Methazolamide and Acetazolamide in Acute Mountain Sickness

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Methazolamide (150 mg/d) was as effective as acetazolamide (500 mg/d) in preventing the symptoms of acute mountain sickness in 20 subjects ascending to 4985 m. Pa_{O_2} and oxygen saturation levels were similar on the two drugs but the fall in Pa_{CO_2} was greater on acetazolamide. Paraesthesiae, a side-effect of carbonic anhydrase inhibitors, tended to be less at high altitude on methazolamide and was significantly less when taking 100 mg/d at low altitude. It is likely that paraesthesiae is similar on the two drugs when given in doses that affect blood gases equally.

THE SYNDROME OF acute mountain sickness (AMS) consists of headaches, anorexia, nausea, vomiting, weakness, confusion, and other disturbances of consciousness occurring on ascent to high altitude. Acetazolamide is useful prophylaxis in most subjects (1), but side-effects, such as paraesthesiae, malaise, anorexia, nausea and drowsiness, are common. One method of reducing these problems may be to use a different carbonic anhydrase inhibitor, such as methazolamide, which has been reported to be better tolerated. In the management of glaucoma, methazolamide compares favourably with acetazolamide (2,3). Metazolamide has been used once in preventing AMS and was successful in seven subjects at 4200 m (4). To extend this work, we have conducted a double-blind trial of acetazolamide and methazolamide in 20 subjects ascending to 4985 m to compare the efficacy and side-effects of the two preparations under similar conditions.

METHODS

Subjects: The group comprised 19 men and 1 woman aged 22–54 years (mean 36 years) of whom 14 were medically qualified. All normally resided at less than 200 m and none had travelled to high altitude within the previous 6 months. Fourteen had been on previous expeditions of the society in 1977 and 1979 (1,5).

The expedition: All subjects flew to Nairobi (1661 m), travelled by road to 3050 m, and then ascended to the top camp at 4790 m on foot over 3 d (Fig. 1). Personal equipment

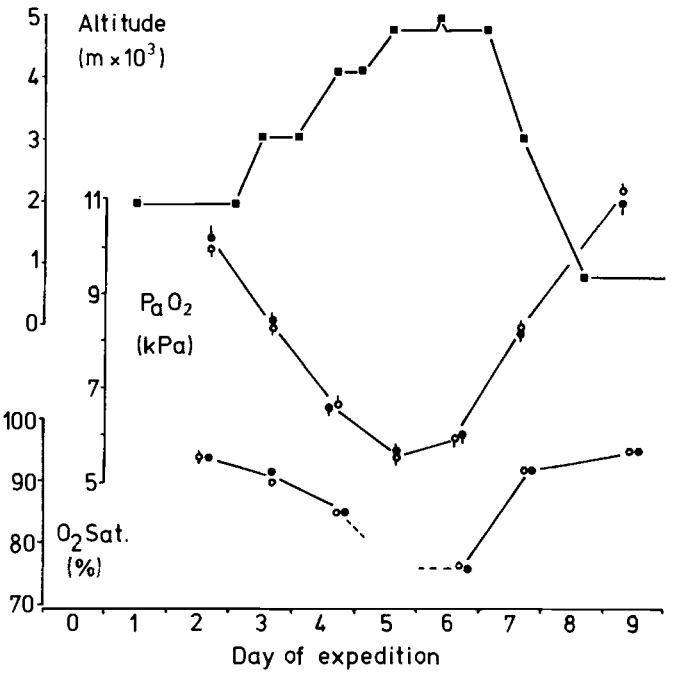

Fig. 1. The mean ± S.E. of the Pa_{O_2} and oxygen saturation of arterialised capillary blood found in 10 subjects on methazolamide (open circles) and 10 subjects on acetazolamide (closed circles) ascending to high altitude. The oxygen saturation was not measured on day 5. (1 kPa = 7.519 mm Hg; 1 mm Hg = 0.133 kPa).

of 10–15 kg was carried apart from a team of four who took turns in carrying the 35-kg generator. In the day spent at the top camp, Nelion (5188 m) was ascended by six subjects and Point Lenana (4985 m) by the remainder. All subjects de-

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scended together on the seventh day and observations were continued at 914 m until the 10th day.

Drugs: Subjects were stratified into four subgroups according to previous experience of AMS—severe (n = 6), moderate (n = 4), trivial or nil (n = 5) or no previous experience (n = 5)—and then randomly allocated to give an equal or approximately equal number of subjects on acetazolamide or methazolamide within each subgroup. Capsules with identical appearance were prepared containing either 250 mg acetazolamide (Diamox), 50 mg methazolamide (Neptazane), or lactose. The total daily dose of acetazolamide was 500 mg (2 active and 1 inactive drug capsule); of methazolamide, the daily dose was 100 mg for the first 5 d and 150 mg for the remainder. Drugs were started 8 d before ascent to high altitude and continued to the end of the observation period after descent. Compliance was 96% with a mean of two capsules per subject being omitted during the study. Details of medication were concealed from all subjects until the clinical and laboratory results had been analysed after the expedition. No diuretics were taken by any subject during the expedition.

Assessment of AMS: Each day, all subjects were interviewed and examined by two clinicians experienced in AMS using a standard series of questions and grading the severity of symptoms from 0–3 (nil to severe). A total AMS score was obtained by summing the individual scores for anorexia, nausea or vomiting, fatigue, headache, and unwell over day 2–8 inclusive. Scores were multiplied by 3 to give a range of 6–78 to facilitate comparison with scores obtained on previous expeditions. The severity of paraesthesiae was similarly graded 0–3. Self assessment was recorded on a modified environmental symptoms questionnaire (6) in which 56 individual symptoms were graded 0–5. A specific question on paraesthesiae was added. The questionnaire was completed twice daily by all subjects during the expedition and once daily on four consecutive days just before the expedition left Birmingham.

Blood gas measurements: Capillary blood was taken from arterialised ear lobes each afternoon after resting. Samples were analysed for pH, oxygen tension (Pa_{O_2}) and carbon dioxide tension (Pa_{CO_2}) with a Radiometer BGA Mark II and for oxygen saturation with an OSM2 hemoximeter. An aneroid altimeter checked in Nairobi on day 1 was used to determine barometric pressure and canisters of standard gas mixtures were used for calibration.

Statistics: Students *t* test was used apart from Spearman's rank correlation for assessment of AMS scores.

RESULTS

The clinical AMS score was not significantly different in subjects on acetazolamide (26 ± 7) compared with those on methazolamide (29 ± 6). In the whole group the AMS score correlated with the Pa_{O_2} recorded on arrival at the highest camp ($p<0.05$ rank correlation). Mean daily Pa_{O_2} and oxygen saturation are shown in Fig. 1. There were no significant differences between the two drug groups. The fall in Pa_{CO_2} was greater in subjects on acetazolamide (Fig. 2), but this was found both at low and high altitude. Similarly, there was a trend for the pH to be lower in the acetazolamide group throughout the study (not significant until the last day).

Paraesthesiae was the most commonly reported side-effect of both drugs and was more troublesome at high altitude (Table I). All subjects reported some paraesthesiae; it was moderate to extreme at some time in seven subjects on acetazolamide and five on methazolamide. The difference in paraesthesiae between the two drugs noted in the days before the expedition ($p<0.05$) continued but was not significant at high altitude. There was no correlation between an individual's paraesthesiae and acute mountain sickness scores ($r = -0.2$). The mean Pa_{CO_2} recorded during the expedition (days 2–9) correlated with the paraesthesiae score for those subjects on acetazolamide ($r = -0.7$; $p<0.02$) but not for those on methazolamide ($r = +0.2$).

Anorexia was noted by three subjects on acetazolamide and by none on methazolamide before ascent. At high alti-

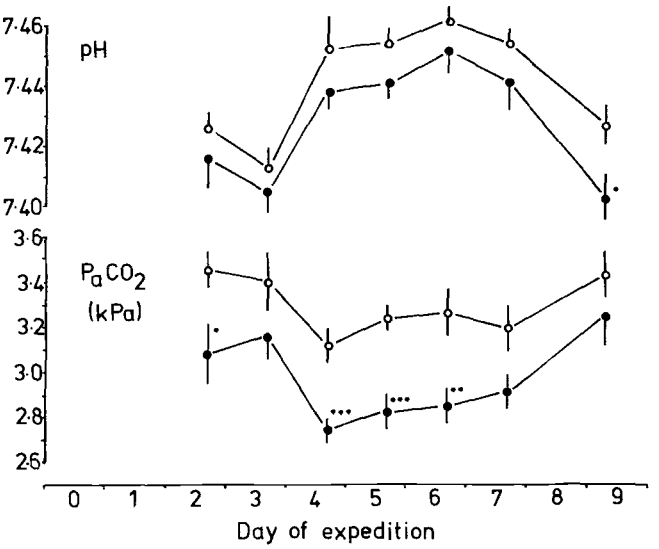

Fig. 2. The mean ± S.E. of the pH and Pa_{CO_2} of arterialised capillary blood found in 10 subjects on methazolamide (open circles) and 10 subjects on acetazolamide (closed circles) ascending to high altitude. *$p<0.05$; **$p<0.01$; ***$p<0.001$ refer to the comparison of two drug groups. (1 kPa = 7.519 mm Hg; 1 mm Hg = 0.133 kPa).

TABLE I. PARAESTHESIAE SCORE.

	Acetazolamide		Methazolamide	
	Mean/day	Accumulated score (M ± S.E.)	Mean/day	Accumulated score (M ± S.E.)
Days before expedition				
1	1.2		1.2	
2	1.7		0.2	
3	1.3		0.4	
4	0.7	4.9 ± 1.0		1.4 ± 0.7
Days of expedition				
2	2.6		1.7	
3	1.9		1.7	
4	2.1		1.5	
5	2.3		2.2	
6	1.9		1.7	
7	2.1		1.2	
8	1.4		1.7	
9	1.3		1.2	
10	1.2	16.8 ± 2.2	0.7	13.6 ± 2.0

The paraesthesiae score calculated as a mean score per subject with a maximum score of 10 per subject per day. The accumulated score for the four days before the expedition was significantly higher on acetazolamide compared with methazolamide ($p<0.05$).

tude, anorexia was troublesome in three subjects on acetazolamide and in one subject on methazolamide.

DISCUSSION

Methazolamide is a carbonic anhydrase inhibitor with actions similar to those of acetazolamide but with important pharmacological differences. Methazolamide is less bound to plasma proteins and diffuses more rapidly into tissues (7). Side-effects from methazolamide in therapeutic doses are thought to be less common than with acetazolamide (2). Comparison of the two drugs is made difficult because side-effects of both drugs are dose-dependent (8) and equivalent therapeutic doses cannot be determined readily. Even with a measureable effect, such as reduction in intraocular pressure, there are substantial disagreements on the optimum dose of methazolamide (3,9). For two of the known pharmacological effects of carbonic anhydrase inhibitors—reduction of intraocular pressure and flow of CSF—methazolamide is approximately 2.5–3 times as active by weight as acetazolamide (10). However, several studies comparing the two drugs have used a 5–10 times greater amount of acetazolamide. In such studies, side-effects are likely to be less common when using methazolamide.

The optimum or minimum effective dose of acetazolamide or methazolamide for the prophylaxis of AMS is unknown. In our studies, 500 mg/d of acetazolamide has been successful in most, but not all, subjects. Many studies have used 500–1000 mg daily (11–14).

A full trial of methazolamide in preventing AMS in unacclimatised subjects has not been reported previously. Methazolamide (200 mg/d) has been used successfully in a limited trial in partly acclimatised subjects working at 4200 m (4) with side-effects noted by over half the subjects. We chose to study methazolamide at 150 mg/d to give a pH effect approximately equivalent to acetazolamide at 500 mg/d. Whether the tissue distribution of the drugs is important in AMS is not known, but it is possible that the greater diffusion of methazolamide into the CSF and aqueous humour could be important. We deliberately gave drugs for 1 week before ascent to high altitude to ensure maximum tissue levels of both preparations.

This study showed that methazolamide was equally effective in preventing AMS but, as with acetazolamide, there was considerable variation between subjects. This was not related to the dose of drug/kg body weight, nor to plasma drug levels of acetazolamide which were measured on a previous expedition (unpublished observation).

The side-effect of paraesthesiae was somewhat more common in subjects on acetazolamide. The greater difference observed before the expedition was presumably due to the lower dose of methazolamide taken at the time that these questionnaires were completed. The increase in paraesthesiae at high altitude found with both drugs is probably due to the hyperventilation and the lowered P_{CO_2}. Other side effects were not troublesome on either drug in most subjects but we did not formally document the unpleasant taste of carbonated drinks.

We suggest that both drugs are useful in preventing AMS: until a predictive test for AMS can be found it would be wiser to use a fixed dose that has been shown to be effective and expect some side-effects.

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