Annotations

The sweat test

A request to the biochemistry laboratory for a 'sweat test' usually implies the measurement of the sweat sodium and chloride concentration or osmolality to support or refute the diagnosis of cystic fibrosis.

The increased concentration of electrolytes in the sweat of patients with cystic fibrosis was first described by Sant'Agnese *et al.*¹ The routine estimation of sweat electrolytes became a practical proposition after the introduction of the pilocarpine iontophoresis method for stimulating the production of sufficient sweat for reliable electrolyte estimations.² Previous methods of sweat collection—enclosing the limb in a plastic bag, overnight collections onto weighed pads, and even heating the whole patient—were less satisfactory and the last potentially dangerous.

The sweat test is a most valuable and relatively specific investigation to support the diagnosis of cystic fibrosis. Unfortunately, the test is performed badly at times and erroneous results, usually false high values of sweat sodium and chloride, have resulted in appreciable overdiagnosis. If false positive results are accepted uncritically by the clinician investigating a patient whose symptoms and signs suggest the diagnosis it is possible that cystic fibrosis will be incorrectly diagnosed. There is now considerable evidence that such mistakes are not rare.³ There are many other patients who are eventually correctly diagnosed only after serious difficulties have occurred in arriving at the diagnosis; not least of the problems has been the reliability of the sweat test.

There are two important aspects to a sweat test. The first is the collection of an adequate weight of the patient's sweat to permit accurate analysis of the electrolyte content. The second is the correct interpretation of a reliable estimation of the sweat electrolyte concentrations in the light of the patient's age, clinical findings, and additional investigations.

Sweat collection

Collection of an adequate weight of sweat is usually facilitated by the prior iontophoresis of pilocarpine into a small area of forearm skin. Sweat is collected from this pretreated area onto a weighed pad applied below a waterproof covering. This classical method of Gibson and Cooke is still used in most

laboratories.² The weight of the pad and thus the sweat is known and the electrolyte content and concentration can be estimated. Volumes over 50 mg are necessary for accurate estimations, and ideally 100 mg should be obtained.

The technical details are of paramount importance and the test has the potential for numerous errors. There may be contamination of the skin, instruments, or collecting apparatus or evaporation of the sweat from the pad from inadequate seals. Problems with dilution of the sweat specimen should be avoided by adequate laboratory quality control.

An alternative method of collection of sweat from stimulated skin uses the Macroduct, which is a concave plastic disc with a central small aperture leading to a spirally configured transparent fine plastic tube; the sweat can be observed travelling along the tube as it collects.^{4 5}

An alternative to collecting sweat is to estimate the chloride content of the sweat *in situ* using a chloride sensitive electrode.⁶ In practice this method is not recommended and, in our experience of patients referred to our unit, is associated with frequent errors when used by routine laboratories.

There is no place for semi-quantitative screening tests: if cystic fibrosis is suspected a formal sweat test should be performed.

Thus adequate sweat collection involves obtaining at least 50 mg, preferably 100 mg, of the patient's sweat, avoiding contamination, evaporation, or dilution errors, permitting an accurate estimation of the true sweat electrolyte concentration.

Interpretation of sweat electrolyte values

The interpretation of the sweat electrolyte results is usually straightforward; virtually all mistakes result from the incorrect determination of the concentration of sweat electrolytes.

There is excellent separation of the sweat electrolyte concentrations of patients with cystic fibrosis and unaffected individuals;⁷ although obligate heterozygotes have intermediate values, the differences are not sufficient to allow their identification in the general population. In cystic fibrosis the sweat sodium and chloride values are above 60 mmol/l, with a mean of around 100 mmol/l, whereas in unaffected individuals the mean is around 30 mmol/l. Five to 10% of normal adolescents and

adults, however, have values greater than 60 mmol/l—that is, in the lower cystic fibrosis range; furthermore, an occasional patient will have sweat electrolytes within the normal range.⁸

Sweat electrolyte values above the normal range, between 60 and 80 mmol/l, usually cause the practical difficulties. The usual response of the clinician and biochemist to such raised values is to repeat the test on a number of occasions. In some patients the first raised values will be revealed as an obvious laboratory error and subsequent values will fall well within the normal range. In many individuals—usually older children and adolescents—there will be genuine sweat electrolyte values, however, of over 60 mmol/l—that is, definitely outside the accepted normal range and within the lower range of values for patients with cystic fibrosis. Such results require careful evaluation, for the repeated sweat tests have usually caused considerable anxiety for the patient and parents.

Other conditions in which there are high concentrations of sweat electrolytes should be considered, but they are rarely the cause of the abnormal result—for example, adrenal insufficiency, glucose-6-phosphate deficiency, nephrogenic diabetes insipidus, hypothyroidism, mucopolysaccharidosis, malnutrition, anorexia nervosa, fucosidosis, ectodermal dysplasia, glycogen storage disease type I, nephrosis, Mauriac syndrome, familial cholestasis, and familial hypoparathyroidism.⁹

The relation of the sodium to the chloride value is helpful, for if a marginal result is from a normal individual the sodium is usually higher than the chloride value. Furthermore, the sum of the sodium and chloride values usually lies below 140 mmol/l. In patients with cystic fibrosis with the marginal results the chloride is usually higher than the sodium and the sum of sodium and chloride values is usually greater than 140 mmol/l.¹⁰ Our own data would support the value of these simple yet valuable observations.¹¹

Further evaluation of marginally raised sweat electrolyte concentrations involves repeating the sweat test after giving oral 9 α -fludrocortisone, 3 mg/m² daily, for two days. There is a greater fall of sweat electrolytes in normal than in affected individuals. The test has been evaluated in a few children¹² and also in adults.¹³ Further evaluation of this test is needed, but impressive falls in the sweat electrolyte concentrations certainly do occur in unaffected individuals.

Further confirmation that marginally raised electrolyte values are not due to cystic fibrosis involves tests other than estimation of sweat electrolytes. These additional investigations have been reviewed

elsewhere and include the exclusion of both malabsorption and a pancreatic lesion.¹⁴

Basis of diagnostic mistakes

Misdiagnosis of cystic fibrosis has usually followed one or more false positive sweat tests with subsequent uncritical acceptance of the results by the clinician; also there has usually been a failure to show either intestinal malabsorption by faecal fat estimation or any evidence of a pancreatic lesion. Such diagnostic mistakes are serious and it is suggested that patients considered to have cystic fibrosis who have no evidence of a gastrointestinal lesion should be referred to a cystic fibrosis centre to confirm or refute the diagnosis.

Conclusion

The sweat test remains one of the most important and specific examinations currently affected by the biochemistry laboratory. The test should be carried out on children with recurrent descending respiratory infections, unexplained failure to thrive, recurrent vomiting, chronic liver disease, rectal prolapse, nasal polyps, pancreatitis, and malabsorption.

The practical difficulties and common problems in carrying out the test should be remembered, and only experienced laboratory staff should perform the test. In patients who have caused diagnostic problems and where the sweat electrolyte values are marginal the clinical team and laboratory facilities of a cystic fibrosis referral centre should assist with the diagnostic problem by showing malabsorption and the presence, or absence, of a pancreatic lesion by non-invasive methods, but, if necessary, by a stimulated pancreatic function test.¹⁵ Individuals who have marginal rises in sweat electrolytes that return to the normal range after 48 hours of 9 α -fludrocortisone and in whom there is no evidence of either malabsorption or a pancreatic lesion do not have cystic fibrosis.

It must be re-emphasised that the implications of a positive test are so serious that the investigation should only be performed by experienced laboratory staff. The clinician should never diagnose cystic fibrosis on the result of one, or even two, sweat tests but only on the results of these tests in the context of the overall clinical picture.

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J M LITTLEWOOD
St James's University Hospital,
Leeds LS9 7TF