Effects of rubidium chloride on the course of manic-depressive illness[1]

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Introduction

Some neurophysiological, neurochemical and behavioural actions of rubidium are opposite from those of lithium (Meltzer *et al.* 1969, Stolk *et al.* 1970, Stolk *et al.* 1971, Carrol & Sharp 1971, Sheard 1970). This has led workers to suggest that rubidium has a disinhibiting action and that it has antidepressant properties (Fieve *et al.* 1971, Platman 1971, Sanghvi & Gershon 1973).

Extensive toxicity studies in animals (Khosid 1967, Meltzer & Lieberman 1971, Johnson *et al.* 1975, Spirter & Garey 1975) have shown that rubidium can be administered orally. It only becomes toxic if the concentration in the erythrocytes or muscle cells reaches 30% of the potassium. Most of the administered rubidium enters the cells in a similar manner to potassium, but it has a greater affinity for the potassium pumping sites (Sachs & Welt 1967). It has a long biological half-life (Fieve *et al.* 1971, Meltzer & Fieve 1975).

Rubidium was used during the last third of the 19th century by European physicians in the treatment of cardiac conditions, syphilis and epilepsy. A brief history of the use of rubidium is given by Meltzer & Fieve (1975), who also conducted the first metabolically controlled study with rubidium chloride in man (Fieve *et al.* 1971, Fieve *et al.* 1973, Fieve & Meltzer 1974). Subsequently, the same workers published the results of a further pilot study in which a dozen patients, mainly manic-depressives, received rubidium chloride up to a maximum retained dose of 486 mmol (Meltzer & Fieve 1975). Although the authors have studied many aspects of rubidium kinetics, their clinical results do not show clear behavioural effects.

This paper tests the hypothesis that rubidium may have antidepressant properties. Some neurochemical and neurophysiological actions of rubidium have also been investigated.

Patients and methods

The study was conducted in a metabolic ward. A solution of rubidium chloride (50 g/l, 410 mmol/l) was administered to 5 patients, each with a fairly short and predictable mood cycle. These patients each had a history of manic-depressive illness for over eight years. They had not responded to any conventional treatment lithium, electroconvulsive therapy, phenothiazines, antidepressant tricyclics).

Patient M C, a 45-year-old housewife, had a 15-year history of manic-depressive illness which had started seven days after a difficult childbirth. She received rubidium chloride in three consecutive loadings. The frequency of her manic-depressive episodes has gradually increased and over the last few years she has had regular predictable mood cycles lasting approximately

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0141-0768/78/0071-0343/$02.00/0

7–8 weeks (approximately 20 days mania, 20 days depression, 1 week well). During her manic phases she becomes very overactive with tremendous pressure of speech. She has flight of ideas, ideas of grandiosity, is at times destructive and completely uncooperative. She sleeps and eats very little and occasionally is incontinent of urine. During her depressive phase she becomes very quiet, has moderate psychomotor retardation and no spontaneous speech. She takes no interest in anything and frequently expresses ideas of guilt. On one occasion she made a serious suicide attempt. Her father died at the age of 70 and he suffered from Parkinson's disease. Her mother died at the age of 62 with a cerebral tumour. There are 5 siblings and she has a twin brother. There is no psychiatric history in the family.

Patient J R, a 41-year-old single female, had a 14-year history of manic-depressive illness. She received rubidium chloride in two consecutive loadings. This patient has a predictable mood cycle lasting approximately 5 weeks (approximately 20 days depression and 15 days of mania). Her IQ appears to be low but perhaps this is because of her psychosis. At times her perceptive wit amazes observers. She left school and worked at semi-skilled factory jobs until 1962. She had a happy childhood and is an only child. There is no psychiatric history in the family. She has had epilepsy since the age of 15. Over the last two years her epilepsy has been almost completely controlled with phenobarbitone 30 mg three times a day. During her manic phase she becomes overactive with high pressure of speech, flight of ideas, grandiose ideas and the content of her speech is rather limited and mainly consists of either sexual material or vulgar swearing.

Patient M J, a 53-year-old female, is married with two daughters. She has an 8-year history of manic-depressive illness with the depressive phases more predominant and prolonged. The duration of her mood cycle is approximately 10–12 weeks (approximately 15–20 days mania with 40–50 days of depression with variable normal intervals). There is no psychiatric history in the family.

Patient N H is a 72-year-old female with over 10 years' history of mood swings. Her depression lasted for approximately 2–3 months. Her hypomanic phases lasted 15–20 days. During the depressive episodes she was severely retarded, had no interest, lacked concentration, had delusions of guilt and occasionally she would become agitated and fearful. During the manic phases she had high pressure of speech, flight of ideas and grandiose ideas but hardly ever became very disturbed. In the past she has been helped by lithium but could not tolerate therapeutic doses. Over the last 8 years she has had several admissions to hospital.

Patient F M, a 39-year-old male, had a 23-year history of periodic catatonic schizophrenia. He has mood swings which follow the catatonic episodes. His catatonic cycles last approximately six weeks.

All patients who took part in the study had been almost permanently hospitalized for several years.

Patients M C and J R took part in a double-blind cross-over trial. Distilled water with lemon flavour was used as a placebo. The solutions were prepared by the pharmacist who kept the code. The concentration of rubidium in the erythrocytes and plasma was estimated. Both patients started the trial simultaneously. M C started on the active preparation and J R on the placebo. When the concentration of rubidium in the erythrocytes of M C reached the level of 9.4 mmol/l (in 35 days) the drugs were switched. Forty-four days later, when the concentration of rubidium in the erythrocytes of J R reached the level of 10.5 mmol/l, rubidium was discontinued and both patients continued to receive the placebo for several weeks. The other patients – M J, N H and F M – received rubidium chloride only once.

Before the commencement of the study, detailed medical and psychiatric histories from the patients, their relatives and their records were obtained. All patients underwent full clinical and laboratory investigations and fluid intake was constant throughout the study. Samples of various biological fluids (blood, urine, saliva, sweat and cerebrospinal fluid (CSF)) were obtained frequently for estimation of rubidium and other parameters. Electrocardiogram, electroencephalogram and nerve refractory period studies were frequently recorded. Total body potassium was estimated by counting the naturally occurring K^{40}. The

patients' behaviour was monitored six hourly by experienced nurses using a 7 point scale mood, as well as speech and activity charts. The nurses also produced detailed descriptions of the behaviour. The reliability of the nurses' ratings was tested by comparing independently obtained scores from different individuals. Patients' activity was recorded by a pedometer and these scores were compared with the activity as rated by the nurses.

Results

Distribution, excretion

The rubidium erythrocyte/plasma ratio is not constant throughout the loading, but increases from approximately 20 in the initial stages of loading to approximately 30 when the concentration of rubidium in the erythrocytes reaches a high level (approximately 10 mmol/l). Throughout the post-loading period, when complete equilibration of the various compart-

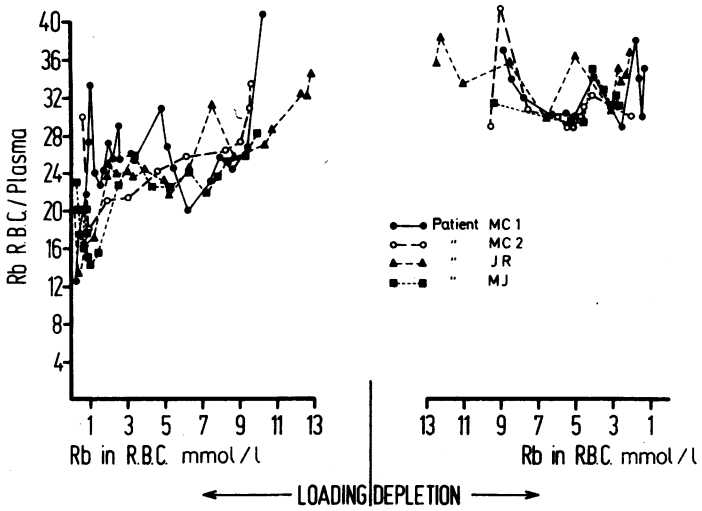

Figure 1. During the loading period the rubidium RBC/plasma ratio increases. Throughout the period of depletion the ratio remains fairly constant

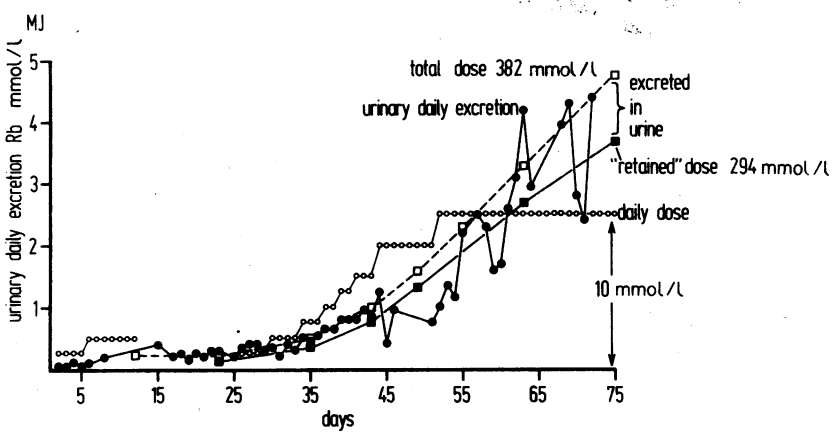

Figure 2. Total rubidium dose administered to M J, the daily dose, the daily and total urinary excretion and the 'retained dose' (retained dose = intake − urinary output). The loss in the stools is not included

ments has occurred, the rubidium ratio remains constant (Figure 1). In patient M J it was estimated that the loss of rubidium in the urine was 23% of the administered dose (Figure 2). If to the amount of rubidium excreted in the urine one adds 8%, which is the amount excreted in the stools (Ray *et al.* 1955), this gives an estimate of the retained dose. The loss of rubidium in saliva and sweat can also be considerable. Sweat rubidium varies considerably depending on the mood phase (results to be published elsewhere). Clearly, under abnormal conditions, such as excessive diarrhoea, sialorrhoea or sweating, simple approximation cannot be very usefully applied.

Biological decay and half-life of rubidium

Plasma rubidium began to fall within 24 hours of discontinuing administration, but erythrocyte rubidium seemed to continue to rise slightly for approximately three days. CSF rubidium may continue to rise for 1–3 weeks (Table 1). After a few days the biological decay curves from the fluids and red cells approached first order kinetics with half-lives of 31–46 days.

Table 1. Rubidium RBC/CSF, plasma/CSF ratios

Patient	Rb in RBC mmol/l	Rb in plasma mmol/l	Rb in CSF mmol/l	Rb RBC/ plasma	Rb RBC/ CSF	Rb plasma/ CSF
M C	1.5	0.065	0.020	23.1	75.00	3.25
1st loading	2.5	0.10	0.041	25.0	60.97	2.44
	6.2	0.31	0.079	20.0	78.50	3.90
	10.0	0.25	0.111	40.0	90.10	3.29
	8.4	0.25	0.076	33.6	110.50	3.29
	5.3	0.17	0.067	31.2	79.10	2.54
	2.3	0.08	0.027	28.7	85.20	2.96
	1.0	0.03	0.012	30.0	83.30	2.77
2nd loading	2.3	0.09	0.029	25.5	79.30	3.10
	8.9	0.28	0.097	31.8	91.70	2.90
	9.2	0.30	0.093	30.7	98.90	3.22
	9.0	0.31	0.100	29.0	90.00	3.10
	8.3	0.28	0.095	29.6	87.40	2.95
J R	1.85	0.08	0.019	23.1	97.40	4.21
	10.20	0.37	0.085	27.6	120.00	4.35
	12.50	0.38	0.103	32.9	121.40	3.69
	10.60	0.31	0.140	34.2	75.70	2.21
	9.20	0.26	0.125	35.4	73.60	2.08
	7.50	0.23	0.102	32.6	73.50	2.25

Figure 3 shows the quite typical results from one (M C) of the three patients studied. The biological decay for the different tissues (erythrocytes, plasma, saliva and CSF) were indistinguishable from each other ('t' test on regression lines of log (Rb) against time). The results also suggest that during the rubidium loading the uptake by the CSF may be slower than by the erythrocytes. The administration of lithium to one patient (M C) did not alter the biological decay rate of rubidium.

Reliability of mood ratings

The correlation between the ratings of the two different groups of nurses was statistically highly significant ($P < 0.001$). The correlations between the activity scores of the nurses' ratings and the scores obtained by the pedometer were also statistically highly significant ($P < 0.001$).

Effect of rubidium on mood, activity and speech

Figure 4 shows M C's cycles of illness before, during and after rubidium loading. During the

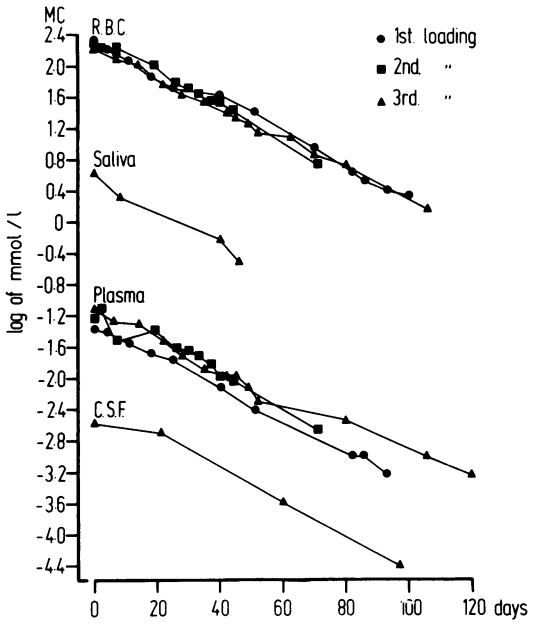

Figure 3. Biological decay of rubidium in the RBC, saliva, plasma and CSF of M C during three rubidium loadings (rubidium concentration expressed in logarithmic scale)

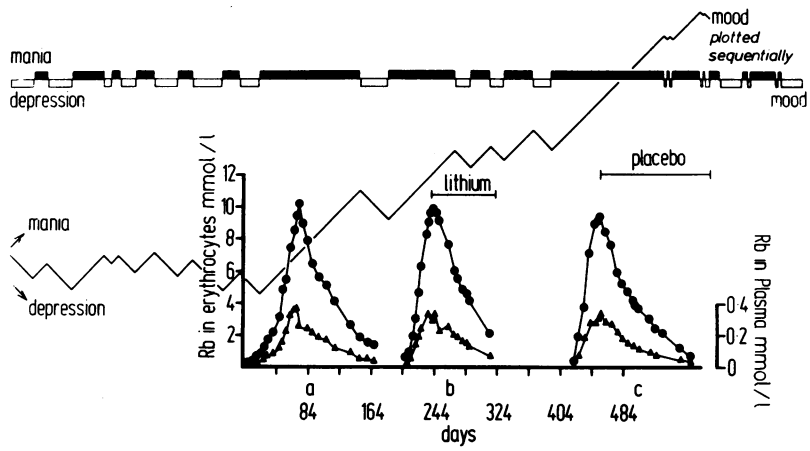

Figure 4. Prolonged manic phases in M C during all three rubidium loadings (a, b, c). The mood phases are illustrated as a daily sequential plot

three rubidium loadings the patient had prolonged manic phases. The third rubidium loading was part of a double-blind cross-over trial. During the second loading (Figure 4b) the manic phase was not as prolonged. Perhaps this was because the patient received lithium carbonate.

Mood showed clearly altered phases during the treatment of J R with rubidium (Figure 5). Comparing the number of days in mania with the number of days in depression, before, during and after rubidium, it is clear that during the effect of rubidium the number of days in mania are significantly higher than in the other two periods at the level of $P<0.001$ (χ^2). The effect of rubidium on the mood cycle is more obvious in Figure 6 where the mood before, during and

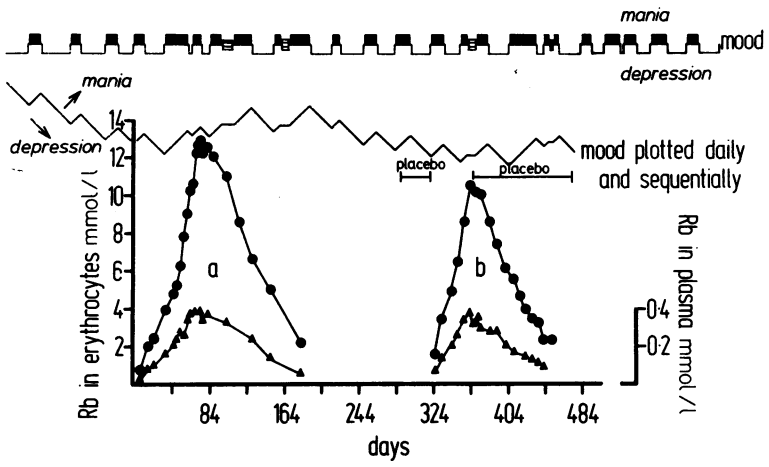

Figure 5. Change of mood in J R during two (a, b) rubidium loadings

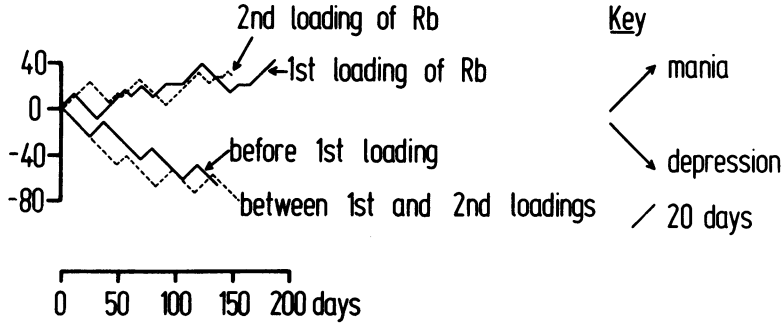

Figure 6. Mood of J R plotted sequentially before administration of rubidium, during same and between two periods of loadings

after rubidium has been plotted daily sequentially (north easterly indicates mania and south easterly depression).

A Markov matrix can be used to show the number of times a day of mania is likely to be followed by a day of depression or of mania. It also shows the changes from depression (Harbaugh & Carter 1970). The transitional matrix by Markov dependence analysis on the data of patient J R (Figure 7) shows that during the effect of rubidium the patient is more likely to remain in mania when she is in a manic phase than she is before rubidium administration or after its depletion. The same matrix also shows that during treatment with rubidium there is a reduction in the severity of the depressive phases.

During the effect of rubidium the overall activity recorded by the pedometer was increased ($P<0.025$). However, the activity during the manic phase was diminished ($P<0.025$), whereas the activity during depressed phases was increased ($P<0.01$) (Figure 8). This figure also shows in detail the severity of the mood changes before, during and after rubidium administration. It shows that when the concentration of rubidium in the red blood cells (RBC) was relatively high, the number of days during which the patient was depressed was not only smaller but the severity of the depression was less than before or after rubidium loading.

The speech and activity scores of patient J R obtained by the nurses' rating scale shows similar results to those of the pedometer (Figure 9). During the effect of rubidium the pressure of speech and over-activity are less severe than before rubidium administration.

FROM \ TO	1	2	3	4	5	6	7
1	0 7 (0·7) 3 (0·5)	1 (1) 3 (0·3) 2 (0·33)	0 0 0	0 0 0	0 0 1 (0·16)	0 0 0	0 0 0
2	1 (0·02) 3 (0·25) 2 (0·06)	36 (0·84) 5 (0·42) 26 (0·74)	4 (0·09) 4 (0·33) 6 (0·17)	1 (0·02) 0 1 (0·03)	0 0 0	1 (0·02) 0 0	0 0 0
3	0 2 (0·07) 1 (0·03)	4 (0·07) 2 (0·07) 7 (0·18)	47 (0·88) 22 (0·73) 27 (0·71)	2 (0·04) 3 (0·1) 3 (0·08)	0 1 (0·03) 0	0 0 0	0 0 0
4	0 0 0	2 (0·09) 0 1 (0·03)	1 (0·05) 4 (0·08) 4 (0·12)	13 (0·62) 36 (0·75) 24 (0·7)	5 (0·24) 5 (0·1) 4 (0·12)	0 1 (0·02) 1 (0·03)	0 2 (0·04) 0
5	0 0 0	1 (0·05) 0 1 (0·04)	0 0 0	2 (0·11) 7 (0·35) 5 (0·23)	12 (0·67) 13 (0·65) 14 (0·64)	3 (0·17) 0 2 (0·09)	0 0 0
6	0 0 0	0 0 0	0 0 0	2 (0·22) 0 1 (0·1)	1 (0·11) 1 (0·33) 1 (0·1)	6 (0·67) 2 (0·67) 8 (0·8)	0 0 0
7	0 0 0	0 0 0	0 0 0	0 0 0	0 2 (0·09) 0	0 0 0	0 20 (0·91) 0

KEY

0	before Rb
0	during Rb
0	after Rb

1 severe depression
2 moderate "
3 slight "
4 slight mania
5 moderate "
6 severe "
7 mixed affective state

Figure 7. Matrix showing the number of times any state was followed by any other state before rubidium administration, during its effect and after its depletion. Probability (*P*) in parentheses

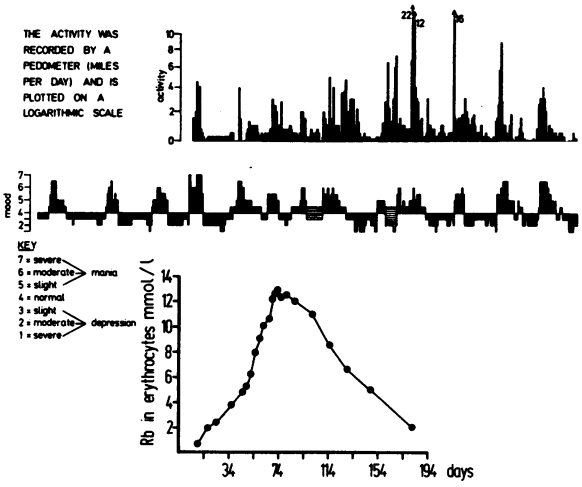

Figure 8. Activity, mood and RBC rubidium levels of J R plotted simultaneously

Soon after the effect of rubidium both patients' mood cycles returned to patterns fairly consistent with the pre-rubidium period. Patient M J remained depressed throughout the rubidium loading. In the other two patients (N H and F M) rubidium had no obvious clinical effect.

During the rubidium study there were changes in thyroid function, the blood and urine alpha-oxoglutarate concentrations, the urine 4-hydroxy-3-methoxyphenylethyleneglycol (MHPG), total body potassium, the duration of sleep induced by intravenous injection of

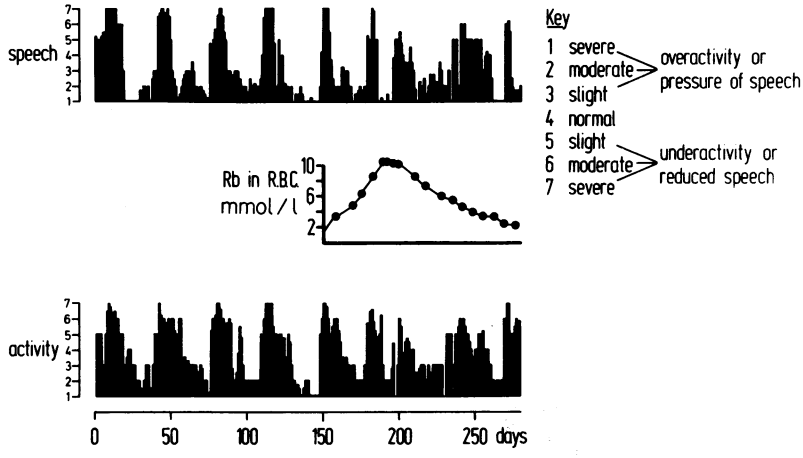

Figure 9. Speech, RBC rubidium and activity of J R plotted simultaneously

methobarbitone Na (Brietal), and also neurophysiological changes. These results will be published elsewhere.

Discussion

The results in this study confirm the findings of other workers (Fieve *et al.* 1971, Fieve *et al.* 1973, Meltzer & Fieve 1975). Rubidium can be safely administered orally and it is readily absorbed. From the concentrations of rubidium in the plasma and erythrocytes, it is apparent that most of the administered dose enters the cells, and when complete equilibration has occurred the rubidium erythrocyte/plasma ratio is approximately 30.

As was shown by Meltzer & Fieve (1975), if a single dose of rubidium is given, approximately three days are required for complete equilibration between the erythrocytes and the extracellular compartment. Meltzer & Fieve (1975) proposed a two compartment model. This could explain the increasing rubidium erythrocyte plasma ratio during the rubidium loading period.

The uptake of rubidium by different organs in different species differs (Kilpatrick *et al* 1956, Bradbury 1970, Meltzer & Lieberman 1971). In man, except for the erythrocytes, there are no other easily accessible tissues for kinetic analysis. However, from the concentration of rubidium in the CSF during the rubidium loading one can surmise that the uptake of rubidium by the CSF is slower than by the erythrocytes. Bradbury (1970) has shown in the rabbit that 'rubidium was relatively lacking in the brain and C.S.F. and that the ratio of rubidium replacement for the brain was 52% of that for muscle'. Most of the administered dose of rubidium is excreted in the urine (approximately 23%), but in abnormal conditions such as diarrhoea, sialorrhoea and excessive sweating, the loss of rubidium in the stools, saliva and sweat can be considerable.

The biological half-life of rubidium in the plasma and erythrocytes is approximately 33–45 days which is similar to that found by other workers (Meltzer & Fieve 1975). The biological half-life of rubidium in the saliva in this study was also found to be approximately 31–46 days. Fieve & Meltzer (1974) suggested that the decay of rubidium in the CSF is slower than that in the plasma. This was not confirmed in the present study. The biological half-life of rubidium in the CSF seemed approximately the same (35–41 days) as that in other fluids. Although there was not a sufficient number of CSF rubidium determinations, it seems that the decay of rubidium in the CSF may show an initial delay compared to that in the plasma and erythrocytes, probably because transport of rubidium and potassium across the blood brain barrier is relatively slow.

The clinical results of the present study showed that rubidium in two of the patients (M C and J R) prolonged mania. The clinical observations in patient M C during all three consecutive rubidium loadings were consistent. The results of the double-blind experiment and the return of the mood cycle to essentially pre-rubidium pattern suggest that the mood changes were due to the effect of rubidium. It has, however, to be emphasized that the studies were designed with great concern for safety and the double-blind component of the study was limited. However, the patient's behaviour was very strikingly different and unusual.

The administration of lithium to patient M C soon after the second rubidium loading possibly accounts for the change from the manic phase while the concentration of rubidium in the erythrocytes was still at a fairly high level when compared with the other two loadings. Meltzer & Fieve (1975) showed that lithium increases the rubidium excretion by up to 20%. This is not supported by the results of the present work.

In patient J R rubidium increased the number of manic days, but the effect was less obvious than in the case of M C. In this case, during the action of rubidium the depressed phases were less severe than before or after rubidium.

The double-blind cross-over trial results confirmed the observations of the previous rubidium loadings. Of course, due to the long biological half-life of rubidium it is not possible to do an accurate switch over of the drugs (active and placebo) unless the trial takes place over a long period.

The results from patient M J suggest that rubidium may prolong either phase (manic or depressive) depending on in which phase the patient happens to be when the level of rubidium reaches the hypothetical effective point. To explore this further, the second rubidium loading in the first patient (M C) was planned in such a way that the erythrocyte rubidium reached an effective level in terms of previous experience (above 8 mmol/l) when the patient was in a depressed phase. The result was not as expected; the patient did not remain in depression as had patient M J.

Animal experiments show that rubidium increases activity (Meltzer *et al.* 1969, Stolk *et al.* 1970). In this present study the effect of rubidium on the activity of one patient (J R), whose activity was recorded by pedometer, was somewhat paradoxical. During depressed phases the activity increased, whereas during manic phase it diminished.

From the results in this study it is probable that, although rubidium had no simple therapeutic effect, nevertheless it produced behavioural changes which seem of scientific interest.

As in the case of lithium, the mechanism for the behavioural effect of rubidium is not understood. The available data in the literature do not provide sufficient information to make a reasonable hypothesis for the neurophysiological mechanism involved. Meltzer & Fieve (1975) suggested a membrane transport hypothesis in which they proposed that the prolongation of the nerve action potential caused by rubidium may result in a greater release of neurotransmitter into the synapse. An alternative hypothesis could be that if rubidium accumulates in the cells (Glendening *et al.* 1956), it may shift the membrane resting potential towards the nerve action potential (Baker *et al.* 1962) and consequently increase the excitability of the neurons and therefore the degree of alertness.

Summary

Clinical studies of the effects of rubidium ions on the course of manic-depressive illness are reported. It seems that rubidium tends to increase the length of manic phases and possibly reduces the extremes of mood. Rubidium did not seem to produce any severe side effects in the dose administered, but it has a long biological half-life and caution is still required. Some details of the CSF, RBC, saliva and plasma and urine kinetics are also reported.

Acknowledgments: We are grateful to G Jennings for the rubidium estimations, the nurses of Northfield Clinic for their help and P Kenyon for the drawings.

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