incidence and type of primary urinary calculi occurring in different parts of the world. It is likely that a combination of factors is responsible, possibly including biochemical changes in the blood and urine resulting from the fluid and electrolyte losses. Dietary changes and perhaps some other metabolic disturbances also need to be considered. These possibilities will not be elaborated on here, but the biochemical changes were discussed briefly in our previous communication (Bennett and Jepson, 1966) and by Clarke and McKenzie (1969). They are also the subject of further investigations which are currently proceeding.

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Lithium-induced Hyperpolarization of the Human Rectum in Vivo

J. RASK-MADSEN, P. C. BAASTRUP, M. SCHWARTZ

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Summary

The transmucosal potential difference across the rectal mucosa was measured in 30 healthy subjects and in 13 psychiatric patients on lithium treatment for manic-depressive psychosis. It was significantly greater in the lithium-treated patients. A highly significant correlation was found between the potential difference and the serum lithium, and in all eight patients in whom it was measured before and one week after starting lithium treatment a rising potential difference was found. This phenomenon may possibly be explained in terms of resistance of the rectal mucosa to vasopressin.

Introduction

As the effect of lithium salts on permeability characteristics and bioelectrical properties of biological membranes has been studied mainly in vitro, by using isolated animal tissues (Zerahn, 1955; Clarkson and Rothstein, 1960; Lindley and Hoshiko, 1964; Leb *et al.*, 1965; Hayashi *et al.*, 1971) or cells (Keynes and Swan, 1959; Carmeliet, 1964; Gardner and Kerkut, 1968) exposed to high concentrations of this ion, it seemed of interest to investigate how lithium treatment of psychiatric patients interferes with the potential difference generated by an intact membrane in the human organism. The rectum is a satisfactory organ for such a study as its epithelium is easily available, well defined, and generates great potential differences across the rectal wall, mucosa being negative to serosa (Geall *et al.*, 1969; Dalmark, 1970; Edmonds and Godfrey, 1970). The action of a powerful sodium-absorbing pump seems to be the source of this transmucosal potential difference (Cooperstein and Hogben, 1959; Curran and Schwartz, 1960; Grady *et al.*, 1970), which consequently reflects the major function of the rectal mucosa—namely, the establishment of a steep concentration gradient for sodium between lumen and blood preventing excessive loss of electrolytes in the stools.

The spontaneous transmucosal potential difference across the rectal mucosa in patients with manic-depressive psychosis might differ from that of normals. In the present study therefore, we used the same technique on 30 healthy subjects and 13 manic and depressed patients; eight of the psychiatric patients were examined before and during lithium medication.

Medical Department F, Glostrup Hospital, Glostrup, Denmark
J. RASK-MADSEN, M.D., Research Fellow, University of Copenhagen
M. SCHWARTZ, M.D., Professor of Medicine

Department O, Glostrup Psychiatric Hospital, Glostrup, Denmark
P. C. BAASTRUP, M.D., Consultant Psychiatrist

Patients and Methods

Seven patients were hypomanic and five moderately depressed at the time of starting lithium therapy. All were ambulatory and in a good general condition, and so were the normal subjects, who comprised healthy volunteers and patients in a medical ward without any recognized disease of the large bowel, liver, kidneys, or circulatory system. The psychiatric patients included in the study received no drugs other than lithium carbonate (16-65 mEq daily) during or within one week of beginning the study. The transmucosal potential difference was measured in five patients who had been on lithium carbonate continuously for one to six years, while it was determined in the other eight patients 12 hours before the first lithium dose and again seven to eight days later. Blood samples were obtained for serum lithium determination about one hour before the investigation, and analysed by flame photometry. Details of the different procedures of the electrical measurement and experiences of reproducibility will be published elsewhere (Rask-Madsen and Dalmark, 1972).

The transmucosal potential difference was obtained at sigmoidoscopy to secure that the mucosa appeared normal and was not contaminated with intestinal contents. As the serosal surface is equipotential to blood, one of two balanced calomel half-cells was connected to the low impedance input of a high impedance electrometer (pH-Meter 51, Radiometer, Copenhagen) and to a vein of the forearm via a flowing 154 mM NaCl salt bridge, which was inserted for security reasons. The other half-cell connected the high impedance input of the electrometer with the exploring salt bridge, which consisted of a

polyethylene tube (internal diameter 0·5 cm) containing 3-M KCl and fitted with a terminal porous plug. The use of a flowing potassium electrode proved not to cause changes in potential difference, the leakage from the porous plug amounting to only 0·1 mEq K^+ per 24 hours. Via the sigmoidoscope the porous plug was placed directly on the mucosa at various distances from the anus. For one to two minutes the transmucosal potential difference was continuously registered by a recorder (Servogor, C. P. Goerz Electro, Vienna) calibrated before and checked after each experiment, and the mean potential difference was determined. The statistical evaluations were by Student's *t* test, and when the mean values of potential difference in the same patients were compared before and during lithium therapy a paired *t* test was used.

Results

The mean values of the transmucosal potentials recorded 5-15 cm from the anus in the group of lithium-treated patients (Fig. 1) were significantly greater than the corresponding values for healthy subjects ($P < 0·001$). Also, a comparison of the results obtained in eight patients before and after one week of lithium treatment (Fig. 2) showed a significant augmentation of the

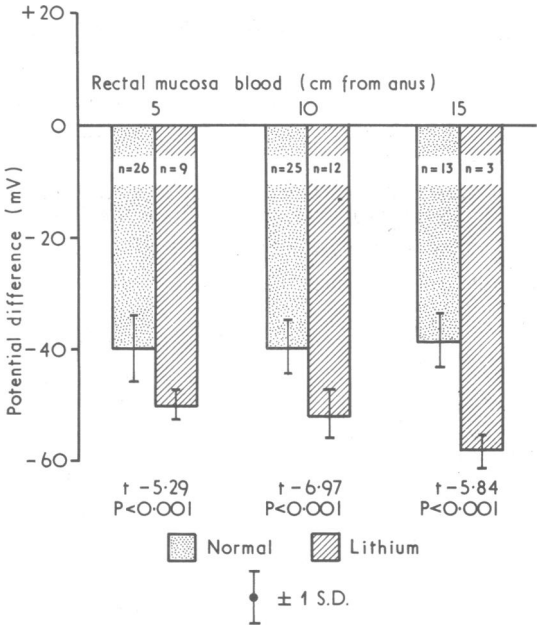

FIG. 1—Transmucosal potential difference in healthy subjects and in lithium-treated patients.

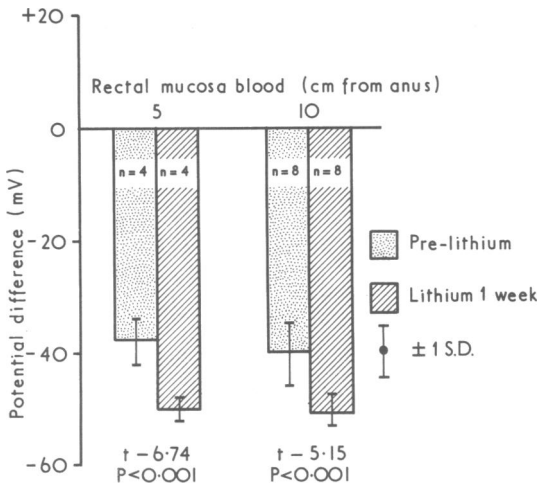

FIG. 2—Transmucosal potential difference in eight psychiatric patients before and one week after starting lithium therapy.

negative mucosal potential ($P < 0·001$). Furthermore, the spontaneous transmucosal potential difference in untreated manic-depressive patients did not differ from that of non-manic-depressive subjects ($P > 0·8$ at the distance 10 cm from the anus).

Figs. 3 and 4 give the individual potential difference values (10 cm from the anus) and the corresponding serum lithium concentrations. Fig. 3 presents the potential difference for all 13 patients as well as for 25 healthy subjects. The coefficient of correlation (r) is only 0·76, but highly significant ($P < 0·001$), and no better estimate could be expected from the accuracy of the present measurement. Fig. 4 shows the increase of the transmucosal potential difference occurring quite consistently in all the patients when lithium had been administered for one week. The mean slope of the line connecting measurement values in the same patient differs significantly from zero ($P < 0·001$).

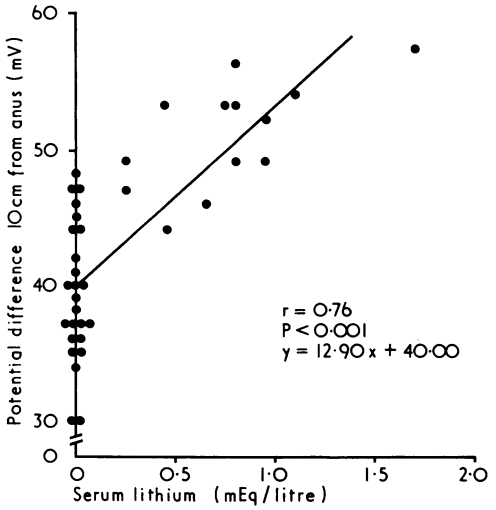

FIG. 3—Transmucosal potential difference and corresponding serum lithium values in 13 lithium-treated patients and in 25 healthy subjects.

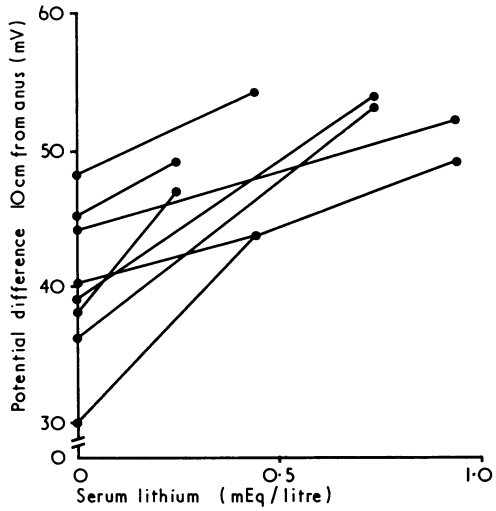

FIG. 4—Transmucosal potential difference and corresponding serum lithium values in eight lithium-treated patients before and one week after starting lithium therapy.

So far as can be seen from this small material the depressed patients did not differ from the hypomanic ones in their electrical response to lithium medication.

Discussion

The results of this study unequivocally show that the transmucosal potential difference increases during the administration

of lithium. However, the mechanism responsible for this phenomenon is not clear. Any change in transmucosal potential difference might result from changes in either the active or the passive movement of ions across the epithelium.

It is the general impression today that the lithium ion has a low affinity for the sodium pump (Skou, 1957; Baker, 1965) but that it is very similar to sodium in passive permeability characteristics (Gardner and Kerkut, 1968). These observations might explain the initial natriuresis and diarrhoea following the intake of lithium salts. A decrease in the potential difference was accordingly to be expected from a decreasing net absorption of positive chargings as it is seen in animal in-vitro studies (Clarkson and Rothstein, 1960; Hayashi *et al.*, 1971). The conflicting results concerning the effect of the lithium ion on membrane permeability and bioelectrical properties may find their solution in the fact that most investigations have been performed in vitro with high "non-physiological" concentrations of lithium. Any comparison with human studies should be considered with great caution as the serum lithium concentration during the treatment of affective disorders amounts to only 0·7-1·5 mEq/litre.

The findings of hyperaldosteronism (Murphy *et al.*, 1969) in response to lithium medication as well as the observation of a tardive and persistent diabetes-insipidus-like syndrome, which is unresponsive to vasopressin (Lee *et al.*, 1971; Viol and Smith, 1971), bear no resemblance to the initial changes in water-electrolyte balance. Edmonds and Godfrey (1970) showed that the potential difference across the human rectum increases within a few hours of starting mineralocorticoid administration, but although the above-mentioned lithium-induced hyperaldosteronism was claimed to be more prolonged than would have been expected from the initial sodium deficit, the aldosterone excretion had returned to normal within one week. The results of the present study indicate that the changes in transmucosal potential difference are more permanent, and thus aldosterone is probably not the source of the increased potential difference.

A very interesting observation is a blocking by the lithium-ion of the action of cyclic adenosine phosphate released by vasopressin (Harris and Jenner, 1972) as well as the adenyl cyclase (Forn and Valdecasas, 1971; Geisler *et al.*, 1972) necessary for its production. Adenosine triphosphate is the precursor of cyclic adenosine phosphate, which is supposed to increase membrane permeability, and also to be the principal substrate of the Na^+-K^+-exchange pump. Since the activity of the latter as well as the shunting capacity of the epithelial membranes will influence the polarization of mucosa, it seems to be the resulting net transfer of Na^+ which determines the transmucosal potential difference.

Some in-vitro (Ussing, 1960) as well as in-vivo (Blickenstaff, 1954) studies of animals indicate that vasopressin enhances sodium net transport from the small bowel, while no change has been found in other animal experiments using colonic tissue from the rat, mouse, and toad colon (Green and Matty, 1966). However, Levitan and Mauer (1968) showed that vasopressin administered intravenously to man (one unit per hour) caused a significant decrease in sodium net absorption when the colon was perfused with 0·85% NaCl, and this effect has also been found in the small intestine of intact man (Soergel *et al.*, 1968).

We would, therefore, tentatively suggest that the change in the transmucosal potential difference found in the present study is due to vasopressin resistance of the rectal mucosa, and the action of lithium on the rectal epithelium might thus bear some resemblance to its action on the kidneys (Lee *et al.*, 1971).

The pronounced increase of potential difference across the rectal mucosa during lithium treatment may have its counterparts elsewhere in the human organism—for example, in the brain—but so far this is pure speculation.

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