THE EFFECT OF CHANGES IN SERUM POTASSIUM UPON MYOTONIA*

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The phenomenon of myotonia is characterized by a delay in relaxation, or more correctly, by a prolonged after-contraction which follows upon a contraction of skeletal muscle, despite the patient's attempts to relax. In some cases, the after-contraction, and the accompanying electrical changes which can be detected in the electromyogram, may last for as long as a minute. Myotonia occurs clinically in the group of disorders which have been referred to as "the myotonic syndrome" (Walton and Nattrass, 1954). The three principal conditions falling into this category are: first, myotonia congenita, in which the myotonia is generalized and present from birth; secondly, dystrophia myotonica in which myotonia usually appears first in adult life and affects comparatively few muscles, while there are signs of an associated peripheral myopathy and other dystrophic features; thirdly, there is the rare condition paramyotonia, in which myotonia occurs only on exposure to cold and is usually accompanied by episodes of profound muscular weakness, resembling in many respects attacks of familial periodic paralysis. Typically myotonia is made worse by cold and it is usually improved by exercise, but very occasionally it is accentuated by exertion (myotonia paradoxa). The pathogenesis of myotonia remains obscure; it is not abolished by blocking of the motor nerve supply of a muscle or by curarization, and hence it is widely believed that the phenomenon results from an intrinsic abnormality of the muscle fibre itself or of its membrane.

Many different forms of treatment have been utilized in an attempt to relieve or abolish myotonia, as it can sometimes be a most disabling symptom. In a recent paper (Leyburn and Walton, 1959) we reviewed the experiences of previous workers in this field and reported the results of a controlled trial of treatment carried out in 20 patients with myotonia. It was shown that both procaine amide and prednisone, if given by mouth, have a beneficial effect upon the condition and that both are much superior to quinine. It must nevertheless be admitted that although procaine amide is a satisfactory and successful remedy in the majority of cases, it does not always abolish myotonia completely, and side-effects are occasionally troublesome. In the hope of finding an even more effective treatment and of elucidating further the nature of the myotonic phenomenon, we decided to investigate the influence of changes in the serum potassium upon myotonia.

In 1953, Grüttnner and Mertens described treatment of a severe case of myotonia congenita using an ion-exchange resin to lower the serum potassium. Later they used the same method in treating 11 patients with dystrophia myotonica and six with myotonia congenita (Mertens and Grüttnner, 1955). The ion-exchange agent used was the ammonium form of polystyrene sulphonic acid which has the disadvantage that it attracts sodium ions as well as those of potassium, although its greatest effect is to decrease potassium absorption. Some of these patients received the resin for periods of several months, with resultant lowering of the serum potassium from an average value of about 19 mg. per 100 ml. (4·7 mEq./l.) to 12 mg. per 100 ml. (3·1 mEq./l.). Accompanying this prolonged fall in serum potassium there was a striking decrease in the severity of the myotonia in all cases, and this persisted for as long as the treatment was continued. Withdrawal of treatment was followed within a week by a rise of serum potassium to former levels and by a return of the myotonia to its previous state. In a small series of cases, Ilyina (1957) also found ion-exchange resins to be of benefit.

Recently, Tompkins, Lascelles, and McKinney (1959) have described the use of a potassium-binding resin in the treatment of two cases of myotonia congenita and one of dystrophia myotonica. Myotonia was said to be greatly diminished in all cases and abnormal electromyograms were restored to normal. In the dystrophic

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patient muscle power was reported to be greatly increased. In one case no significant fall in serum potassium and no constant change in other electrolyte values were noted during prolonged treatment and yet myotonia was improved by 90% in the forearm muscles. The authors agree that this finding is difficult to explain.

In this paper we report the results of a clinical trial in which we have studied the effect of a potassium-binding resin in seven patients with myotonia. In one case we also studied the effects of chlorothiazide and of insulin and glucose, and in another we were able to study the clinical phenomena which accompanied shifts in body potassium.

Material and Methods

Of the seven patients treated with the resin, five were suffering from dystrophia myotonica and two from myotonia congenita. None of the dystrophic patients was severely disabled but each of them showed clear-cut clinical myotonia in the muscles subserving the grip. In the two patients with Thomsen's disease myotonia was widespread and severe, but neither showed any dystrophic features; one of these patients had been included in our previous trial of treatment and had since taken procaine amide with good effect. For the period of the present trial, however, procaine amide therapy was discontinued. Of the other six patients, three had had no previous treatment and three had shown a poor response to procaine amide.

The resin used was sodium polystyrene sulphonate; it was supplied by Bayer Products Ltd., under the commercial name of "resonium-A". The dose of this recommended for hyperkalaemia of renal origin is 60 g. daily, and we gave our patients at least this amount, in four daily doses, taken after meals. Each patient was admitted to hospital before treatment was started and remained under in-patient supervision throughout the course of the trial.

In an attempt to define any possible relationship between the severity of myotonia and the level of the serum potassium, the latter was estimated in venous blood daily as far as possible; usually estimations of serum sodium, chloride, and bicarbonate were also performed. The serum calcium was estimated weekly but magnesium levels were not determined. Electromyograms were taken weekly. The duration of the myotonic after-discharge in the forearm muscles was assessed daily by the clinical method described previously (Leyburn and Walton, 1959). The patient squeezed two of the examiner's fingers as tightly as possible for three seconds and then, on command, he attempted to straighten out his fingers and thumb completely and as rapidly as possible in one smoothly continuous movement. Care was taken to ensure that the wrist was fully extended throughout. Both hands in turn were "timed" and the average time in seconds was taken as being the figure to represent the severity of the myotonia on that occasion. The estimations were always made at the same time of day and under similar conditions of temperature and patients were instructed not to use the muscles concerned for at least 15 minutes before each examination. The figure representing the duration of myotonia on any one day had little value in itself but possessed meaning when compared with results obtained on other occasions.

Case Reports and Results

Case 1.—G.S.P., a man, aged 35, had dystrophia myotonica. Dystrophic features included myopathic facies, atrophic sternomastoids, marked weakness of peripheral limb muscles with weakness of the grip and bilateral foot-drop, and slight testicular atrophy. Myotonia of the grip was severe and the electromyogram showed a typical abnormality.

Before treatment the average serum potassium on three successive days was 4·0 mEq./l. and after 18 days of treatment with "resonium-A" 60 g. daily, the reading was 2·6 mEq./l. The duration of myotonia as measured with our technique was an average of nine seconds and towards the end of the course of treatment it averaged just over seven seconds. Despite the fall in serum potassium the patient's myotonia did not improve in a parallel manner (Fig. 1a). As an example, on the second day of treatment the serum potassium was 4·8 mEq./l. and myotonia lasted six-and-a-half seconds, while on the seventeenth day the serum potassium was 2·6 mEq./l. and the duration of the myotonia was over seven-and-a-half seconds. No increase in the power of dystrophic muscles was noted.

While the resin was being given, the patient's serum sodium rose from its pre-treatment value of about 145 mEq./l. to 155 mEq./l. on the sixteenth day. There was no significant trend in the slight day-to-day changes in serum chloride or bicarbonate, while the total and diffusible serum calcium, measured weekly, remained unchanged. Slight electrocardiographic changes observed towards the end of the course were consistent with mild hypokalaemia.

After 10 days of treatment, when the serum potassium was falling and the sodium was beginning to rise, ankle oedema was observed. This increased steadily until the resin was stopped, when it gradually disappeared. The patient suffered no other ill-effects and no cause for this oedema, other than treatment he had received, could be found. In confirmation of our objective findings, this patient considered that the treatment had been of no benefit.

Case 2.—S.S., a man aged 40, had dystrophia myotonica. The patient showed frontal baldness, testicular atrophy, early cataracts, a myopathic facies, weakness and wasting of peripheral muscles and of the sternomastoids, and myotonia of grip. Treatment was begun with "resonium-A", 60 g. daily, and the serum potassium fell steadily from an initial level of 4·2 mEq./l. to a value on the seventeenth day of 2·2 mEq./l. Although there was some fluctuation in the duration of the myotonia, and this appeared to be independent of the biochemical changes, the overall trend was one of improvement (Fig. 1b). Before treatment the duration of
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Case 5.—E.H., a man aged 20, had myotonia congenita. The patient had been stiff since early childhood and had noticed myotonia in most muscle groups, especially in his legs when he started walking after a rest. Delay in relaxation of the grip was also troublesome. There were no dystrophic features.

The change in the serum potassium level while the patient received 60 g. of "resonium-A" daily for 16 days was negligible (Fig. 1e). On the first day of treatment the value was 3.8 mEq./l. and on the sixteenth day it was 3.7 mEq./l. There was no significant change in the severity of the patient's myotonia throughout.

No other recorded biochemical changes of note occurred and the electrocardiogram remained normal. There were no side-effects. The patient noticed no benefit from the treatment and was not prepared to remain long enough in hospital for larger doses of resin to be given.

Case 6.—M.H., a woman aged 17, had myotonia congenita. Stiffness in many muscle groups had been noticed since early childhood. The most troublesome symptom was the stiffness in the legs, but myotonia in the forearm muscles was also severe. The muscles were generally bulky, but there were no dystrophic features.

On a daily dosage of 60 g. of "resonium-A" the patient's serum potassium level fell from 4.2 mEq./l. before treatment to 2.4 mEq./l. after 17 days. The duration of the myotonic after-discharge showed considerable day-to-day fluctuations but the overall trend was one of slight improvement (Fig. 1f). The average figure for the three days immediately preceding treatment was 10 seconds, while the average of the last three figures obtained during the treatment period was just under eight seconds.

The serum calcium, sodium, chloride, and bicarbonate did not change appreciably during treatment. There were no side-effects, but the patient was not aware of any subjective improvement in her myotonia.

Case 7.—W.C., a man aged 39, had dystrophia myotonica. This patient had frontal baldness, a myopathic facies, and wasting and weakness of the sternomastoids and of distal limb muscles. There was severe myotonia of the forearm muscles and the electromyogram was typical.

In this case treatment with "resonium-A" in a dosage of 60 g. daily failed to produce any appreciable lowering of the serum potassium. Because of our similar experience with Case 5, we increased the dose steadily up to 180 g. daily, a figure which is three times that recommended by the manufacturers. The patient was given 90 g. for 14 days, 120 g. daily for three days, and then 180 g. daily for a further week. There was no consistent change in the value of the serum potassium. For the first four days of the treatment period this was 4.2 mEq./l. and the average for the last four days of the 24-day period was 4.25 mEq./l. The degree of myotonia, although showing the daily fluctuations so commonly seen, did not alter significantly during this time (Fig. 7). The duration of the after-contraction was approximately 20 seconds throughout. The values of other serum electrolytes also remained unchanged and no side-effects were noted.
FIG. 1.—The response to treatment shown by cases in this series.
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Chlorothiazide (saluric) was then given in a further attempt to lower the serum potassium. The dosage employed was 0·5 g. b.d. for three days followed by 1·0 g. b.d. for four days and 1·5 g. b.d. for 13 days. During this 20-day period the serum potassium fell from 4·2 mEq./l. to 3·3 mEq./l. on the last day. Once again the severity of the myotonia varied considerably from day to day but there was no clear-cut and progressive improvement (Fig. 1g).

Finally an attempt was made to produce a sharp fall in serum potassium by using insulin and glucose; 50 g. of glucose was given by mouth and 20 units of soluble insulin were injected subcutaneously. Over the course of the next three hours the serum potassium fell from 4·1 mEq./l. to 2·5 mEq./l.; the latter was the lowest value we recorded in this patient. As the serum potassium fell there was progressive improvement in the myotonia, in that the figure of 14 seconds noted at the beginning of the test was reduced to one of five seconds after three hours (Fig. 1h). However, it is difficult to explain why, at the two-hour stage, when the potassium had already fallen to 3·1 mEq./l., the duration of the after-discharge was measured as 20 seconds, a figure higher than that recorded at the beginning of the experiment.

Case 8.—J.R.W., a woman aged 36, had myotonia paradoxa, complicated by periodic paralysis. The patient had experienced stiffness in many voluntary muscle groups for 15 years, and had noticed that this stiffness seemed to be made worse rather than better by repeated contractions. The patient herself showed no dystrophic features at all on full examination but she came from a family containing several persons with typical dystrophia myotonica.

For eight years she had suffered from episodes of severe weakness which recurred about once a month or rather more often. In each of these she would notice increasing weakness, especially of the proximal muscles of the limbs and trunk. The weakness would increase to a maximum over a period of five or six hours and then the patient would be unable to stand or to raise her arms; normal strength would then return gradually after a total period of 12 to 16 hours. These episodes of paralysis did not recur with any regularity of pattern and no precipitating cause was apparent. In particular, they were not precipitated by cold as in paramyotonia. The patient was at work and was unwilling to spend a long period in hospital but she was visited at home when an attack was beginning. She was found sitting in a chair unable to move any but the muscles of respiration and deglutation (these latter only weakly) and the more distal muscles of the limbs. She was able to exert a grip of appreciable power, though she was totally unable to lift her arms. Despite the weakness, myotonia of considerable degree was still present in the forearm muscles which flexed the fingers, and typical myotonic "dimpling" was present on percussion of muscles such as the deltoid which were paralysed. Myotonic after-contraction in the fingers was measured at 30 seconds. A specimen of blood taken at the time showed the serum potassium to be 1·9 mEq./l. After complete recovery from the attack the serum

![Diagram showing response to treatment](http://jnnp.bmj.com/content/23/2/119)

**Fig. 1.—** The response to treatment shown by cases in this series.
potassium was at the lower end of the normal range. The patient has since been treated with daily doses of potassium chloride orally with good results as far as the periodic paralysis is concerned, as the attacks have virtually ceased. The myotonia was unaffected by this therapy but has been greatly improved by procaine amide.

Discussion

Discussion of a possible theoretical basis for the use of a potassium-absorbing resin in the treatment of myotonia must include some reference to the known influences of potassium upon muscle function. The normal ratio between intracellular potassium in muscle and extracellular potassium is probably in the neighbourhood of 158 mEq./l. : 4.5 mEq./l. or about 35 : 1 (Keitel, Jones, and Berman, 1953). Upon this ratio must partly depend the value of the resting muscle membrane potential and hence the resistance of this membrane to depolarization. Under physiological conditions, depolarization follows upon the arrival of an adequate impulse at the neuromuscular junction and is an essential part of the processes involved in muscle contraction. If the intracellular : extracellular potassium ratio (Ki/Ke) is increased to a value greater than 35 the resistance of the membrane to depolarization is also increased, while if the ratio is decreased, the muscle membrane appears to be...
more easily depolarized. Grob, Liljestrand, and Johns (1957) have carried out extensive clinical studies on potassium movement in normal subjects and its effect on muscle function. They used several methods to alter the Ki/Ke ratio and noted the effect of these changes upon the ease with which depolarization could be produced by the intra-arterial injection of acetylcholine. The results achieved by these workers provide further evidence for the hypothesis that a decrease in the Ki/Ke ratio decreases resistance to depolarization and gives increased excitability, while an increase in the ratio has the opposite effect.

Cumings (1939) found that muscle from patients with dystrophia myotonica contained considerably less than the normal amount of potassium. Mertens and Grütner (1955) reported that in their series of 17 myotonic patients the serum potassium, although usually just within normal limits, was in most cases at the upper end of the normal range. If these observations are correct, then the Ki/Ke ratio in myotonic patients would be \(<158 \text{ mEq./l.} : >4.5 \text{ mEq./l.}, i.e., it would be decreased to considerably below the normal figure of 35. This decrease would be accompanied by a decreased resistance of the muscle cell membrane to depolarization and therefore by increased excitability. Although it seems unlikely that this biochemical change could be the entire cause of the phenomenon of myotonia it is reasonable to suppose that it may play some part in the production of the symptom.

Further evidence in support of this view is reviewed in detail by Thomasen (1948). For instance, it has been shown that acetylcholine given by intra-arterial injection produces a protracted contraction in myotonic muscles (in myotonic goats) but not so readily in unaffected ones (Brown and Harvey, 1939). Intra-arterial potassium chloride, too, will increase the severity of myotonia or may produce a contraction in denervated myotonic muscle which is similar to a myotonic contraction and after-contraction (Russell and Stedman, 1936; Kennedy and Wolf, 1937; Brown and Harvey, 1939). Potassium so administered would have an immediate effect of reducing further the Ki/Ke ratio. The well-known aggravating effect of cold upon myotonia is probably due, at least partly, to the fact that low temperatures cause a loss of potassium from muscle cells. Warmth, which improves the symptom, probably has the opposite effect on potassium movement, while calcium ions and cortisone, among substances which are also beneficial, lower the level of the serum potassium.

It must, however, be noted that whereas prosta- mine will raise the potassium content of myotonic muscle cells towards the normal level (Cumings, 1939) this drug has an adverse clinical effect upon myotonia. Furthermore, repeated strong contraction of muscle results in movement of potassium out of the cells in normal persons (Grob et al., 1957) and if this same process occurs in myotonic subjects it would tend to make the Ki : Ke ratio even more abnormal. But clinically, repeated contractions improve myotonia in most cases. Finally, quinine and procaine amide, which improve myotonia when administered either locally or systemically, are not known to alter the Ki/Ke ratio of the resting muscle. It seems more likely that they affect a property of the cell membrane itself, making the membrane more "stable" in some way not yet understood, and that although this "stability" can be affected by the potassium ratio across the membrane, abnormalities in this ratio are not the primary cause of myotonia. Myotonia is not seen in other clinical conditions in which there is a change in this ratio, and if the ratio is altered experimentally in normal subjects myotonia is not produced.

None of the patients in this series noticed any subjective improvement in muscular stiffness after two to three weeks of intensive therapy with the resin. However, our objective measurements of the duration of the myotonic after-discharge during the treatment showed that in some cases there was a gradual though slight improvement in the myotonia as the serum potassium fell. For example, in Case 2 a reduction of the serum potassium to half of its previous level after 16 days of treatment reduced the duration of the myotonic after-contraction by one-third.

This same patient later received a three-week course of a dummy powder which was similar in appearance and taste to "resonium-A" and during this period there was no significant change in the myotonia. Hence we may conclude that the improvement produced with the active resin was genuine. Our original intention was to treat all cases with the dummy powder as well as with "resonium-A", but the latter produced so little effect in the majority of cases that we did not consider it necessary to use the control remedy in all cases.

Our negative results fell into two groups. In one group of patients there was no significant fall in serum potassium while the patients received the recommended dose of 60 g. "resonium A" daily and indeed in one (Case 7) no recognizable effect upon serum potassium was produced with three times this dose. In a second group of patients, e.g., Cases 3 and 4, the serum potassium level was reduced satisfactorily but no concomitant reduction in myotonia occurred. The negative results in the second group could not be dismissed as due to inadequate dosage of the resin, which was also given...
over a period long enough to produce an effect. These results clearly indicate that the resin is an ineffective remedy for myotonia.

Additional observations worthy of comment are first, the experiment in which one patient (Case 7) who had proved particularly resistant to treatment, was given insulin and glucose; and secondly our findings in the patient (Case 8) who still showed clinical myotonia during an episode of periodic paralysis. In each of these cases it can be concluded that there was an excessive uptake of potassium by the muscle cells with concomitant reduction in the serum potassium; this would have the effect of altering the Ki/Ke ratio in the direction of hyperpolarization. By contrast, ion-exchange resin therapy, which produces a total body deficit of potassium, certainly results in a reduction of the serum potassium but probably reduces the intracellular potassium as well, though not perhaps to an equal extent (Grob et al., 1957). Hence it would be expected that the insulin test and the attack of periodic paralysis should have produced even more reduction of myotonia than treatment with the resin, had the potassium ratio been of major importance. Yet the insulin test produced only a doubtful reduction in myotonia even though the serum potassium fell from 4.1 to 2.5 mEq/l., while the other patient, though partially paralysed with a serum potassium of only 1.9 mEq/l., still showed definite clinical myotonia. Too much stress should not be laid on the latter observation since the nature of the metabolic defect in this patient has not been investigated fully, but nevertheless we believe that even this single observation is of significance. While the usual type of periodic paralysis in which there is a shift of potassium into the muscle cell might be expected to improve myotonia, attacks of the closely related condition, adynamia episodica hereditaria, in which potassium moves out of the muscle into the extracellular fluids, would be expected to produce a phenomenon like myotonia, if the potassium ratio were all-important. In fact, myotonia does not occur during these episodes of paralysis in patients with adynamia (Gamstorp, Hauge, Helweg-Larsen, Mjønes, and Sagild, 1957).

The principal aim of this trial was to discover whether ion-exchange resin therapy was of practical value in the management of patients disabled by myotonia. Our results do not confirm previous claims that this form of treatment is of practical value. Myotonia is sometimes slightly improved, but other therapeutic agents, and procaine amide in particular, are much superior for clinical use. It also seems justifiable to conclude that although others have found a consistent abnormality in the ratio of intracellular to extracellular potassium in patients suffering from myotonia, this abnormality does not appear to be the entire cause of the myotonic phenomenon.

**Summary**

The results are described of a clinical trial in which the effect upon myotonia of reduction in the serum potassium was studied. Five patients with dystrophy myotonica and two with myotonia congenita received a potassium-binding ion-exchange resin by mouth for periods varying from 15 to 24 days; during treatment the serum potassium and the duration of the myotonic after-contraction were measured daily. In three cases the resin did not produce a satisfactory and consistent fall in the serum potassium and there was no improvement in myotonia.

A progressive reduction in the serum potassium was achieved in four cases and in three this produced slight objective reduction in myotonia, but only in one case was this improvement convincing. No patient obtained subjective benefit from the treatment. In one case, a rapid fall in serum potassium was obtained following the administration of insulin and glucose, with only slight improvement in myotonia. Myotonia persisted in another patient who suffered from both myotonia and periodic paralysis, during an episode of weakness in which the serum potassium fell to a very low level.

The theoretical significance of these results is discussed. It is concluded that potassium-absorbing ion-exchange resins are of no practical value in the treatment of myotonia; the results of this trial do not suggest that the ratio of intracellular to extracellular potassium in muscle is of primary importance in the production of the myotonic phenomenon.

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