95% CI 1.04–23.41), nausea (OR 2.99; 95% CI 1.26–7.49) and fatigue (OR 16.48; 95% CI 2.39–702.40) were higher in the acetazolamide group than in the placebo group.

Conclusion: Acetazolamide appears to have an acceptable safety profile at dosages up to 4 g/d in the treatment of idiopathic intracranial hypertension. The majority of participants in the Idiopathic Intracranial Hypertension Treatment Trial were able to tolerate acetazolamide above 1 g/d for 6 months.

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Acetazolamide is the most commonly prescribed carbonic anhydrase inhibitor for the medical management of idiopathic intracranial hypertension (IIH). Carbonic anhydrase is present in red blood cells, plasma, the proximal tubule of the kidney, and to a lesser extent in the liver, the ciliary body of the eye and the choroid plexus (1). Its inhibition limits formation of bicarbonate and hydrogen ions. This may be the mechanism for whereby acetazolamide lowers intracranial and intraocular pressure as well as causing diuresis (2–4).

Acetazolamide is effective in the treatment of glaucoma (5–7), seizures (8), and edema (9). Additional uses include treatment of altitude sickness (10,11), Meniere disease (12,13), and IIH (14). The use of acetazolamide (1 g/d) to treat IIH was first suggested by Lubow and Kuhr (15) and it has been subsequently shown to reduce optic disc edema (16). Dosages of 3–4 g/d have been reported to lower intracranial pressure (17).

Side effects associated with acetazolamide include dysgeusia, paresthesia, fatigue, nausea, diarrhea, and polyuria (9). It may produce mild hypokalemia and metabolic acidosis. Uncommon but more severe adverse events (AEs) include anaphylaxis, Stevens–Johnson syndrome, renal stones, and blood dyscrasias (18). Although the safety and tolerability of acetazolamide dosing at 1 g/d has been documented (16), there is uncertainty regarding the safety and tolerability of acetazolamide beyond 1 g/d due to the lack of high-level clinical evidence.

The recent Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) provided the first evidence-based

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treatment recommendations, showing that acetazolamide caused significant improvement in visual field, papilledema grade, cerebrospinal fluid (CSF) pressure, and quality of life measures in participants with mild visual field loss (14). The purpose of this report is to present the safety data related to acetazolamide use in IIHTT participants.

METHODS

Participants and Study Design

The institutional review board at each site approved the study and individual informed consent was obtained before any study-related procedures being performed. The IIHTT was registered on ClinicalTrials.gov (NCT01003639). As previously described, participants aged 18–60 years from 38 sites in North America were eligible if they met the modified Dandy criteria and had reproducible mild visual loss (-2 to −7 dB perimetric mean deviation [MD]) (14). Participants were randomly assigned to receive a supervised diet and either acetazolamide 250 mg (acetazolamide USP, lactose, starch, magnesium stearate) or matching placebo (naringin, lactose, starch, magnesium stearate).

The study drug dosage was initiated with 1 tablet twice daily with subsequent dosage increases of 1 tablet every week up to a maximum of 8 tablets twice daily (4 g/d of acetazolamide). The dosing range was selected based on routine clinical practice where 1 g/d is the usual starting dosage, and 4 g/d is the only dosage to show efficacy in reducing CSF pressure simultaneous with CSF pressure measurements (17). The dosage escalation was stopped if the subject reported related symptoms that interfered with activities of daily living. All participants remained at the maximally tolerated dosage until the 6-month visit before optionally transitioning to open-label acetazolamide. The study medication was discontinued if it was not tolerated at half tablet (125 mg acetazolamide) daily and no other medication was substituted. Verification of drug compliance was assessed at each study visit by pill counts.

Evaluation Criteria

In addition to clinical evaluations that were performed at screening, baseline, and at 1, 2, 3, 4.5, and 6 months after baseline, AEs were collected by questioning participants regarding the occurrence of any untoward events since their last visit and by assessment of clinical and laboratory findings.

An AE was defined as any symptom, sign, illness, or experience which developed or worsened during the course of the study, whether or not the event was considered to be related to the study drug. A serious AE (SAE) was defined as any AE that resulted in any of the following outcomes: death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

For each AE, causality (perceived relationship to study medication) was determined by the local site treating subinvestigator and recorded as either unrelated, or unlikely, possibly, or probably related to the study medication.

Statistical Methods

Results are described as the frequencies and percentages of subjects reporting AEs by specific AE and by system organ class. The total numbers of events are also presented. Fisher exact tests were used to compare treatment groups with respect to the percentages of participants reporting a particular event (or an event belonging to a particular system organ class) at least once after the baseline visit. Treatment effects are described with odds ratios (OR) and their corresponding exact 95% confidence intervals. The distributions of the number of AEs per participant were compared between the treatment groups using a Wilcoxon rank sum test.

RESULTS

One hundred sixty-five participants were randomized to receive either placebo (n = 79) or acetazolamide (n = 86) (14). Thirty-eight participants randomized to the acetazolamide group (44.2%) tolerated the maximum daily dosage of 4 g/d. The average time to attain a 4 g/d dosage in the acetazolamide group was 13 weeks (median 12 weeks, range 10–24 weeks). Thirty-nine participants (45.3%) randomized to the acetazolamide tolerated between 1 g and 3.75 g as their maximum daily dosage. The remaining 9 patients (10.5%) tolerated between 0.125 g and 0.75 g as their maximum daily dosage.

Ten participants permanently discontinued the study drug during the trial: 9 in the acetazolamide group (7 of whom completed follow-up) and 1 in the placebo group (who completed follow-up). Eight participants (4.8%) discontinued study medication due to AEs, and the remaining 2 (both in the acetazolamide group) stopped the drug because of a pregnancy or the desire to become pregnant (14).

A total of 676 AEs (acetazolamide, n = 480, placebo, n = 196; Table 1) and 9 SAEs (acetazolamide, n = 6, placebo, n = 3; Table 2) were reported. The median (range) number of AEs reported per participant was 5 (1–22) in the acetazolamide group and 3 (1–12) in the placebo group; the distributions in the 2 groups were significantly different ($P < 0.001$). At least 1 AE was reported in 84% of the 165 participants (92% of participants in the acetazolamide group and 76% of participants in the placebo group, Table 3). Notably, significant differences were found in the percentages of participants reporting at least 1 AE associated with the nervous ($P < 0.001$), gastrointestinal ($P = 0.003$),

TABLE 1. All adverse events reported during the Idiopathic Intracranial Hypertension Treatment Trial*

Clinical Setting	Placebo (n = 79)		Acetazolamide (n = 86)		*P* Value†
	Participants, No. (%)	Events, No.	Participants, No. (%)	Events, No.	
Nervous	24 (30.4)	34	54 (62.8)	106	<0.001
Paresthesia		9		54	
Dysgeusia		0		13	
Headache		16		17	
Dizziness		4		10	
Other		5		12	
Gastrointestinal	17 (21.5)	23	38 (44.2)	89	0.003
Nausea		10		30	
Diarrhea		4		14	
Vomiting		3		12	
Acid reflux		2		12	
Dry mouth		0		3	
Constipation		0		2	
Other		4		16	
Investigations (i.e., abnormal laboratory finding)	11 (13.9)	18	27 (31.4)	44	0.009
Infections (e.g., cold, flu, pneumonia)	26 (32.9)	43	26 (30.2)	43	0.740
Musculoskeletal (e.g., myalgia, joint pain)	11 (13.9)	13	21 (24.4)	27	0.115
Metabolic	1 (1.3)	1	17 (19.8)	23	<0.001
Metabolic acidosis		0		6	
Loss of appetite		0		6	
Hyperchloremia		0		4	
Hypokalemia		0		4	
Dehydration		0		2	
Other		1		1	
Skin	5 (6.3)	5	15 (17.4)	19	0.033
Rash		3		8	
Hives		1		3	
Acne		1		2	
Pruritus		0		2	
Other		0		4	
Eye/vision	9 (11.4)	14	10 (11.6)	16	1.000
Transient visual obscuration		2		7	
Permanent visual obscuration		3		2	
Flashes/floaters		3		3	
Other		6		4	
Respiratory (e.g., dyspnea, hypercapnia)	5 (6.3)	6	13 (15.1)	16	0.084
Psychiatric (e.g., depression, anxiety)	3 (3.8)	3	12 (14.0)	15	0.030
Ear (e.g., tinnitus, other)	3 (3.8)	5	13 (15.1)	15	0.017
General	11 (13.9)	12	26 (30.2)	39	0.015
Fatigue		1		19	
Other		5		12	
Seasonal Allergies		1		3	
Gynecologic abnormalities		5		3	
Allergic reaction		0		1	
Pelvic pain		0		1	
Renal (e.g., polyuria, renal stones)	0 (0.0)	0	7 (8.1)	8	0.014
Vascular (e.g., blood pressure changes)	1 (1.3)	1	2 (2.3)	3	1.000
Pregnancy	0 (0.0)	0	3 (3.5)	3	0.247
Cardiac (e.g., palpitations, tachycardia)	0 (0.0)	0	3 (3.5)	3	0.247
Unrelated surgery	1 (1.3)	1	1 (1.2)	1	1.000
Procedural complications (e.g., post LP, other)	13 (16.5)	17	9 (10.5)	10	0.360

*Values reported are the numbers (percentages) of participants experiencing at least 1 AE after the baseline visit; total numbers of events are also described.

†From Fisher exact test comparing the treatment groups.

TABLE 2. Serious adverse events reported during the Idiopathic Intracranial Hypertension Treatment Trial*

Treatment	SAE	Daily Dosage	Degree of Relatedness*
Placebo	Vision loss-nonspecific threshold depression	1 g	Unrelated
Placebo	Pneumonia and bronchitis	2.25 g	Unrelated
Placebo	Vision loss-nonspecific threshold depression	1.75 g	Unrelated
Acetazolamide	Decreased kidney function	4 g	Probably
Acetazolamide	Transaminitis	4 g	Possibly
Acetazolamide	Allergic reaction	2.5 g	Possibly
Acetazolamide	Elevated lipase with pancreatitis	1.5 g	Unlikely
Acetazolamide	Hypokalemia	2.25 g	Unrelated
Acetazolamide	Acute diverticulitis	2.25 g	Unrelated

*Degree of relatedness was ascertained by the Treating Sub-Investigator at the site.

renal (P = 0.014), ear (P = 0.017), skin (P = 0.033), and psychiatric (P = 0.03) systems (Table 1). AEs associated with metabolic disturbances included acidosis, loss of appetite, hyperchloremia, hypokalemia (associated with concomitant use of valsartan and hydrochlorthiazide), and dehydration. Collectively, the number of participants reporting at least 1 AE associated with these disturbances was significantly higher in the acetazolamide group ($P <$ 0.001, Table 1). In addition, abnormal laboratory findings [complete blood count (CBC), liver, kidney, and pancreatic function] were significantly higher in the acetazolamide group (P = 0.009). Of the 44 abnormal laboratory results that were reported in 27 participants in the acetazolamide group, the study drug dosage was unchanged in 22 participants.

Two participants in the acetazolamide group, one with transaminitis and the other with elevated lipase and WBC counts, were hospitalized and discontinued study drug use but remained in the study for follow-up. One participant in the acetazolamide group whose white blood cell counts were dropping discontinued the study drug and did not complete follow-up. A decrease in the study dosage was directed for 10 AEs experienced in the acetazolamide group as a result of abnormal liver, kidney, and CBC results. Study drug was suspended for 8 participants in the acetazolamide group with abnormal kidney and liver results. No participant required additional medication or supplementation as a result of the abnormal laboratory values. As previously reported, mean decreases in potassium (0.23 mmol/L) and carbon dioxide (3.90 mmol/L) levels were found at 6 months in the acetazolamide group relative to the placebo group (14).

TABLE 3. Frequency of adverse events per participant reported

Number of AEs Reported Per Participant	Placebo No (%)	Acetazolamide No (%)	Total No (%)
0	19 (24)	7 (8)	26 (16)
1	13 (16)	9 (10)	22 (13)
2–4	33 (42)	24 (28)	57 (35)
5–10	13 (16)	32 (37)	45 (27)
>10	1 (1)	14 (16)	15 (9)
Total	79 (100)	86 (100)	165

AE, adverse events.

The odds of experiencing common symptoms of the nervous and gastrointestinal systems, such as paresthesia (OR 9.82; 95% confidence interval (CI) 3.87–27.82), dysgeusia (OR ∞; 95% CI 3.99–∞), vomiting and diarrhea (OR 4.11; 95% CI 1.04–23.41), and nausea (OR 2.99; 95% CI 1.26–7.49) were increased in the acetazolamide group (Table 4). The odds of experiencing fatigue were also increased in the acetazolamide group (OR 16.48; 95% CI 2.39–702.40; Table 4). Common AEs were also examined by daily dosage received at the time of the AE. These data (Table 5) show that common AEs in participants in the acetazolamide group were generally reported at lower dosages.

DISCUSSION

Conventional medical management of IIH consists of using a carbonic anhydrase inhibitor, typically acetazolamide, and encouraging weight loss. Surprisingly, until the IIHTT was performed, there was insufficient evidence to support either of these recommendations. The dosage of acetazolamide commonly used by practitioners to treat IIH is 1 g/d and is presumably based on the literature that studied aqueous suppression in the setting of glaucoma (5–7).

Inhibition of carbonic anhydrase using acetazolamide reduces the formation of hydrogen and bicarbonate ions from carbon dioxide and water resulting in decreased sodium ion transport across the choroidal epithelium and thus reducing the formation of CSF (2–4). In 1978, Gucer and Viernstein (17) reported that acetazolamide, at dosages of 3–4 g/d, reduced CSF pressure. Based on this finding, the IIHTT protocol was to give the maximally tolerated dosage up to 4 g/d. The IIHTT protocol stipulated a slow dosage escalation of acetazolamide (or matching placebo) from 1 g/d to a maximum of 4 g/d. The dosage escalation

TABLE 4. Symptoms commonly associated with acetazolamide use*

Adverse Event	Placebo (n = 79) Participants, No. (%)	Placebo (n = 79) Events, No.	Acetazolamide (n = 86) Participants, No. (%)	Acetazolamide (n = 86) Events, No.	Odds Ratio	95% CI	*P*
Nervous							
Paresthesia	7 (8.9)	9	42 (48.8)	54	9.82	3.87–27.82	<0.001
Dysgeusia	0	0	13 (15.1)	13	∞	3.99–∞	<0.001
Gastrointestinal							
Nausea	10 (12.7)	10	26 (30.2)	30	2.99	1.26–7.49	0.008
Diarrhea	3 (3.8)	4	12 (14.0)	14	4.11	1.04–23.41	0.03
Vomiting	3 (3.8)	3	12 (14.0)	12	4.11	1.04–23.41	0.03
Metabolic							
Metabolic acidosis	0	0	3 (3.5)	6	∞	0.54–∞	0.25
Loss of appetite	0	0	6 (7.0)	6	∞	1.47–∞	0.03
Hypokalemia	0	0	4 (4.7)	4	∞	0.84–∞	0.12
General							
Fatigue	1 (1.3)	1	15 (17.4)	19	16.48	2.39–702.40	<0.001
Renal							
Renal stone	0	0	2 (2.3)	2	∞	0.27–∞	0.50
Polyuria	0	0	3 (3.5)	3	∞	0.54–∞	0.25

*Values reported are the numbers (percentages) of participants experiencing the event at least once after the baseline visit; a total number of events are also provided.
∞, infinity.

was stopped if the subject reported related symptoms that interfered with activities of daily living. Forty-four percent of the participants in the acetazolamide group tolerated the maximum dosage of 4 g/d.

Acetazolamide is well known to be associated with a high incidence of AEs. Over 10% of users experience malaise, diarrhea, anorexia, metallic taste, or polyuria (20). Furthermore, 1%–10% of users will experience drowsiness, depression, or dizziness. Given that some AEs may be dosage related, it was anticipated that the acetazolamide group in the IIHTT would report a larger number of adverse reactions. Indeed, 92% of participants in the acetazolamide

TABLE 5. Frequencies of adverse events commonly associated with acetazolamide use by daily dosage (g) at the time of the occurrence of the event

Common AEs	Daily Dosage (g) 0–1.0 P (No.)	0–1.0 A (No.)	1.25–2.0 P (No.)	1.25–2.0 A (No.)	2.25–3.0 P (No.)	2.25–3.0 A (No.)	3.25–4.0 P (No.)	3.25–4.0 A (No.)
Nervous Disorders								
Paresthesia	1	29	5	18	—	6	3	1
Dysgeusia	—	9	—	2	—	2	—	—
Gastrointestinal Disorders								
Vomiting	1	5	—	1	1	3	1	3
Nausea	1	12	3	7	2	7	4	4
Diarrhea	2	3	—	5	—	2	2	4
Metabolism and Nutrition								
Loss of appetite	—	2	—	4	—	—	—	—
Hypokalemia	—	—	—	2	—	2	—	1
Metabolic acidosis	—	—	—	2	—	3	—	1
Renal and Urinary Disorders								
Renal stone	—	—	—	—	—	1	—	1
Polyuria	—	2	—	1	—	—	—	—
Other								
Fatigue	—	7	—	8	—	4	1	—

—, AE not reported; A, acetazolamide; AE, adverse event; No., number of AEs reported; P, placebo.

group experienced at least 1 AE (compared to 76% of participants in the placebo group). Nearly two-thirds of the acetazolamide group reported between 2 and 10 AEs over the course of the study. The incidence of AEs commonly associated with acetazolamide did not increase with dosage. Indeed, some AEs tended to occur at lower dosages (i.e., paresthesia, dysgeusia, nausea) perhaps because the symptoms were dose-limiting in the affected individuals. It is possible that longer durations of treatment with acetazolamide at higher dosages may result in higher incidences of some of the less common reactions such as urolithiasis.

SAEs were rare in the IIHTT. Six participants reported SAEs in the acetazolamide group while 3 participants reported SAEs in the placebo group. Five of the 6 SAEs in the acetazolamide group occurred at a daily dosage greater than 2 g/d. The participant with transaminitis was asymptomatic and the liver function normalized after discontinuation of acetazolamide.

Allergic reactions to acetazolamide were uncommon. Furthermore, there is no evidence to suggest that an allergy to sulfonamide antibiotics increases the risk of an allergic reaction (21,22). In the IIHTT, there was only 1 allergic reaction. This participant did not have a known sulfa allergy. In this case, the study drug was suspended and the participant was advised to remain permanently off study drug. The participant agreed to continue in the study in follow-up alone. No participant on acetazolamide alone required potassium supplementation; thus, routine monitoring of potassium levels is not recommended. Importantly, none of the SAEs resulted in persistent or significant disability and all SAEs resolved.

The percentages of participants experiencing an AE at least once after the baseline visit in the nervous, gastrointestinal, and renal systems were significantly higher in the acetazolamide group than in the placebo group; the same was true of AEs associated with metabolic disturbances. A relationship between metabolic changes and systemic symptoms such as malaise has been postulated but never proven (19). When considered individually, the odds of experiencing paresthesia, dysgeusia, vomiting, nausea, diarrhea, and fatigue were all significantly higher in the acetazolamide group.

Kass et al (23) reported an 11-fold higher risk of urolithiasis in those receiving chronic acetazolamide therapy for a mean duration of 41 months and the rate of stone formation was highest in the first year of treatment. The annual incidence of stone formation in adults has been reported at 5.2% in the united states, and Caucasian men appear to be at the highest risk (23–25). Overall, the rate of urolithiasis in the IIHTT was low at 2.4% over 6 months. However, the study duration of the IIHTT was not long enough to warrant any conclusions regarding the long-term effects of acetazolamide use on renal stone formation. The mechanism by which acetazolamide leads to renal stone formation is not fully understood; however, elevated urinary citrate and magnesium levels have been implicated (26).

Pregnancy, or the desire to become pregnant, is a relative contraindication to using acetazolamide because of a report of a sacrococcygeal teratoma (27). There have been no reported teratogenic abnormalities associated with acetazolamide use in the third trimester or during parturition (28). Because IIH predominantly occurs in women of child-bearing age, treating physicians should always inquire about the possibility of pregnancy in their patients before initiating therapy. In the IIHTT, there were 2 such cases, one that became aware of a pregnancy while on acetazolamide, the other who stopped acetazolamide before becoming pregnant. In the first case, the participant delivered a healthy baby with no congenital defects. Others have reported use of acetazolamide during pregnancy without resultant birth defects (28).

As expected, participants in the acetazolamide group had significantly lower mean levels of CO_2 than participants in the placebo group at all time points after baseline (14). Whether the observed low CO_2 levels are responsible for some of the systemic adverse reactions that were reported (such as malaise, headache, and gastric reflux) is not known.

We acknowledge certain limitations of this study. As in all clinical trials, the results are not necessarily generalizable to patients who fall outside the eligibility criteria of the study or are not treated according to the IIHTT dosing protocol. In particular, the study was limited to individuals between the ages 18 and 60 years. Lichter (19) showed that the tolerance to acetazolamide is lower in the elderly. The duration of double-masked follow-up in this study was only 6 months; the safety and tolerability of acetazolamide for longer treatment periods remains to be determined. Lastly, the IIHTT was designed to have adequate power for the primary outcome variable (visual loss); it was not primarily designed to detect treatment effects with respect to safety outcomes, especially relatively rare AEs. Nonetheless, this is one of the largest cohorts reported with data collected prospectively regarding acetazolamide usage in a randomized trial.

We found that acetazolamide at dosages up to 4 g/d in patients with IIH was safe and well tolerated in most patients. Elevated liver function tests occurred in 2 participants, who were asymptomatic and experienced normalization of hepatic enzymes after discontinuing acetazolamide. Monitoring of transaminases in the dosage escalation phase of acetazolamide treatment should be considered. No patient experienced aplastic anemia and periodic monitoring of blood cell counts is not necessary or cost-effective (29). In the IIHTT, no subject required potassium supplementation in the absence of other concurrent diuretic use and there were no cases of permanent morbidity.

Now that there is established benefit for the use of acetazolamide in IIH, clinicians can be reassured that

dosages of up to 4 g/d are well tolerated and safe. Further study is required to determine whether the results of the IIHTT extend to those requiring longer periods of treatment.

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M. W. ten Hove had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. **Reynolds JEF**, ed. Martindale: The Extra Pharmacopoeia. London, United Kingdom: The Pharmaceutical Press, 1993.
2. **Davson H,** Luck CP. The effect of acetazoleamide on the chemical composition of the aqueous humour and cerebrospinal fluid of some mammalian species and on the rate of turnover of 24Na in these fluids. J Physiol. 1957;137:279–293.
3. **Davson H,** Segal MB. The effects of some inhibitors and accelerators of sodium transport on the turnover of 22Na in the cerebrospinal fluid and the brain. J Physiol. 1970;209:131–153.
4. **Maren TH**. Carbonic anhydrase: chemistry, physiology, and inhibition. Physiol Rev. 1967;47:595–781.
5. **Becker B**. Decrease in intraocular pressure in man by a carbonic anhydrase inhibitor, diamox; a preliminary report. Am J Ophthalmol. 1954;37:13–15.
6. **Becker B,** Middleton WH. Long-term acetazoleamide (diamox) administration in therapy of glaucomas. AMA Arch Ophthalmol. 1955;54:187–192.
7. **Joyce PW,** Mills KB, Richardson T, Mawer GE. Equivalence of conventional and sustained release oral dosage formulations of acetazolamide in primary open angle glaucoma. Br J Clin Pharmacol. 1989;27:597–606.
8. **Reiss WG,** Oles KS. Acetazolamide in the treatment of seizures. Ann Pharmacother. 1996;30:514–519.
9. Available at: http://reference.medscape.com/drug/diamox-acetazolamide-342809. Accessed July 25, 2014.
10. **Grissom CK,** Roach RC, Sarnquist FH, Hackett PH. Acetazolamide in the treatment of acute mountain sickness: clinical efficacy and effect on gas exchange. Ann Int Med. 1992;116:461–465.
11. **Low EV,** Avery AJ, Gupta V, Schedlbauer A, Grocott MP. Identifying the lowest effective dose of acetazolamide for the prophylaxis of acute mountain sickness: systematic review and meta-analysis. BMJ. 2012;345:e6779.
12. **Brookes GB,** Hodge RA, Booth JB, Morrison AW. The immediate effects of acetazolamide in Meniere's disease. J Laryngol Otol. 1982;96:57–72.
13. **Brookes GB,** Booth JB. Oral acetazolamide in Meniere's disease. J Laryngol Otol. 1984;98:1087–1095.
14. **NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee,** Wall M, McDermott MP, Kieburtz KD, Corbett JJ, Feldon SE, Friedman DI, Katz DM, Keltner JL, Schron EB, Kupersmith MJ. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. JAMA. 2014;311:1641–1651.
15. **Lubow M,** Kuhr L. Pseudotumour cerebri: comments on practical management. In: Glaser JS, Smith JL, eds. Neuro-Ophthalmology. Vol 9. St. Louis, MO: CV Mosby, 1976:199–206.
16. **Tomsak RL,** Niffenegger AS, Remler BF. Treatment of pseudotumor cerebri with Diamox (acetazolamide). J Clin Neuroophthalmol. 1988;8:93–98.
17. **Gucer G,** Viernstein L. Long-term intracranial pressure recording in the management of pseudotumor cerebri. J Neurosurg. 1978;49:256–263.
18. **Warden CR,** Burgess JL. Acetazolamide Product Monograph [online]. Available at: www.inchem.org/documents/pims/pharm/acetazol.htm. Accessed October 8, 2014.
19. **Lichter PR**. Reducing side effects of carbonic anhydrase inhibitors. Ophthalmology. 1981;88:266–269.
20. **Association CP**. Compendium of Pharmaceuticals and Specialties. Ottawa, Canada: Canadian Pharmacists Association, 2014.
21. **Platt D,** Griggs RC. Use of acetazolamide in sulfonamide-allergic patients with neurologic channelopathies. Arch Neurol. 2012;69:527–529.
22. **Lee AG,** Anderson R, Kardon RH, Wall M. Presumed "sulfa allergy" in patients with intracranial hypertension treated with acetazolamide or furosemide: cross-reactivity, myth or reality? Am J Ophthalmol. 2004;138:114–118.
23. **Kass MA,** Kolker AE, Gordon M, Goldbert I, Geiser DK, Kropia T, Becker B. Acetazolamide and urolithiasis. Ophthalmology. 1981;88:261–265.
24. **Ferrandino MNPP,** Preminger GM. Campbell-Walsh Urology, 10th edition. Philadelphia, PA: Saunders Elsevier, 2011.
25. **Romero V,** Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. Rev Urol. 2010;12:e86–e96.
26. **Constant MA,** Becker B. The effect of carbonic anhydrase inhibitors on urinary excretion of citrate by humans. Am J Ophthalmol. 1960;49:929–934.
27. **Worsham F Jr,** Beckman EN, Mitchell EH. Sacrococcygeal teratoma in a neonate. Association with maternal use of acetazolamide. JAMA. 1978;240:251–252.
28. **Lee AG,** Pless M, Falardeau J, Capozzoli T, Wall M, Kardon RH. The use of acetazolamide in idiopathic intracranial hypertension during pregnancy. Am J Ophthalmol. 2005;139:855–859.
29. **Zimran A,** Beutler E. Can the risk of acetazolamide-induced aplastic anemia be decreased by periodic monitoring of blood cell counts? Am J Ophthalmol. 1987;104:654–658.