BRIEF REPORT

Cognitive Effects of Dexamethasone at High Altitude

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Objective.—The major therapeutic effect of dexamethasone on persons affected by high-altitude illness may be upon vascular leakiness with a consequent decrease in cerebral edema. We set out to determine if dexamethasone ameliorates the cognitive/psychomotor effects of acute exposure to high altitude on asymptomatic subjects.

Methods.—Six adult subjects were tested at baseline (2500 m) with standard, computerized cognitive and psychomotor tests. Over the next 4 days, subjects were acclimatized to an altitude of 3700 m. On the fifth day, subjects ascended to 4800 m where predexamethasone testing was administered. No subject had symptoms of frank altitude illness at 4800 m. To limit acclimatization, subjects descended to 3700 m within 4 hours. The first 4-mg dose of oral dexamethasone was given in the evening of day 5. A second 4-mg dose of dexamethasone was given the following morning, and subjects reascended to 4800 m where postdexamethasone testing was performed.

Results.—All cognitive and psychomotor tests showed improved reaction times in subjects who were given dexamethasone. Mean reaction time ($\pm$ SD) for shape recognition went from 1.20 ± 0.36 seconds at 2500 m to 1.40 ± 0.37 seconds at 4800 m. After dexamethasone administration, mean shape recognition time declined to 1.26 ± 0.32 seconds ($P = .052$).

Conclusion.—These data show a trend toward decreased cognitive deficits in subjects pretreated with dexamethasone. One possibility for this trend is that cognitive deficits in otherwise asymptomatic subjects exposed to high altitude are caused by subclinical cerebral edema.

Key words: high altitude, cognitive performance, dexamethasone, cerebral edema, acute mountain sickness, corpus callosum

Introduction

An improved ability to perform certain tasks after acute exposure to high altitude has been shown in subjects pretreated with dexamethasone.¹ The leading theory,^{2,3} though not yet conclusively proven, is that dexamethasone decreases leakiness of cerebral vessels and thus diminishes cerebral edema. Although evidence shows that cerebral edema is present in persons with moderate to severe acute mountain sickness (AMS) after 24 hours at altitude, no strong evidence shows any cerebral edema in persons without symp-

toms of AMS or persons with symptoms during the first 24 hours at high altitude.⁴ Typical AMS usually manifests itself most strongly after at least 1 night at altitude, yet some investigators have noted that subtle cognitive deficits are seen transiently during the first few hours at high altitude.^{1,5} The phenomenon of transient, early cognitive deficits may represent the early stages of an incomplete adaptation to the new altitude. Symptoms of AMS after a night at the new altitude probably represent a breakdown in this adaptive mechanism brought on by the relative hypoxia of sleep. We devised a protocol to test the hypothesis that there are cognitive deficits reversed by dexamethasone, even in asymptomatic subjects immediately upon arrival at high altitude. One possible inference is that such cognitive deficits may be caused by an early, altitude-induced cerebral edema.

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Raw data for 6 subjects showing time in seconds for test of pattern comparison at baseline (2500 m), predexamethasone (4800 m), and postdexamethasone (4800 m)

Subject No.	2500 m	4800 m	4800 m
1	0.83	1.05	0.88
2	1.63	2.10	1.80
3	1.68	1.37	1.44
4	0.98	1.19	1.15
5	0.97	1.37	1.14
6	1.11	1.32	1.16

Methods

Six healthy adults (4 men and 2 women, ages 26–51) resident at sea level gave informed consent to participate in the study. Psychomotor testing was done at 2500 m after 4 days of acclimatization. A battery of 3 tests previously used as part of the Automated Performance Test System (APTS) to study the psychomotor/cognitive effects of exposure to high altitude were chosen. Testing was administered on a laptop computer and included tests of shape recognition, code substitution, and 4-choice reaction time.^{6,7} Before testing, all subjects trained until a plateau performance was achieved. Testing at all altitudes was performed indoors with adequate light at the same time of day. After baseline testing at 2500 m, subjects gradually acclimatized to 3700 m over the next 4 days. To minimize ongoing acclimatization between day 5 and day 6 at 4800 m, all subjects took acetazolamide 250 mg 3 times a day starting on day 1 for the duration of the study. On day 5, subjects ascended to 4800 m by car to the Jose Ribas refuge on Cotopaxi in Ecuador where testing was performed over the course of 4 hours. Subjects then descended again by car to 3700 m where 4 mg of dexamethasone was administered in the evening. On day 6, all subjects received a second 4-mg dose of dexamethasone and then proceeded to ascend again by car to 4800 m where testing was repeated a second time. All subjects remained active and healthy, and none had symptoms of AMS on the testing days. A paired *t* test was used to compare mean differences between test scores pre- and postdexamethasone at 4800 m.

Results

The Table shows raw data for all subjects' performance on the test of pattern comparison. Figure 1 graphically displays grouped results for each of the 3 APTS tests. Figure 2 shows individual results for the 3 psychomotor tests. The mean score ($\pm$ SD) for pattern comparison

Figure 1. Grouped data at baseline (2500 m), predexamethasone (4800 m), and postdexamethasone (4800 m).

went from 1.20 ± 0.36 seconds at 2500 m to 1.40 ± 0.37 seconds at 4800 m. After dexamethasone administration, mean reaction time for pattern comparison declined to 1.26 ± 0.32 seconds ($P = .052$). Four-choice reaction time and code substitution at 4800 m showed similar, though smaller, improvements after dexamethasone administration. These results show a trend toward improved reaction time after subjects received dexamethasone.

Discussion

Three important variables that relate to the ability to measure cognitive and psychomotor effects of acute exposure to altitude are 1) the absolute altitude change, 2) the rate at which that change occurs, and 3) the length of the delay between arrival at high altitude and the per-

Figure 2. Individual data at baseline, predexamethasone, and postdexamethasone.

formance of cognitive and psychomotor testing. Delays of as little as 15 hours, even with an abrupt change in altitude as great as 4300 m, can fail to reveal cognitive deficits that are initially present.^{1,5} Our data reveal cognitive deficits after a change in altitude of only 1000 m, which is a fairly routine altitude change among recreational mountain climbers. We were able to detect cognitive deficits probably because we tested subjects within 2 hours of arriving at high altitude.

Kramer et al,⁸ using the same APTS, found that subjects did not show any deficits at 4360 m. However, after initial testing at sea level, their subjects spent from 5 to 9 days walking between 2195 and 4360 m; therefore, they were better acclimatized to the higher altitude upon testing than were the subjects in our study. Leiffen et al⁹ tested psychomotor effects of acute exposure to altitude in 4 subjects, using the 4-choice reaction time test in a hypobaric chamber. No deficit was seen in this study, even with exposure to 7000 m. However, this study had a small number of subjects, and choice reaction time appears to be less sensitive to the cognitive changes brought on by acute exposure to high altitude⁶ (probably because choice reaction time is a test of lower-level psychomotor skills). Mackintosh et al,¹⁰ also using a version of choice reaction time, did find deficits in reaction time among subjects with symptoms of AMS on ascent to 4790 or 5008 m; however, no significant effect was seen in subjects who did not have frank symptoms of AMS. Subjects in their study ascended at the relatively fast rate of 1000 m per day, a change in altitude similar to that used in our study protocol.

Jobe et al,¹ in a study of the effects of dexamethasone on cognition, found that altitude-related deficits were less pronounced in subjects pretreated with dexamethasone than in subjects taking placebo. In their study, subjects were transported from sea level to 4300 m with no intermediate acclimatization. In another study of cognitive deficits, during a simulated ascent of Mount Everest in a hypobaric chamber (Operation Everest II), Kennedy et al⁶ found that subjects showed a marked increase in reaction time on APTS tests of grammatical reasoning and shape recognition. Their study showed that tests of cognition were more sensitive to hypobaric hypoxia than were tests of psychomotor performance. Cognitive deficits at a simulated altitude of 4800 m during Operation Everest II were negligible. However, because of study design, testing may have been delayed hours or days once a given altitude had been reached; therefore, acute effects might have been missed.

Our data suggest that acute exposure to altitude in asymptomatic subjects results in subtle cognitive deficits that are largely reversed by dexamethasone. Our data and others⁶ show the greatest effect is upon tests of

pattern recognition. The physiologic mechanism through which dexamethasone may have exerted the effect that we observed may be related to the effect of dexamethasone on brains that more overtly manifest altitude pathology. It is generally accepted that dexamethasone can reduce abnormal leakiness of the blood brain barrier. In an article on high-altitude cerebral edema and AMS, Hackett et al⁴ review the evidence that AMS results from mild cerebral edema, and therefore the 2 conditions exist on a continuum and are not pathophysiologically distinct disease processes. Hackett et al find evidence in the literature for vasogenic edema in subjects with moderate to severe AMS after more than 24 hours at high altitude. In subjects with only mild AMS, or more severe AMS but less than 24 hours at altitude, there is evidence of brain swelling, but the literature does not support the conclusion that these subjects have vasogenic edema.¹¹⁻¹³ Although brain swelling may be caused by subtle edema, which is not discernible on the available imaging modalities, it may also be caused by vascular engorgement from increased cerebral blood flow. Because there is no reason to believe that dexamethasone would reverse changes due only to vascular engorgement, our data support the hypothesis that the onset of vasogenic edema may occur in subjects without AMS symptoms and within a very short time of arriving at high altitude. Our data support this hypothesis only by inference, and direct testing of this hypothesis was not undertaken in this study.

If the cognitive deficits we found are due to mild cerebral edema, why is pattern recognition more affected than the other psychomotor/cognitive faculties that are tested? In another recent paper, Hackett et al¹⁴ report on magnetic resonance imaging (MRI) findings in persons affected by high-altitude cerebral edema. They found white-matter edema mostly in the splenium of the corpus callosum. This part of the corpus callosum is important in the transfer of visual information between the cerebral hemispheres, as would occur during the comparison of 2 shapes on either side of a computer screen.¹⁵

Is there evidence elsewhere in the literature that shows acute altitude exposure resulting in cerebral edema in asymptomatic subjects? In a hypobaric chamber study, Morocz et al¹⁶ studied cerebral MRI changes after 32 hours at 4572 m. They found significant changes only in cerebral grey matter and were unable to find any focal cerebral volume changes. Interestingly, they also were unable to show a correlation between incidence and degree of AMS symptoms and degree of brain swelling after acute altitude exposure. This circumstance led them to conclude that brain swelling is possible after acute exposure to high altitude, even in subjects without symptoms of AMS. However, we also note that the MRI data

of Morocz et al did not reveal whether the brain swelling they identified was due to vascular engorgement or edema. Although there is no proof yet that acute exposure to high altitude results rapidly in subtle cerebral edema in subjects with no overt symptoms of altitude illness, the evidence is interesting and suggestive. Certainly, further studies would help lay the question to rest.

Limitations of this study include the small number of subjects and the use of subjects as their own controls. This necessitated the testing of subjects on different days and opened up the possibility that the beneficial effect attributed to dexamethasone might in part be due to increased acclimatization. To minimize this possibility, subjects acclimatized gradually to 3700 m and spent as little time as possible above this altitude during the 2 days when testing was done at 4800 m. A larger, double-blind, placebo-controlled study would be ideal. Another limitation of this study is that its main finding, that dexamethasone reverses subtle cognitive/psychomotor deficits in asymptomatic subjects exposed acutely to high altitude, is mostly of interest in the light of the possibility that these cognitive/psychomotor deficits are caused by subclinical cerebral edema. Our study protocol allows only inferences about this subclinical cerebral edema, for we did not study it directly.

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