Reducing the Incidence of High-Altitude Pulmonary Edema

TO THE EDITOR: In their randomized trial, Maggiorini and colleagues (1) report their impressive outcome that both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema. They used a dosage of 10 mg twice daily for tadalafil or 8 mg twice daily for dexamethasone from the morning of the day before ascent until the end of the study. We are concerned about the dose adjustments of both drugs for the trial. A previous study used the phosphodiesterase-5 inhibitor sildenafil at a dosage of 40 mg 3 times daily at 6 to 8 hours after arrival at high altitude that was used for 6 days to inhibit altitude-induced hypoxemia and pulmonary hypertension (2). Similarly, another study used a sildenafil dosage of 25 mg or 100 mg every 8 hours for 12 weeks to treat high-altitude pulmonary arterial hypertension (3). Both studies found the treatments to be effective. In the case of dexamethasone, an initial dose of 8 mg, followed by 4 mg every 6 hours, has been used to treat high-altitude cerebral edema (4).

Could the authors explain how they chose the drug regimen for their prophylaxis trial?

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Potential Financial Conflicts of Interest: None disclosed.

References

TO THE EDITOR: The article by Maggiorini and colleagues (1) and its editorial (2) do not comment on the important mental side effects of dexamethasone, which may include euphoria and mental disorientation. These are potentially dangerous adverse side effects, especially if you are climbing a jagged edge or trekking in remote high-altitude mountain regions, and they deserve mention.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: We thank Mr. Pun and Dr. Ghimire and Dr. Basnyat for their interest and comments on our recent publication. When we designed and performed our study, Richalet and colleagues (1) and Aldashev and colleagues (2) had not yet published their work on sildenafil, which both showed that sildenafil decreases hypoxic pulmonary hypertension. Sildenafil must be taken in rather brief intervals because of its short half-life of 4 to 5 hours. Because we tested the effectiveness of 2 drugs in our study, we needed to match the time of drug intake and chose the phosphodiesterase-5 inhibitor tadalafil with a long half-life (17 hours). The recommended dose of tadalafil to treat erectile dysfunction is 10 to 20 mg; thus 10 mg of tadalafil every 12 hours seemed reasonable.

Rock and colleagues (3) reported that 4 mg of dexamethasone every 12 hours statistically significantly reduced symptoms and signs of acute mountain sickness, whereas 1 mg or 0.25 mg of dexamethasone was ineffective. We decided to increase the dose to the maximum used to treat acute mountain sickness, which was 16 mg/d (8 mg twice daily) on the basis of previous trials that used 4 mg four times daily. On the basis of our participants’ clinical background, applying this dosage on only 4 consecutive days seemed safe, an assumption that was confirmed in our study.

Dr. Basnyat noticed that we did not comment on possible dangerous mental side effect of dexamethasone. During our study, we assessed the mental status of all participants daily and did not observe any symptoms of inappropriate euphoria or mental disorientation. Moreover, to our knowledge, no studies indicate that dexamethasone impairs cognitive functions at high altitude. Conversely, 2 studies on mountaineers at altitudes higher than 4000 meters, who received 8 to 16 mg of dexamethasone daily, showed an improvement of reaction times and mood status but no effects on personality in cognitive and psychomotor tests (4, 5). Thus, these results suggest that the use of dexamethasone at high altitude might even improve a mountaineer’s awareness while climbing exposed ridges or trekking paths. However, we cannot generally recommend the routine use of dexamethasone for high-altitude pulmonary edema prophylaxis for longer than a few days because of its well-known long-term side effects and the lack of safety data in the context of a trekking or climbing expedition in remote areas.

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Potential Financial Conflicts of Interest: None disclosed.
Letters

References

Lack of Evidence for Recommended Low-Density Lipoprotein Cholesterol Treatment Targets

TO THE EDITOR: Although Hayward and colleagues’ narrative review (1) on treatment targets for low-density lipoprotein (LDL) cholesterol levels raises several important issues, one glaring omission in the relevant studies is that high-density lipoprotein (HDL) cholesterol values are not incorporated into the model. Many clinical studies have found that the relationship between LDL cholesterol and HDL cholesterol levels is more predictive of cardiac events than LDL cholesterol level alone (2). Impressive data suggest that HDL cholesterol is cardioprotective through several mechanisms, including its role in the reverse transport of LDL cholesterol and in transporting antioxidants to LDL cholesterol, making LDL cholesterol less susceptible to oxidation and presumably less atherogenic. In addition, HDL cholesterol decreases blood viscosity, improves endothelial dysfunction (promoting nitric oxide), stabilizes prostacyclin, inhibits platelets, inhibits adhesion molecule expression, and blocks matrix metalloproteinase expression (3). It’s certainly possible that a patient with coronary artery disease whose LDL cholesterol level is decreased to 2.59 mmol/L (100 mg/dL) but has an HDL cholesterol level of 1.42 mmol/L (55 mg/dL) might have a lower likelihood of another cardiac event than that of a patient with an LDL cholesterol level less than 1.81 mmol/L (<70 mg/dL) but an HDL cholesterol level of 0.91 mmol/L (35 mg/dL). This information is extremely important clinically and may dictate a more rational use of lipid-lowering agents. Some data may be gleaned from further analysis of previous studies that have reported only LDL cholesterol goals and should be evaluated prospectively in future studies.

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Potential Financial Conflicts of Interest: None disclosed.

References
5. Ravnskov U. High cholesterol may protect against infections and atherosclerosis. QJM. 2003;96:927-34. [PMID: 14631060]

TO THE EDITOR: Hayward and colleagues (1) rightly point out the extreme weakness of ecological comparisons among statin trials. Their concern is justified by the lack of dose response between the degree of cholesterol lowering and the clinical (2, 3) or angiographic (4) outcome found in the trials where dose response was calculated by using individual data. The fact that patients with the worst pre-randomization LDL cholesterol level response received the same benefit as that of patients with the best response strongly indicates that most if not all benefits from the statins are mediated through their pleiotropic effects and not through cholesterol lowering. But even if cholesterol lowering is unimportant, we should have expected dose response because both cholesterol lowering and the pleiotropic effects are due to the same drug. The lack of dose response suggests that high LDL cholesterol levels may have a protective effect and thus may counteract the expected (but false) dose response in accordance with the findings. Indeed, several observations and experiments have shown that cholesterol, or rather the LDL molecule itself, protects against infections, probably by binding and inactivating bacterial endotoxin (5). In accordance, many cohort studies have shown that a high cholesterol level is not a risk factor for older people and that older people with high cholesterol levels live longer than older people with low cholesterol levels (5). Because statin treatment is intended for the rest of the patient’s life, finding the lowest effective statin dosage would be more relevant than to titrate to an arbitrarily determined, unnecessarily low LDL cholesterol level.

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Potential Financial Conflicts of Interest: None disclosed.

References
5. Ravnskov U. High cholesterol may protect against infections and atherosclerosis. QJM. 2003;96:927-34. [PMID: 14631060]

IN RESPONSE: I agree with Dr. Modest that considerable evidence suggests that HDL cholesterol level is an important risk factor in predicting cardiovascular risk, but I disagree that it was a “glaring omission” in our paper. Space constraints prevented us from discussing details of each cardiovascular risk factor, but our paper highlighted the critical importance of overall cardiovascular risk, mentioned the complexities of risk factor interactions, and included references that discuss HDL cholesterol effects in detail (1, 2). How-

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ever, although we agree that HDL cholesterol level is an important independent risk factor, we could not find clinical evidence meeting our inclusion criteria (valid epidemiologic evaluations in patients with LDL cholesterol levels <3.36 mmol/L [<130 mg/dL]) of whether HDL cholesterol is more important than any other cardiovascular risk factor in predicting the benefits of statin therapy. Future work should examine whether HDL cholesterol is important simply because it is one of many risk factors or whether there are HDL cholesterol–specific interaction effects.

We disagree with Dr. Ravnkov’s assessment that substantial clinical evidence suggests that harmful effects are related to achieving very low LDL cholesterol levels. As we stated in our paper: “Our point is not that there is strong evidence against the current recommendations; it is that there is no valid clinical evidence to suggest that using treatments other than statins to pursue proposed LDL cholesterol goals is safe or effective.” We hope that our study will stimulate those with access to the clinical trial data to more rigorously assess these questions by using the methodological approaches outlined in our paper.

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Potential Financial Conflicts of Interest: None disclosed.

References

First-Line Therapy for Hypertension

TO THE EDITOR: In the recent Update in Cardiology (1), Rapaport draws conclusions from the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) (2) and recommends that physicians consider “using amlodipine as a first-line antihypertensive therapy” (3). However, since the Medical Research Council trial (3) showed that atenolol was not better than placebo in preventing cardiovascular disease, many physicians have had reservations about the use of β-blockers as first-line antihypertensive therapy. Second, the dosage of bendroflumethiazide (1.25 to 2.5 mg/d) was lower than the 10-mg/d dosage used in previous trials that showed a benefit. This, in part, may account for the difference in blood pressure between the groups, favoring the amlodipine group. Third, the diuretic was added to treatment for only 56.6% of patients during the first year and about two thirds of patients during the following years.

Finally, the choice of an angiotensin-converting enzyme (ACE) inhibitor as an add-on therapy for the amlodipine group could have positively influenced the results because ACE inhibitors were shown to lower cardiovascular mortality and morbidity among high-risk patients (4).

Thiazide diuretics were found to be superior to calcium-channel blockers and ACE inhibitors in lowering rates of cardiovascular disease among many patients with diverse racial backgrounds (5, 6). The ASCOT-BPLA study confirms the existing data that β-blockers should not be used as first-line antihypertensive therapy unless there are compelling indications. However, it does not change the current evidence that thiazide diuretics should be the first-line therapy for most patients with hypertension (7, 8).

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References

CLINICAL OBSERVATION

The Perils of PERRLA

Background: The pupillary examination is arguably the single most useful clinical test of the nervous system in the conscious or unconscious patient. When properly done with a few swings of a light, the examination can assess the functional status of the retina, optic nerve, contralateral optic tract, cranial nerve III, dorsal midbrain,
and sympathetic chain from the hypothalamus down to the lower cervical spinal cord and up to the cavernous sinus and orbit. The results of normal pupil testing are frequently documented with PERRLA (pupils equal, round, reactive to light, and accommodation). But PERRLA is not only incorrect and inexact—it is also, more seriously, incomplete.

**Objective:** To describe the limitations of PERRLA and to review the proper approach to pupillary examination.

**Discussion:** Accommodation is not tested with PERRLA. Three pathways are activated when a healthy person looks at a near target. The eyes converge, the pupils constrict, and the lens focuses closer. Together, these 3 responses make up the near reflex. When an examiner notes pupillary constriction to a near target, only the second of the 3 pathways is being tested and the third pathway—accommodation—is not measured unless retinoscopy or other techniques are used. The “A” in PERRLA is, therefore, incorrect.

Testing the near reflex is superfluous when the light reflex is normal. Even if the correct terminology (response to near) were used, the test is not even worth performing in most cases. If the pupils respond poorly to light, testing their constriction with a near stimulus is informative. The reverse is not true. Constriction to near but not light, that is, light–near dissociation, is commonly produced by damage to the anterior visual pathways, the Parinaud (dorsal midbrain) syndrome, the Adie syndrome (ciliary ganglion parasympathetic dysfunction), and—the perennial favorite of medical school limericks—the Argyll Robertson pupil of neurosyphilis. Yet while pupils may constrict with near but not to light, most neuro-ophthalmologists have probably never seen a case of the reverse, and if they did, they would have difficulty in coming up with implications for the patient’s health.

Testing for a relative afferent pupillary defect (RAPD) should be routinely performed instead. But if accommodation is unhelpful for most cases of pupil testing, looking for the presence of an RAPD is of tremendous benefit. An RAPD results from asymmetric afferent input from the retina or optic nerves to the midbrain nuclei responsible for the pupillary reflex. It is best detected with the swinging flashlight test of Levatin (1) (not Marcus Gunn): As the light alternates between eyes, the pupil of the diseased optic nerve or retina becomes larger when illuminated and the pupil of the healthy eye becomes smaller. An RAPD is frequently seen as a result of optic neuritis (often from multiple sclerosis); infectious, ischemic, or other inflammatory optic neuropathies; asymmetric glaucoma; and some more severe retinal problems. Media opacities, such as cataract or corneal disease, do not cause an RAPD. Because the RAPD test does not rely on patient cooperation, it is one the few tests of vision that can be done in an unconscious patient, although the correlation between degree of visual impairment and degree of RAPD is poor.

What if there is anisocoria? In an ideal world, the size of the pupils would be measured in the dark (neither pupil illuminated) and in the light (both pupils illuminated simultaneously), but the former is only an estimate unless infrared pupillography is used. Fortunately, the relative size of the pupils in the dark and light is much more clinically relevant than the absolute size. For example, in a patient with the Horner syndrome, the sympathetic denervation results in anisocoria that is more obvious in the dark than in the light, while the opposite is true for the parasympathetic denervation associated with a compressive third-nerve palsy.

**Conclusion:** Medicine is moving away from error-prone and ambiguous abbreviations, which may well disappear when the electronic medical record becomes widespread. Until that time, I recommend that PERRLA be used instead of PERRLA to document a normal pupillary examination. Even in settings where abbreviations are no longer used or allowed, the acronym might serve as a mnemonic to guide performance of a more efficient and relevant pupillary examination. Anisocoria in light and dark may also be noted if present. Accommodation is not tested in routine examination of the pupils nor should it be, but detection of an RAPD is almost always germane to the patient’s health—even at the cost of 4 extra letters.

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**Potential Financial Conflicts of Interest:** None disclosed.

**Reference**

**Corrections**

**Correction: BiDil for Heart Failure in Black Patients**
The recent article by Bibbins-Domingo and Fernandez (1) incorrectly stated that “increased levels of nitric oxide in black people that are associated with adverse heart failure outcomes and may be reduced by hydralazine hydrochloride–isosorbide nitrate therapy.” This statement should read that “lower levels of available nitric oxide in black people are associated with adverse heart failure outcomes and may be enhanced by hydralazine hydrochloride–isosorbide nitrate therapy.”

**Reference**

**Correction: In the Clinic: Type 2 Diabetes**
The recent In the Clinic (1) contained some errors. The doses of pramlintide and exenatide on pages ITC-8 and ITC-9 were reported with the wrong units. These units should be been μg, not mg. In Table 5, the American College of Physicians recommends thiazide diuretics, not α-blockers, as first-line therapy for type 2 diabetes.

**Reference**