Letters to the Editor

In Response to Reduced Acetazolamide Dose for AMS by McIntosh et al

To the Editor:

Referring to the recently published RADICAL trial,¹ the authors have alluded to the possibility their sample was statistically underpowered. As a result of both study design and increased education, I feel that this is certainly the case.

The mountaineering community should celebrate the increasing difficulty of studying acute mountain sickness (AMS) prophylaxis as a result of increased education and awareness. However, care should be taken when determining sample size from previous studies, largely because of the changed nature of ascent profiles. A greater emphasis is now placed on acclimatization through a slowed rate of ascent above 3000 m. This may differ from the rates of ascent and the final height attained described in previous papers. An increased rate of ascent and greater final height are thought to be associated with an increased risk of developing AMS. Additionally, severe signs and complications of AMS will become more infrequent as education prompts early recognition and intervention.

Although this study was powered to detect noninferiority and a difference in severity of AMS based on a previous study,² the authors have identified that such a study may have biased sample size calculation.

In the study by van Patot et al, participants lived between 1400 and 1600 m and were taken from 2000 m to 4300 m by car over a 2-h period.² In contrast, McIntosh et al recorded altitudes of residence of 632 ± 804 m and travel altitudes from 745 ± 803 m.¹ The high-risk period will have been the drive or flight, likely to Lukla airport (2860 m) from Kathmandu (1400 m), which represents a significantly different ascent profile when compared with the study by van Patot et al. The exact nature of this risk is not known because participants followed their own itinerary.

This leads me to offer 2 cautions: 1) the recommendation of 62.5 mg twice daily acetazolamide as prophylaxis should be delayed until a consensus has been reached on its efficacy in reducing incidence and severity of AMS based on studies of suitable sample size; and 2) future studies should ensure they are powered from studies engaging in similar ascent profiles where applicable.

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References

1. McIntosh SE, Hemphill M, McDevitt MC, Gurung TY, Ghale M, Knott JR, et al. Reduced acetazolamide dosing in countering altitude illness: a comparison of 62.5 vs 125 mg (the RADICAL trial). *Wilderness Environ Med.* 2019;30(1):12–21.
2. van Patot MC, Leadbetter G, Keyes LE, Maakestad KM, Olson S, Hackett PH. Prophylactic low-dose acetazolamide reduces the incidence and severity of acute mountain sickness. *High Alt Med Biol.* 2008;9(4):289–93.

In Reply to Dr Bennett

To the Editor:

We thank Dr. Bennett¹ for his interest in our publication of the RADICAL (Reduced Acetazolamide Dosing in Countering Altitude Illness) trial.² This trial was the first to examine a dose of acetazolamide lower than the 125 mg twice daily typically recommended to prevent acute mountain sickness (AMS). During our treks and climbs in the Himalaya, we encountered guides on Mount Everest who were taking acetazolamide 62.5 mg instead of 125 mg because they believed that these smaller doses were just as effective without the side effects. We sought to rigidly examine this anecdotal use in a prospective double-blind randomized trial.

Past studies that have examined acetazolamide for preventing AMS have started acetazolamide while already at altitude, even as high as 3000 m. Our study was the first to use methods of acetazolamide administration that parallel real-life use. Participants took their first dose of acetazolamide while they were in Kathmandu (1400 m) and continued during their climb or trek. Because no published studies used these exact methods, we necessarily calculated sample sizes based on the best available information. We stand by our calculations and recognize that using a study to determine sample size that does not precisely match the population, elevation, latitude, and ascent rate has limitations. Indeed, these studies do not exist.