in digital vessel patency rates between 15°C and 21°C justify using this thermal stress.

In our patients plasma exchange significantly improved digital vessel patency rates at both 15°C and 21°C. Plasma exchange is known to be a potent method of defibrination.[15] Furthermore, plasma fibrinogen is a major determinant of whole blood viscosity at low shear rates. Thus the concept that narrowed digital vessels, initially impassable to viscous blood, are able to transmit blood rendered less viscous by plasma exchange appears attractive. Nevertheless, like Browse[16] we cannot explain why short-term reduction in plasma fibrinogen concentrations results in a long-term symptomatic improvement, and, in our patients, also quantitative evidence of improvement. This long-term improvement may be explained partly by changes which have been observed in the deformability of the red blood cells,[17] but the possible role of circulating immune complexes[8] still needs clarification and is the subject of continuing investigation.

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Indomethacin increases plasma lithium

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Summary and conclusions

The effects of indomethacin on plasma lithium concentrations and renal lithium clearance were investigated in three psychiatric patients and four normal volunteers. After steady-state plasma lithium concentrations had been reached, the subjects received indomethacin placebo for three to seven days, indomethacin (50 mg thrice daily) for seven days, and placebo again for three to seven days. Indomethacin increased plasma lithium concentrations by 59% in the psychiatric patients and 30% in the volunteers. Renal lithium clearance was reduced by indomethacin by 31% in the group as a whole, and prostaglandin synthesis, determined by measuring the major metabolite of PGE_2 with mass spectrometry, was reduced by 55%.

These results show that indomethacin reduces renal lithium clearance to an extent which may be clinically important. They also suggest that the renal clearance may be affected by a prostaglandin-dependent mechanism, possibly located in the distal tubule.

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Introduction

Lithium is being given to increasing numbers of patients for the treatment of manic depressive and other psychiatric illnesses.[1] This treatment is not without hazards, and fatal lithium intoxication has been reported.[1] We describe here a drug interaction between lithium and indomethacin which could make the simultaneous administration of these drugs hazardous. We also provide evidence for a novel prostaglandin-mediated excretory mechanism of lithium.

Patients and methods

The study was carried out in three psychiatric patients in the manic phase of their disease and in four normal volunteers. The study was started when steady-state lithium concentrations had been reached, which usually required over three weeks of constant lithium intake in the patients and 10 to 14 days in the normal volunteers. Steady state was defined as plasma lithium concentrations on three consecutive days within 0·1 mmol(mEq)/l of each other. The patients and volunteers were kept on free diet throughout the study and received no other drugs.

The study consisted of three periods in which lithium intake was constant. In the first period an indomethacin placebo was given for three to seven days, in the second indomethacin was given in a dose of 50 mg three times a day for seven days, and in the third placebo was given for three to seven days. Throughout the study we determined plasma lithium concentrations daily 12 hours after the last dose and lithium and creatinine in daily 24-hour urine samples. On the last day of each period 7α-hydroxy-5, 11-diketotetranorprosta-1, 16 dioic acid (PGE-M) was determined by gas chromatography-mass spectrometry[2] to assess the rate of prostaglandin synthesis, and each patient underwent psychiatric evaluation on the brief psychiatric rating scale, sad-glad scale, and Minnesota personality inventory.

Results

Indomethacin increased plasma lithium concentrations in all the psychiatric patients and volunteers. The average increase in the plasma lithium concentration (average of the last two days on indomethacin) over values in the first placebo period was 59% in the psychiatric patients and 30% in the normal volunteers (fig 1). In all subjects studied plasma lithium values increased by $42 \pm 8\%$ (mean $\pm$ SE; $P < 0.01$) and fell in the second placebo period to $116 \pm 5\%$ ($P < 0.01$) of control ($= 100\%$). A representative study in one of the psychiatric patients is shown in fig 2. Indomethacin increased the plasma lithium concentration from 0·95 to 1·5 mmol/l within five days. The patient was switched back to placebo at that point to avoid toxicity and the plasma concentrations promptly declined. Indomethacin also reduced urinary lithium excretion.

Renal lithium clearance was suppressed by indomethacin in all the subjects by an average of $31 \pm 3\%$ (fig 3) and tended to return to pre-indomethacin values in the second placebo period.

The values for PGE-M in the three study periods were $8{\cdot}1 \pm 3$, $3{\cdot}7 \pm 0{\cdot}5$ ($P < 0.01$), and $10{\cdot}8 \pm 3$ μg/g creatinine ($P < 0.01$).

None of the psychiatric tests showed that indomethacin had any harmful effect.

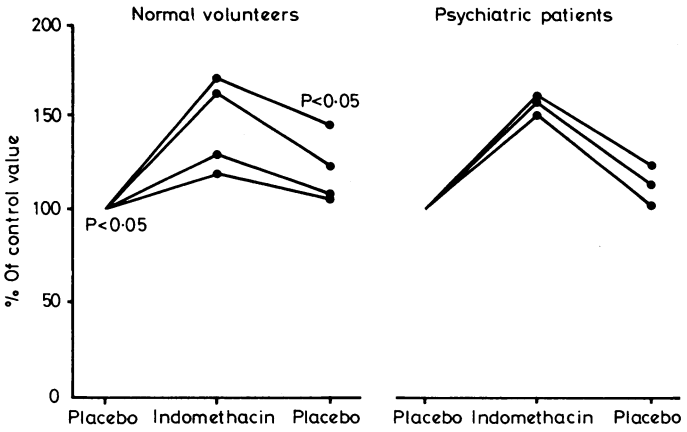

FIG 1—Effect of indomethacin on plasma lithium concentrations in normal volunteers and psychiatric patients.

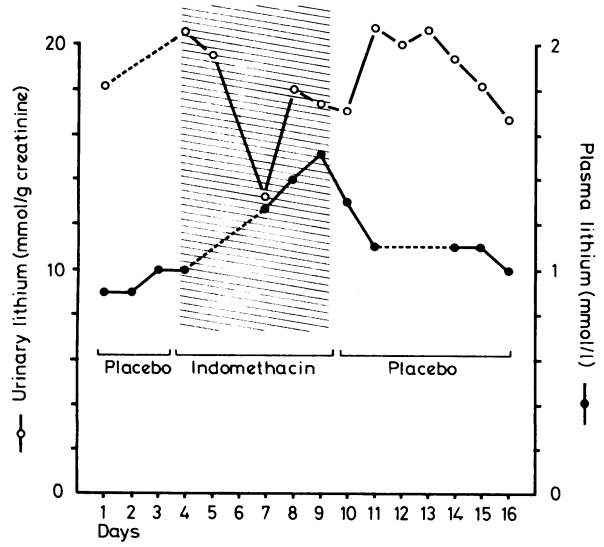

FIG 2—Effect of indomethacin on plasma lithium concentrations and renal lithium excretion in a psychiatric patient.

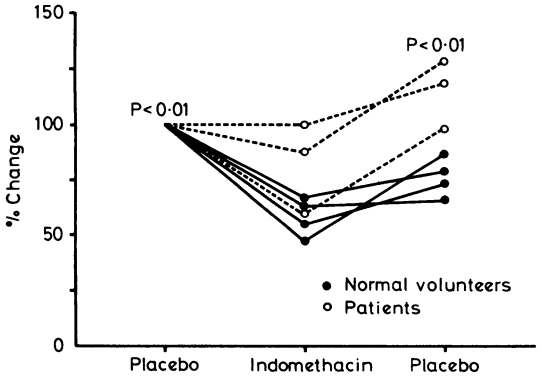

FIG 3—Effect of indomethacin on renal lithium clearance in patients and normal volunteers.

Discussion

Our results show that indomethacin causes a clinically relevant drug interaction with lithium. The increase in plasma lithium concentration was enough to lead to toxicity, and seems to have been caused by a reduction in renal clearance of lithium, since the size of the increase in the plasma concentration corresponded reasonably well to the size of the decrease in renal clearance. The cause of the reduction in renal lithium clearance by indomethacin is obscure. Indomethacin has no effect on glomerular filtration rate in man.[3]

Indomethacin regularly causes sodium retention in man, however,[4] thus suggesting that enhanced sodium and lithium reabsorption might be caused by a similar mechanism. Recent studies on the site of action of prostaglandin synthesis inhibitors such as indomethacin on sodium transport have shown that these inhibitors cause an enhanced medullary sodium concentration.[5] Furthermore, prostaglandin E_2 injected into the distal tubule decreases net distal tubular sodium efflux,[6] and in the isolated cortical collecting tubule peritubular prostaglandin E_2 inhibits sodium transport.[7] All these findings suggest that prostaglandins have an effect on distal tubular transport. Nevertheless, lithium is thought to be reabsorbed only in the proximal tubule[8] because diuretics that decrease distal sodium reabsorption do not enhance lithium excretion.[9]

Our results show that indomethacin reduces renal clearance of lithium to an extent that may be clinically important. They also suggest that the renal clearance of lithium may be influenced substantially by a prostaglandin-dependent mechanism, possibly located in the distal tubule.

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