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Statement

Monitoring of Patients in Prophylactic Lithium Treatment

An Assessment Based on Recent Kidney Studies

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The effect of long-term lithium treatment on the kidneys has generated concern among psychiatrists, and proposals have been made that routine determinations of serum lithium and serum TSH should be supplemented with control of the kidney function through regular determinations of serum creatinine, glomerular filtration rate, and renal concentrating ability, as well as through kidney biopsy in certain circumstances.

The choice of laboratory investigations must, however, depend on whether the purpose of the investigation is to collect data for scientific research or to guard the individual patient's safety. A scientific programme may include any investigative procedures that serve to test currently interesting hypotheses and to create data bases which will permit examination of problems emerging in the future. When, on the other hand, the individual patient is concerned, one must for each examination weigh its value as a safeguard and a guide for therapeutic decisions against its inconvenience to patient and clinic and its consumption of resources.

A considerable number of studies have now been published about lithium effects on the kidneys; kidney morphology has been examined in more than 150 and kidney function in more than 1000 lithium-treated patients. It is the aim of the present paper to assess the outcome of these investigations and to discuss on this basis which laboratory methods are best suited to guard the patient's health and safety.

Outcome of the kidney studies

The glomerular filtration rate is largely unaffected by lithium treatment (except during severe poisoning). Filtration rates lower than 70 per cent of the normal are infrequent and values lower than 50 per cent of the normal extremely rare. Examination of large patient groups has failed to disclose patients with filtration rates which were so low that survival was threatened. The risk of progressive renal insufficiency with terminal azotemia is remote even in patients given lithium for many years.

Tubular function is often affected during lithium treatment. A number of studies have revealed impairment of renal water reabsorption, leading to the development of polyuria and polydipsia. These side effects may be troublesome for the patients (increased thirst, nycturia, possibly weight gain), but they do not lead to lowering of the renal lithium clearance or rise of the serum lithium concentration, and they are not in themselves dangerous. However, because of the lowered renal concentrating ability the patients are apt to become dehydrated if fluid intake is restricted or if additional fluid is lost, and dehydration may lead to lowering of the lithium clearance and increased risk of lithium poisoning. It is therefore important that the patients do not neglect feelings of thirst.

Morphological kidney changes may be found in perhaps 10–20 per cent of patients given long-term lithium treatment, and there is some evidence that they are associated with impairment of water reabsorption. There is no evidence that the occurrence of such morphological changes is indicative of reduction in glomerular filtration rate or development of renal insufficiency.

Is routine examination of the kidneys necessary?

Lithium is eliminated almost exclusively through the kidneys, and the renal lithium clearance is under most circumstances a constant fraction of the glomerular filtration rate. A stable glomerulus function is therefore a prerequisite for safe lithium treatment. Lithium treatment itself does not lead to pronounced changes of the glomerular filtration rate, but glomerulus function may be affected by other factors, for example kidney disease, prolonged use of anal-

gesics, or conditions that may lead to dehydration. Lithium treatment should be monitored with extra care when this happens, and it is therefore important that such disturbance of kidney function is detected.

This purpose may be served by regular determinations of the serum lithium and serum creatinine concentrations, and these tests are discussed in detail below. As long as there is no rise of the lithium and creatinine concentrations to indicate that glomerulus function is disturbed, direct determinations of the glomerular filtration rate through infusion methods or methods involving quantitative urine collection are not needed. Such procedures consume resources and are inconvenient for patients and clinics, and in our opinion their use on a routine basis cannot be considered mandatory for patients without kidney disease in the history.

Water reabsorption is often impaired during lithium treatment, and the concentrating ability of the kidneys may be followed quantitatively through determinations of urine osmolality after thirst (by withholding fluids in a test) or after administration of vasopressin or vasopressin analogues. Examinations of this kind are clearly of interest for clinics doing research on the treatment and prevention of lithium-induced polyuria, but the question is whether such examinations provide information of sufficient value for therapeutic decisions, for example for decisions about discontinuing lithium treatment, to justify the effort and inconvenience of their inclusion in a routine monitoring program.

Even if in some patients the maximum osmolality of the urine may fall to a low value, this does not mean that these patients are going to develop renal insufficiency or die prematurely, and it does not constitute grounds for discontinuing prophylactically effective and otherwise well tolerated lithium treatment. The findings signify merely that the patients should respond readily to feelings of thirst and avoid situations involving risk of dehydration. Regular determinations of maximum urine osmolality may serve to identify patients for whom this is particularly important, but admonitions about drinking and avoidance of dehydration should be given to *all* patients in lithium treatment, and it is our view that lithium treatment can be monitored adequately without regular determinations of the concentrating ability of the kidneys.

It has been suggested that the renal concentrating ability might be followed as an indicator of the occurrence of morphological changes and that kidney biopsy should be considered when the maximum urine osmolality reaches a low value. There is, however, no evidence that the morphological changes which may be induced by lithium have any functional or prognostic significance other than, possibly, the lowered concentrating ability itself, and patients and clinics may well be spared such investigations.

Laboratory examinations

By far the most important laboratory examination during lithium treatment is regular determination of the serum lithium concentration. The *absolute value* of the serum concentration is a measure of the degree to which the organism is exposed to lithium, and it is this concentration which should be adjusted to, and then maintained at, a level which in the individual patient provides a maximum of therapeutic and prophylactic benefit with a minimum of inconvenience and risk. Moreover, since at steady-state there is a dynamic equilibrium between lithium dosage, lithium clearance and serum lithium concentration, *change* of the serum lithium concentration with unaltered dosage is a sensitive indicator of change of the renal lithium clearance (and, under most circumstances, of the glomerular filtration rate). A consistent rise of serum lithium shows that there has been a fall of the lithium clearance and should lead to further examinations.

In order to serve these two purposes reliably the serum lithium concentration should be determined under standardized circumstances, for example in the morning 12 hours (± 1 hour) after the last intake of lithium and under steady-state conditions, that is at least 4–5 days after start of treatment and after dosage changes. If blood samples are drawn under different conditions, serum lithium values may be misleading and may give rise to unwarranted and possibly harmful changes of the lithium dosage.

When blood samples are drawn for determination of the serum lithium concentration, the serum creatinine concentration may be determined in addition without extra inconvenience to the patients and at small extra cost. The serum creatinine concentration serves as an indicator of the glomerular filtration, but attention should again be focused on *change* of the concentration, since a consistently rising serum creatinine concentration can be a danger sign even at levels which are below the upper normal limit.

Under most circumstances the serum lithium concentration and the serum creatinine concentration vary in parallel when the lithium dosage is constant, because the renal lithium clearance is a fairly constant fraction of the glomerular filtration rate. One may therefore ask whether determinations of serum creatinine are worth the, admittedly small, extra cost and effort. We think that the following reasons speak in favour of including serum creatinine determinations among the routine tests:

(i) Assessment of the serum creatinine concentration does not, as does assessment of the serum

lithium concentration, rely on precise timing of the blood sample in relation to the last intake of lithium and is therefore independent of such patient co-operation.

(ii) Use of change in the serum lithium concentration as an indicator of change in kidney function presupposes that the lithium dosage has been kept constant; assessment of change in the serum creatinine concentration is subject to no such condition.

(iii) Determinations of serum lithium and serum creatinine are both subject to analytical variation; it is useful to have two independent indicators of change in renal function.

(iv) Psychiatrists are perhaps more accustomed to pay attention to the absolute value of the serum lithium concentration than to its changes; a rise of serum creatinine may therefore, rather than a rise of serum lithium, lead them to think of changes in the kidney function and to seek nephrological assistance.

Determination of serum lithium and serum creatinine at intervals during lithium treatment serves to disclose gradual changes in kidney function. Such regular laboratory control has the added benefit of serving as a frame for the close contact between patient and physician that is essential for optimum treatment outcome, and this is perhaps not the least important function of the visits to the clinic. Their frequency may vary individually, but intervals of two to four months are appropriate for many patients.

Examination of patients at intervals of two to four months does not guard against rises of the serum lithium concentration that take place over weeks or days, for example as a result of intercurrent disease with fever, start of treatment with diuretic drugs, loss of fluid and salt during heavy sweating, etc. It is therefore important that patients and relatives are instructed about such risk situations and are informed about clinical signals of impending lithium poisoning. The appearance of any such signs and symptoms should lead to clinical examination and determination of the serum lithium concentration.

Conclusion

Safe and effective lithium treatment must be based on proper selection of patients, on thorough instruction of patients and relatives about treatment management and precautions, and on careful clinical observation so that ineffectual dosages and adverse reactions can be detected early.

The choice of laboratory tests must depend on whether they serve a scientific purpose or are used to guard the individual patient's safety and health. We suggest here that extensive examinations of glomerular filtration rate and renal concentrating ability are of limited value for the latter purpose and that lithium treatment can be monitored adequately through determinations of serum lithium and serum creatinine every two to four months and of serum TSH every six months. The appearance of unexpected signs and symptoms should lead to closer clinical and laboratory examination.

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