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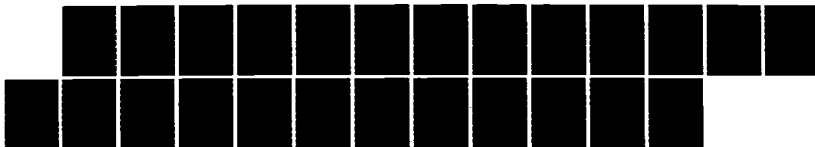
EFFECT OF DEXAMETHASONE ON SYMPTOMS OF ACUTE MOUNTAIN
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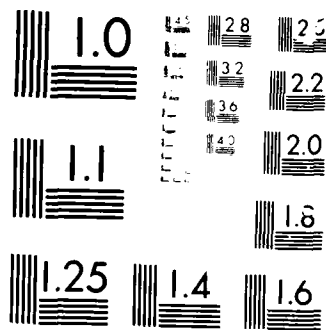
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EFFECT OF DEXAMETHASONE ON SYMPTOMS OF ACUTE
MOUNTAIN SICKNESS AT PIKES PEAK, CO (4300m)

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Running Head: Dexamethasone and AMS

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ABSTRACT

In a previous controlled study, dexamethasone (DEX) was shown to prevent acute mountain sickness (AMS) during exposure to simulated high altitude. To determine the effect of DEX during actual altitude exposure, sixteen young men were treated with either DEX (4 mg every 6 h) or placebo for 48 h prior to and 48 h after being rapidly transported from sea level to the summit of Pikes Peak, CO (4300 m). Symptoms of AMS were evaluated twice daily at Pikes Peak using the Environmental Symptoms Questionnaire and a clinical assessment. During treatment the mean symptom scores were higher for subjects taking placebo in 18 out of 20 comparisons. On an individual basis, 60% of the subjects receiving placebo met the criteria for being "sick" compared to 31% of subjects receiving DEX. Beginning 24 h after cessation of treatment, DEX subjects experienced a progressive increase in symptom scores which lasted through the end of the altitude sojourn (day 6). The results indicate that DEX is an effective prophylactic treatment for AMS in an actual mountain environment, but that AMS symptoms can occur if the drug is stopped abruptly.

Index Terms: Altitude Illness, Corticosteroid, Altitude Exposure

INTRODUCTION

Acute mountain sickness (AMS) is a syndrome of hypoxia-induced symptoms occurring in unacclimatized low altitude residents who are rapidly exposed to altitudes greater than 3000 m. The syndrome is characterized by headache, nausea, vomiting, lassitude, anorexia and sleep disturbances. Symptoms appear within three to eight hours after ascent and generally remit spontaneously over a period of several days as the afflicted person becomes acclimatized. The incidence of AMS has increased greatly over the last 25 years due to both an increased participation in mountain recreation and rapid access to high altitude environments brought about by improved air and ground transportation. As the incidence of AMS has increased, so has the interest in its prevention; for although the syndrome is self-limited, people on brief sojourns into the mountains for recreational purposes are disinclined to spend one to several days suffering AMS while they acclimatize.

Several drug regimens have been proposed or actively investigated as potential prophylaxis for AMS (2,4,7,9,14,15,17). To date, the drug which has had the widest acceptance has been acetazolamide. It has not been found to be universally effective (8,9,15), however, and it can have unpleasant side effects (1,10). Recently, the synthetic corticosteroid, dexamethasone, was shown to prevent AMS in subjects exposed to 4750 m in a hypobaric chamber (13), suggesting that it may be a potential prophylactic for AMS. However, that study examined only a small number of subjects exposed to altitude for a relatively short period of time in a controlled and somewhat artificial environment. Consequently, several questions remain unanswered concerning the

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use of dexamethasone. Among these are whether the drug works in the actual mountain environment and what effect it has on normal acclimatization. The latter concern is especially important. If acclimatization does not take place, the person taking the drug will have to continue taking it throughout the period of altitude exposure or run the risk of AMS symptoms occurring when the drug is discontinued. We examined these questions in 16 young men receiving either dexamethasone or placebo during a six-day residence at 4300 m altitude on the summit of Pikes Peak in Colorado.

MATERIAL AND METHODS

Sixteen healthy male volunteers participated in this study. Each was also a participant in a concomitant study of energy metabolism during exercise at altitude. The sixteen men ranged in age from 19-26 yrs, had a mean ($\pm$ S.D.) height of 177.5 ± 9.5 cm and a mean weight of 73.4 ± 11.8 kg. All were life-long sea-level residents and had no exposure to altitudes greater than 1000 m for at least six months prior to their participation. None had any illness or medical contraindication to altitude exposure or dexamethasone administration and all gave their informed consent.

The study was conducted as a double-blind, placebo-controlled trial. Subjects had been assigned at random to either a treatment or a control group for purposes of the concomitant metabolism study. Of the 16 men who began this study, nine were in the control group and seven in the treatment group. One subject was removed from the control group for medical evaluation after two days of altitude exposure when he developed mild chest pain following a submaximal exercise test. His data were not included in the analysis. Subjects

in the treatment group received 4 mg dexamethasone by mouth every 6 h for 48 h at sea level (Natick, MA; 50 m). They were then transported to the USARIEM Pikes Peak Laboratory Facility (Pikes Peak, CO; 4300 m) in less than six hrs, where they remained for six days. They continued to take dexamethasone for 48 h after their arrival at Pikes Peak after which time the treatment was discontinued. The control group followed the same drug/altitude schedule, but received an identically-appearing placebo in place of dexamethasone. While at Pikes Peak, subjects were given unrestricted access to fluids and a nutritionally balanced diet and were allowed to walk about the summit at will. Each also participated in submaximal exercise testing at Pikes Peak on three separate days as part of the study on energy metabolism.

AMS symptoms were assessed twice daily using the Environmental Symptoms Questionnaire (ESQ) and a physician's clinical interview. Four measures of AMS were calculated from these assessments: two symptom scores based on the ESQ data and two symptom scores based on data gathered during the physician's interview. A fifth subjective score was assigned by the interviewing physician at the time of the clinical interview. The bases for these measures are detailed below.

The ESQ is a 67-question symptom inventory designed to quantitate symptoms induced by altitude and other stressful environments (19). The questionnaire was self-administered, but all subjects took it concurrently while resting comfortably in a seated position. A weighted average of "cerebral" symptom scores (labeled AMS-C) and a weighted average of "respiratory" symptom scores labeled (AMS-R) were calculated to identify the presence of AMS (18). Scores greater than 0.7 for AMS-C and 0.6 for AMS-R were considered to indicate subjects who were "sick." The ability of these scores

to accurately identify individuals experiencing AMS has been established in previous studies (18).

The majority of the physician's clinical assessments (CA) were performed by one of two physicians experienced in altitude-induced medical problems. The second physician substituted for the first on a limited number of occasions randomly distributed throughout the study. At the time of each assessment, the physicians were unaware of which treatment the subject was receiving. They recorded the presence of specific altitude-related symptoms such as headache, nausea, dyspnea and sleep disturbances and examined the subjects for the presence of rales or peripheral edema. Immediately following the interview, the physician rated the subject on the presence and severity of AMS using a scale of 0 (no AMS) to +3 (severe AMS).

Following completion of the study, two separate symptom scores were calculated from the symptoms recorded during the physician's interview. The first, originally reported by Johnson et al. (13), was based on the scale: 0 - no symptoms; 1 - mild headache or nausea; 2 - moderate headache and nausea; and 3 - severe headache, nausea, vomiting, or some combination of these. A score of 1 or more was considered to be indicative of AMS. The second score was based on the scale of Hackett and coworkers (11,12). In that scale 1 point each is assigned for emesis and headache, nausea, insomnia and anorexia ; 2 points each for headache unrelieved by analgesics and 3 points each for dyspnea at rest, ataxia and severe lassitude. Scores greater than or equal to two are felt to identify individuals with AMS (12).

Venous blood samples were taken at rest without stasis in the morning prior to the test subjects' arising on three occasions at sea level and daily at Pikes Peak. Hematocrit (Hct) was measured in triplicate using a microhematocrit

centrifuge and hemoglobin (Hb) was measured, also in triplicate, using the cyanmethemoglobin technique. From these values the percent change in plasma volume between sea level and altitude was calculated using the formula of Strauss et al. (20).

All urine was collected and the volume recorded for 24 h periods on three occasions at sea level (one occasion on medication and two occasions off medication) and throughout the entire sojourn at Pikes Peak.

Data are reported as mean $\pm$ S.D. except where noted. A sign test was employed to determine the significance of the difference between mean values of all five measures of AMS for the dexamethasone and placebo-treated groups in the treated and untreated condition at altitude. The relationship between paired mean scores was considered "improved" and designated by a "+" if the dexamethasone score was lower than the control value. If the dexamethasone score was higher, the relationship was designated by a "-". Tied scores were discarded. Values for mean Hb, Hct, plasma volume and 24-h urine volume were analyzed using a 2-way analysis of variance.

RESULTS

Mean scores for each of the measures of AMS are presented in Table 1. All five measures showed the same general pattern of differences between groups during treatment at altitude. The pattern differed after treatment was discontinued (Figure 1).

Dexamethasone appeared to reduce the incidence and/or severity of AMS symptoms during the treatment period (days 1 and 2). The mean scores for the dexamethasone group during this time were generally lower than those of the

placebo. For three of the five measures (AMS-R, CA and Johnson scale score), the mean dexamethasone scores were always lower than placebo; however, the AMS-C and Hackett scale each showed one occasion in which the dexamethasone mean scores were higher than placebo. Overall, the dexamethasone means were lower than placebo in 18 out of 20 comparisons ($p < 0.01$).

The same conclusion was reached when the number of individuals who were sick while taking dexamethasone or placebo at altitude were considered rather than the mean scores. Four of eight individuals taking placebo and two of seven taking dexamethasone were identified as being "sick" on the basis of their AMS-C scores during at least one trial. On the basis of AMS-R scores, three of the placebo group and one of the dexamethasone group were identified as having AMS. The physician's clinical assessment suggested six of the eight subjects on placebo had AMS compared to four of the seven taking dexamethasone, while the Johnson score identified six versus three, respectively. Similarly, the Hackett score showed five placebo and one dexamethasone treated subject to have AMS. Taken together, 60% of placebo-treated subjects and 31% of dexamethasone-treated subjects exceeded the criterion for AMS on at least one occasion.

While dexamethasone appeared to prevent or reduce symptoms of AMS during treatment, the dexamethasone-treated subjects seemed to develop symptoms after the treatment was discontinued. Beginning 24 h after cessation of treatment and lasting to the end of exposure (days 4-6), the original pattern of scores was reversed in that the dexamethasone group mean scores were generally higher than placebo. A sign test showed the difference to be significant ($p < 0.01$). The AMS-C and AMS-R mean scores were always higher for the dexamethasone group, as were the Hackett and Johnson scale scores.

Clinical assessment scores were higher in the dexamethasone group only during the third day after cessation of treatment. Again, the same pattern persisted when the data on number of sick individuals was considered rather than mean scores. Beginning 24 h after cessation of treatment, six individuals in the dexamethasone treated group were "sick" during at least one trial according to the Johnson scale, four on AMS-R criteria, three on clinical assessment and two by the Hackett scale. During that same period, three individuals in the control group were identified as being "sick" on the basis of clinical assessment and the Johnson scale, one by AMS-C and none by AMS-R or the Hackett scale.

The mean values for Hct and percent change in plasma volume are presented in Figure 2. The values reflect the normal pattern of hemoconcentration seen in males of this age range when exposed to altitude, ie. an apparent increase in the Hct resulting from a decrease in plasma volume (5,16). There were no significant differences between dexamethasone and placebo treated subjects in this regard.

Although the previous dexamethasone study showed an increase in urinary output in dexamethasone-treated subjects at altitude (13), no consistent effect of altitude exposure or treatment was found in the urinary output data from this study. The mean ($\pm$ S.D.) 24-h urine output was 1512 ± 467 ml and 1325 ± 246 ml for placebo and dexamethasone treated subjects respectively at sea level and 1235 ± 354 ml and 1295 ± 373 ml during the treatment period at Pikes Peak. The mean urine output following cessation of treatment were 1324 ± 589 ml and 1745 ± 835 ml at altitude compared to 1092 ± 305 ml and 1455 ± 468 ml at sea level off treatment.

DISCUSSION

The results of this study suggest that dexamethasone decreased symptoms of AMS in young men during the acute phase of high altitude exposure. This confirms the findings of the previous hypobaric chamber study (13). Five separate measures of AMS based upon subjective and objective assessments of symptoms were used to identify subjects with AMS. The mean values for AMS-C, AMS-R and the Johnson scale scores were lower in the present study than those found in the hypobaric chamber study, and fewer individuals were classified as "sick" on the basis of those scores. This may reflect the slightly lower altitude of the Pikes Peak facility compared to the altitude used in the chamber study (4300 m vs. 4572 m), for AMS is generally felt to be positively correlated with altitude. Lower altitude could have decreased the incidence and severity of initial symptoms and possibly also allowed for more rapid acclimatization and consequent remission of symptoms. Indeed, the mean symptom scores during treatment were lower in the placebo group on Pikes Peak than were seen in the chamber. The relative lack of confinement compared to the hypobaric chamber may also have had an effect on symptom reporting.

Higher symptom scores in dexamethasone-treated subjects compared to controls after treatment was discontinued resulted from both an increase in dexamethasone scores and a drop in the placebo scores relative to the treatment period. The decrease in placebo scores is consistent with the self-limiting nature of AMS and is similar to the pattern consistently observed in previous studies at Pike Peak (4,6,18). The increase in symptom scores of dexamethasone-treated subjects during this period is a new finding with at least two possible explanations. The first is that dexamethasone somehow interfered with normal acclimatization, causing the treated subjects to

develop symptoms after the medication was withdrawn and its protective influence diminished. Such an explanation is consistent with the onset of symptoms 24 h after the last dose of drug. The only non-symptomological measures of acclimatization in this study were Hct and plasma volume, which are known to increase and decrease respectively with acclimatization in men of this age group (5,16). Both groups followed that pattern, which suggests that at least some of their "normal" responses to altitude were similar.

Another possible explanation is that symptoms resulted from drug withdrawal independently of altitude exposure. Dexamethasone is capable of producing a withdrawal syndrome when it is suddenly discontinued, especially when used in the relatively high doses used in this study. Withdrawal symptoms are more common in prolonged administration of the drug, however. The time course of symptom development in treated subjects in this study is consistent with withdrawal. Although subjects were treated on the same regimen at sea level three weeks prior to the Pikes Peak sojourn, no measures of symptoms were made more than 24 h after the drug was discontinued and there was thus no way to detect withdrawal symptoms. One anecdotal report has been received of post-treatment symptoms in scientists who took dexamethasone for two days after being flown to 4200 m on Mt. McKinley (R. Roach, personal communication). The symptoms which were experienced after abruptly discontinuing the drug were consistent with steroid withdrawal and did not resemble AMS.

The development of symptoms in treated subjects who were previously asymptomatic has implications for the potential usefulness of dexamethasone as a prophylactic modality in the high altitude setting. Two strategies have been used in constructing prophylactic regimens for AMS. In the first, no

consideration is made for acclimatization over time, and the drug is administered throughout the entire period of altitude exposure. The second strategy assumes the body will acclimatize and, therefore, the drug is administered only during the first several days of altitude exposure while the body is acclimatizing and AMS symptoms are most intense. The results of the present study suggest that dexamethasone may belong in the first category. If this is the case, the usefulness of dexamethasone as prophylaxis is questionable, for there are serious risks in long term administration of this potent corticosteroid. An alternate approach would be to slowly taper the steroid, as is often undertaken in clinical practice. These strategies deserve further investigation.

In summary, dexamethasone was found to reduce symptoms of AMS during the first three days of altitude exposure, but symptoms occurred after treatment was discontinued. Further studies are needed to document this effect and determine the mechanism by which it occurs.

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Human subjects participated in these studies after giving their voluntary informed consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on the use of volunteers in research. The views, opinions and findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy or decision unless so designated by other official documentation.

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Figure 1. Mean scores for five measures of acute mountain sickness in 15 young men during and after treatment with 4 mg dexamethasone every 6 h (n=7) or placebo (n=8) at 4300 m altitude.

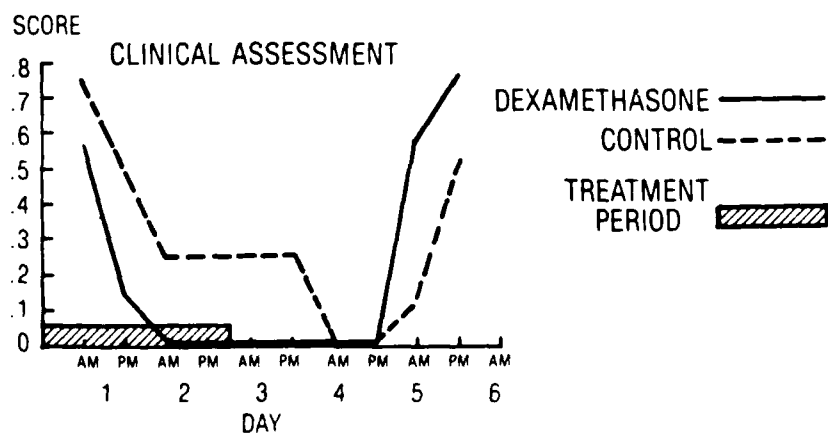
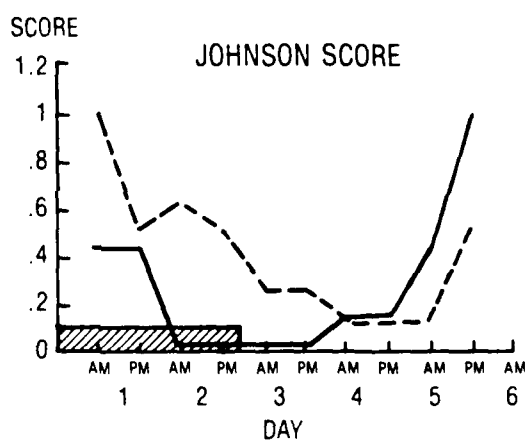
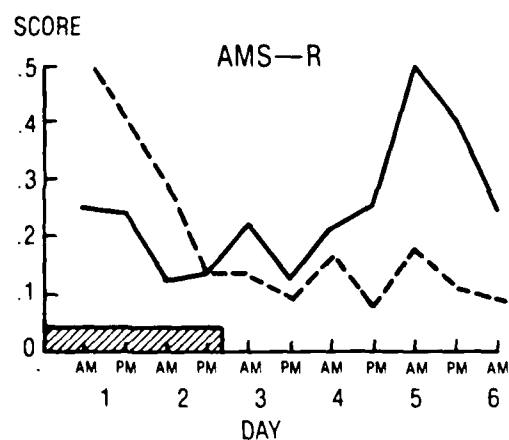
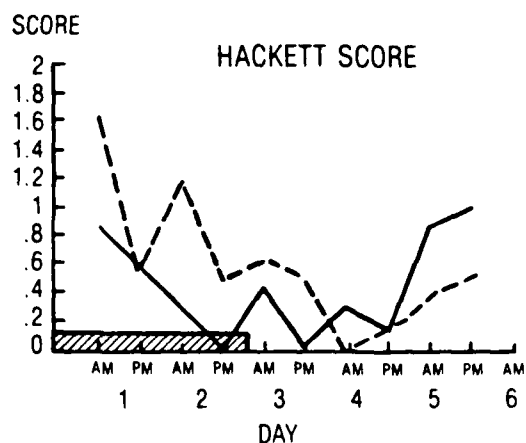
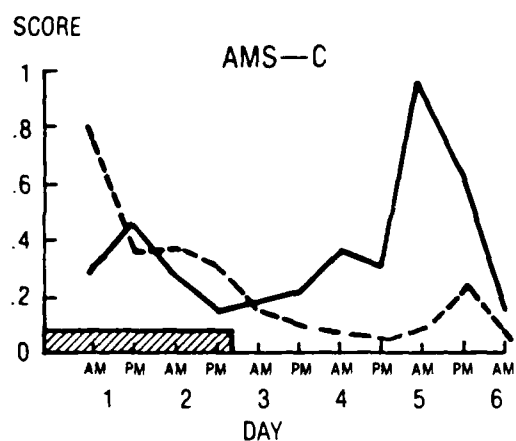


Figure 2. Mean scores for hematocrit and percent change in plasma volume compared to sea level in 15 young men during and after treatment with 4 mg dexamethasone every 6h (n=7) or placebo (n=8) at 4300 m altitude.

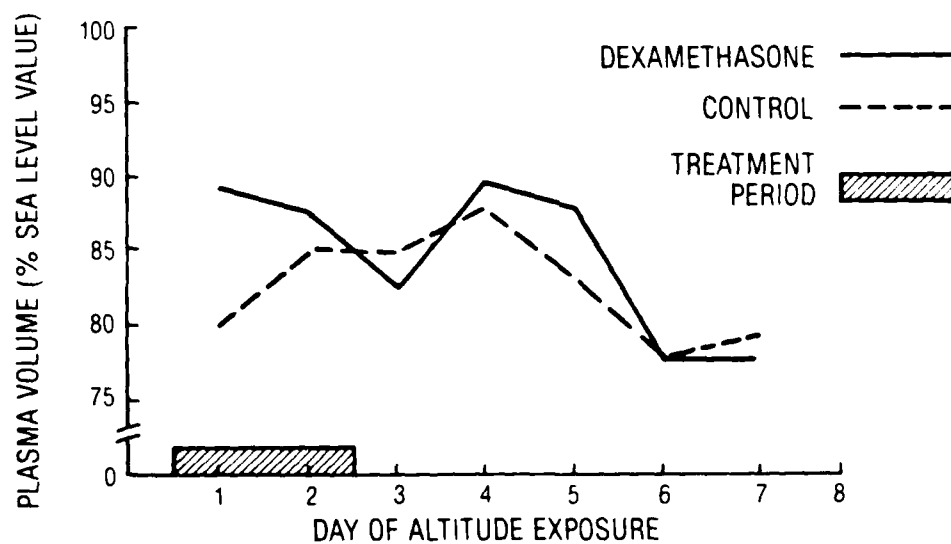
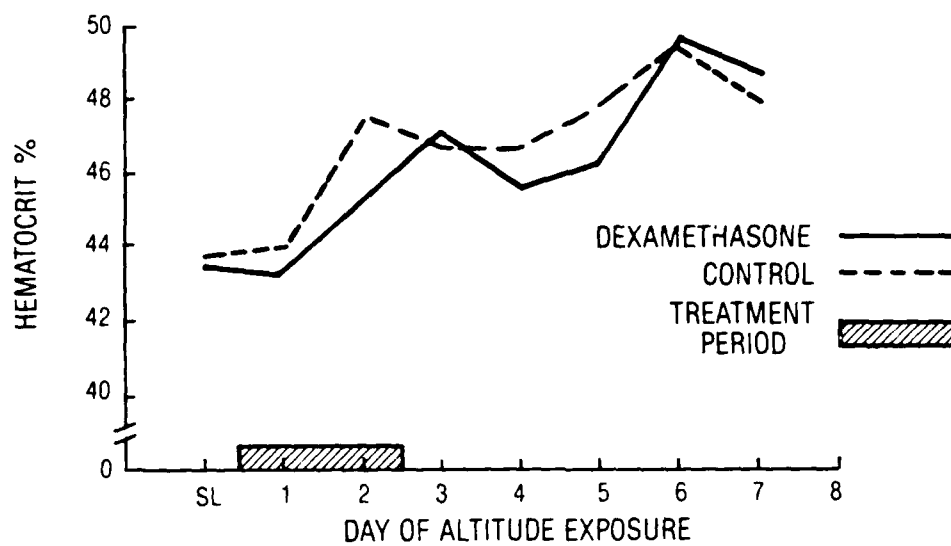


TABLE 1. MEAN SCORES FOR FIVE MEASURES OF ACUTE MOUNTAIN SICKNESS.

SCORE	day #	1		2		3		4		5		6	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
		treated				untreated							
Dexamethasone (n=7):													
ESQ-C		.305	.459	.273	.141	.162	.196	.338	.274	.923	.586	.086	
ESQ-R		.250	.241	.119	.132	.219	.121	.211	.254	.502	.402	.234	
CA		.57	.14	0	0	0	0	0	0	.57	.75	----	
Hackett Score		.86	.57	.28	0	.43	0	.29	.14	.86	1.00	----	
Johnson Score		.43	.43	0	0	0	0	.14	.14	.43	1.00	----	
Placebo (n=8):													
ESQ-C		.793	.365	.367	.283	.137	.090	.045	.023	.057	.187	.022	
ESQ-R		.533	.407	.300	.137	.132	.095	.167	.067	.166	.094	.071	
CA		.75	.50	.25	.25	.25	.25	0	0	.13	.50	----	
Hackett Score		1.62	.50	1.13	.50	.63	.50	0	.13	.38	.50	----	
Johnson Score		1.0	.50	.63	.50	.25	.25	.13	.13	.13	.50	----	

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