

Improvement of muscle strength in familial hypokalaemic periodic paralysis with acetazolamide

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SUMMARY A double blind cross-over study of eight patients with familial hypokalaemic periodic paralysis was made to assess the influence of acetazolamide on muscle strength. All patients had a reduced interictal muscle fibre conduction velocity. Five patients had no attacks at the time of the study. One patient withdrew from the study because of an adverse reaction. The muscle strength of 11 muscle groups was measured with a hand-held dynamometer. The sum of force improved significantly in the seven patients (mean increase: 17%, $p < 0.05$; 95% confidence interval: 7.2–26.8%). Endurance tests showed an improvement in the performance of 30 full knee bends. Surface EMG measurement showed no change in the muscle fibre conduction velocity or power spectra during treatment. The integrated EMG showed a (non significant) mean increase of 21%.

Primary hypokalaemic periodic paralysis is characterised by different kinds of muscle weakness. The paralytic attacks are the most well known. In addition a permanent muscle weakness (PMW) has been described. This can be the result of the destruction of muscle tissue due to myopathy.¹ Alternatively, “abortive attacks” occur, that is, long lasting episodes with fluctuating weakness.^{2,3} As this weakness can be reversed by acetazolamide, these “abortive attacks” are probably due to a functional disturbance of the muscle membrane.

We have found⁴ that the mean strength of affected persons with hypokalaemic periodic paralysis is lower than the mean of normals. This implies that the cause of this “less than average strength” could be the same as the cause of abortive attacks. To test this hypothesis the influence of acetazolamide on the interictal strength in eight patients was assessed.

Patients and methods

All patients were members of a large family suffering from hypokalaemic periodic paralysis described in an earlier report.⁴ The main inclusion criterion was the finding of a reduced interictal muscle fibre conduction velocity (MFCV). The methods and the control group have been fully described.⁴ Briefly, the MFCV was measured with two

bipolar surface EMG electrodes placed parallel to the fibre direction of the biceps muscle between the motor point and the distal tendon. The average MFCV was estimated from the delay of the signals derived from the two electrodes using the cross-correlation method.⁵ In addition, the median frequency of the power spectrum and the integrated EMG of the signal were calculated. The diagnosis was reinforced by the history of typical attacks in five patients (nos 1, 2, 5, 7, 8), and the characteristic muscle biopsy findings in three of them (nos 3, 4, 8). Initially patients nos 1 and 2 suffered almost daily from paralytic attacks. In patients nos 5, 7 and 8 the last attacks were more than 5 years previously. These patients and patients nos 3, 4 and 6, who had never suffered from paralytic attacks, all complained of lack of strength in general and stiffness and pain of their upper legs during cold days and after rest.

Acetazolamide (3×125 mg daily) and placebo (lactose) were given in randomised order according to a cross-over design for 2 weeks each. The patients were seen weekly at the same time by the same blinded observer experienced in the use of the dynamometer. At every visit blood samples were taken to measure the serum electrolytes, venous pH, $p\text{CO}_2$, HCO_3^- , and the muscle enzymes creatine kinase and myoglobin.

Muscle strength of 11 muscle groups (see fig 1) was measured by a hand-held dynamometer, which was a modified Wika pressure gauge⁶ with a pressure range of 0–250 Newton. The exact anatomical location of the dynamometer and the position of the extremities were all standardised. All patients were trained before the trial to cooperate with measuring the maximal voluntary contraction. Every measurement was done twice and the mean strength was used for calculations. The ability to perform the following endurance tests was scored: raising arms for 3 minutes, raising the head and one leg for 1 minute in recumbent position and doing 30 knee bends without support.

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The significance of the difference between two means was determined by means of Student's *t* test for matched pairs.

Results

Seven women and one man (numbered 1–8) were studied. The mean age of the patients was 41 years

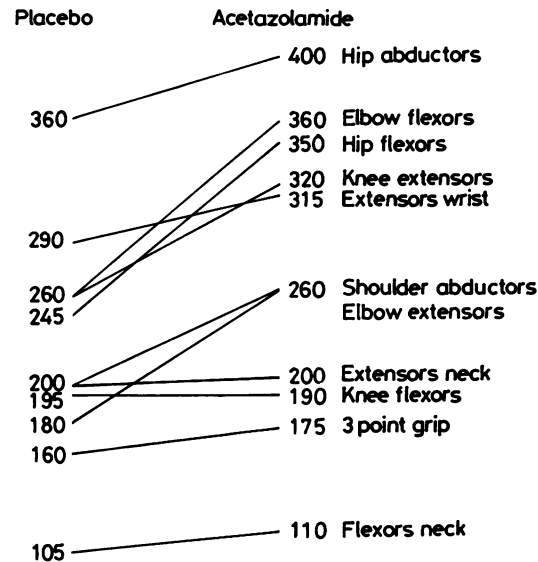


Fig 1 The muscle strength in Newtons (sum left and right) of patient no. 4 during the second placebo week and the second diamox week, measured with a hand-held dynamometer.

Table 1 Sum of the muscle strength of 11 muscle groups in Newtons (sum of 2 weeks)

Patient	Acetazolamide	Placebo	Difference	% increase
1	5060	4820	240	5
2	7925	6630	1295	19.5
3	5300	4845	455	9.4
4	5600	4955	645	13
5	6340	5775	565	9.8
6	5680	4430	1250	28.2
7	6715	4995	1720	34.4

Table 2 Results of laboratory measurements

	Placebo			Acetazolamide		
	Mean;	SEM	(range)	Mean;	SEM	(range)
pH*	7.34;	0.01	(7.29–7.39)	7.32;	0.01	(7.28–7.36)
pCO ₂ (kPa)†	5.83;	0.17	(4.8–6.9)	5.10;	0.20	(4.1–6.2)
HCO ₃ ⁻ (mmol/l)†	23.36;	0.39	(21–26)	19.64;	0.77	(16–25)
Cl ⁻ (mmol/l)†	105.50;	0.57	(102–108)	110.91;	0.64	(108–114)
CK (u/l)‡	96.79;	15.89	(38–264)	79.00;	15.85	(29–175)
Myogl. (u/l)‡	149.29;	32.01	(60–530)	199.09;	53.18	(50–530)

*difference between the two means is significant: $p < 0.02$

†difference between the two means is significant: $p < 0.001$

‡difference between the two means is not significant

CK = Creatine kinase, Myogl. = Myoglobin

(range 19–64 yrs). One woman (no 8) withdrew from the trial because of an unusual reaction to acetazolamide (dizziness, nausea, and being tearful). All patients noticed paraesthesias, especially during the first week, but these were not reported to the blind observer. One patient felt drowsy during acetazolamide. Two patients, who drank an aerated drink, complained of a bitter taste.

Muscle strength The sum of the muscle force of 11 muscle groups on both sides was calculated for every patient and the results obtained on the two visits (during either placebo or acetazolamide) were added. For all patients the strength during the treatment weeks was greater than during the placebo weeks (table 1) (mean strength of the seven patients during acetazolamide 6089 N, during placebo 5207 N, $p < 0.05$). So the mean strength increased by 17% during treatment (95% confidence interval: 7.2–26.8%). The total muscle strength during the second acetazolamide week was always higher than during the first week (fig 2) (mean increase 10%). The strength of abductors and extensors of the legs sometimes fell outside the range of the dynamometer (> 250 N). In calculations the value 250 N was used. Four of the seven patients did not need their hands to

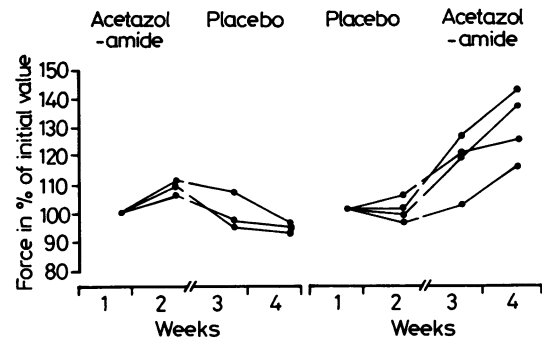


Fig 2 The change in the sum of muscle force of all muscle groups of the seven patients (divided in two groups according to the cross-over sequence) as measured with the hand-held dynamometer. The values have been normalised to initial value (= 100%).

Table 3 Results of the surface EMG measurements

	Placebo			Acetazolamide		
	Mean;	SEM	(range)	Mean;	SEM	(range)
MFCV (m/sec)*	3.15;	0.09	(2.6-3.7)	3.00;	0.08	(2.5-3.5)
Fmed (Hz)*	60.75;	3.86	(45.2-86.0)	57.54;	2.43	(41.8-67.8)
I-EMG (μ V)*	188.5;	21.6	(102-382)	229.4;	20.5	(94-400)

MFCV = muscle fibre conduction velocity

Fmed = median frequency; I-EMG = integrated emg

*difference between the two means is not significant

raise themselves after 15 kneebends, which was necessary during the placebo period. One patient could finish seven and eight bends during the placebo period and 12 and 13 during treatment. For two patients no differences were found. In the other endurance tests there was no objective difference between the placebo and treatment week although all patients performed the tests more easily during acetazolamide (less tired, less pain, less trembling of the used muscle groups).

In the two placebo weeks patient 1 had two minor paralytic attacks. Patient 2 used 10-15 g potassium daily during the trial and suffered from minor paralytic attacks every night. All patients except no. 5 said they were stronger in one part of the trial which afterwards appeared to coincide with the use of acetazolamide.

The laboratory results indicated the presence of a metabolic acidosis during treatment with acetazolamide (table 2). The surface EMG measurements (table 3) did not indicate an improvement of the MFCV or power spectrum during treatment. Although the mean integrated EMG raised from 188.5 to 229.4 V (21.7%) during treatment, this difference was not significant.

Discussion

The results confirm our hypothesis that acetazolamide improves muscle strength in patients with hypokalaemic periodic paralysis. The benefit of the medication was such that six of the seven patients who finished the trial continued to use acetazolamide. Remarkably, the most pronounced improvement of strength was generally seen in the limb-girdle muscles (fig 1). These are also preferentially affected in the myopathy of hypokalaemic periodic paralysis.⁷

Though attention has always been drawn to the paralytic attacks as the consequence of the membrane disturbance, this study shows another clinical expression: a permanent muscle weakness which was partially reversible in six of the patients without concomitant attacks. The improvement of muscle strength with acetazolamide agrees with the notion that the muscle strength in patients with hypokalaemic periodic paralysis is less than average.^{4,8} As

the muscle strength improved with acetazolamide, we suppose that this is probably caused by a small and changing amount of depolarised (and thus inactive) muscle fibres. From this point of view a paralytic attack is a sudden increase of the amount of inactive muscle fibres. In this way the clinical features of this disease can be more easily understood (fig 3): the less than average strength, the interictal muscle weakness and the paralytic attacks are all on a sliding scale, depending on the proportion of depolarised muscle fibres. In addition, there is a permanent weakness as a consequence of destruction of muscle fibres.

Because the electrophysiological expression of the altered membrane function in hypokalaemic periodic paralysis (the reduced MFCV) does not change under the influence of medication, acetazolamide could have a stabilising effect on the muscle membrane, preventing the dropout of muscle fibres. The reduced MFCV is probably due to the known membrane disturbance^{4,9}: an increased conductance of the muscle membrane to sodium, resulting in decreased membrane resistance. The mean increase of the integrated EMG of 21.7% during treatment, though not significant, supports this view. The large intertrial variability of the amplitude measurements of surface EMG could well be responsible for this lack of significance.

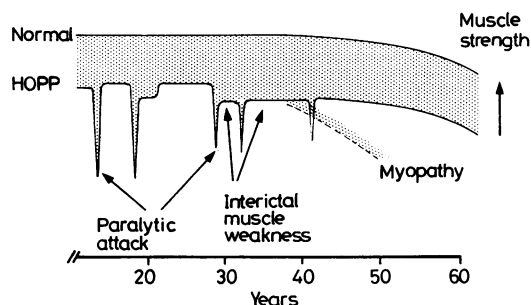


Fig 3 Schematic drawing of the various forms of muscle weakness in familial hypokalaemic periodic paralysis. The dotted area indicates the difference between the average force of normals and the hypokalaemic periodic paralysis patients.

The acid base equilibrium and chloride concentration changed significantly during the medication resulting in a metabolic acidosis. Though supported by some,¹⁰ it is not likely that this change is related to the improvement of the muscle strength, because the influence of acetazolamide on the acid base equilibrium is maximal within several days¹¹ and the improvement of muscle strength continued during the second week of therapy (fig 2). This is in accordance with Buruma,¹² who found no relation between electrolyte changes and the beneficial effect on attack frequency.

We conclude that acetazolamide improves the muscle strength in patients with hypokalaemic periodic paralysis even in the absence of paralytic attacks, probably by stabilising the muscle membrane.

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