Inconsistencies in sweat testing in UK laboratories

J M Kirk

Abstract

Background—Sweat testing procedures are perceived to vary widely.

Aim—To evaluate variability in sweat collection, analysis, and interpretation.

Methods—Questionnaire responses from 30 self selected centres: 15 paediatric centres, and 15 district general hospitals.

Results—Centres carried out 30–400 sweat tests per year (median 100), with a diagnostic rate of 1:5–152 (median 1:30). Staff performed 5–268 tests per year. Minimum test age varied from 24 hours to four months. All stimulated sweating by pilocarpine iontophoresis using varying currents and times. Twenty six had observed urticaria or skin reddening, and nine blistering or burns. Sweat was collected for 10–60 minutes onto filter paper or into Macroduct coils. Between 2% and 25% of tests were considered insufficient. Twenty eight measured sodium, 24 chloride, and one osmolality and conductivity. Fifteen used literature and five in house reference ranges. Eleven would not test severely eczematous children.

Conclusions—Local audit is required to improve performance, as well as a national guideline to standardise collection, and external quality assessment to provide analytical feedback.

(Arch Dis Child 2000;82:425–427)

Keywords: sweat testing; laboratory testing; cystic fibrosis diagnosis

Sweat testing has been the most widely used diagnostic test for cystic fibrosis for almost 50 years.1 Diagnostic criteria have become less straightforward as referrals have widened to include neonates with abnormal screening results by immunoreactive trypsin and/or DNA mutation studies,2 and less severely affected patients for investigation of atypical cystic fibrosis.3

In most laboratories sweat and routine plasma samples are analysed by separate methods. The United States has a well established external quality assessment (EQA) programme administered by the College of American Pathologists, and a guideline document on sweat test performance.4 Cystic fibrosis centres in the USA must comply with the guideline. Until a recent national pilot study of sweat analysis, no UK based EQA existed to assess analytical performance. Although laboratory regional audit groups have reviewed sweat collection and analysis procedures and produced consensus guidelines, such as the Welsh sweat standard,5 no national standard exists for the sweat test procedure.

This paper assesses sweat testing variability within a self selected group of UK centres, and considers how performance can be assessed and improved.

Methods

A questionnaire was circulated to Biochemical Investigations in Metabolic Disease Quality Assessment (BIMDG QA) committee members and participants enrolled for a sweat testing workshop at an Association of Clinical Biochemists national meeting. The responses represent large paediatric centres, and those with a particular interest or concern regarding sweat testing who were prompted to attend the workshop.

Results

Replies were received from all 15 BIMDG QA committee members and from 15 workshop participants representing eight children's hospitals, seven teaching hospitals, and 15 district general hospitals.

Centres carried out 30–400 sweat tests per year (median 100). The number of tests carried out for each diagnosis made varied from five to 152 (median 30). Tertiary referral centres had a higher ratio of abnormal tests. The highest ratio was reported by a centre which followed up infants in whom neonatal screening revealed increased immunoreactive trypsin. In most centres (n = 22) laboratory staff carried out sweat collection, varying from the most junior staff member to the head of department, with the majority (n = 12) using medical laboratory scientific officers (MLSOs). Some centres used nursing staff, physiotherapists, or respiratory measurement technicians. No centre reported the once common practice of using junior medical staff, medical students, or student nurses to carry out sweat tests as part of their training. Most centres restricted sweat collection to one or two trained staff. The extreme responses were a single operator carrying out 268 tests per year and 13 MLSOs sharing 64 tests per year. Centres using two staff either equally shared tests (n = 8) or had one operator carry out the majority, with the other as back up when necessary (n = 7). Five centres, all specialist hospitals, had a single trained operator.

The minimum test age quoted varied from 24 hours to four months. The commonest medical condition cited as a reason for deferring sweat testing was severe eczema (11 centres). Three centres were reluctant to test acutely ill children, and two were reluctant to test infectious children. Other conditions mentioned once each were: on mineralocorticoids, on flucloxacinill, on antibiotic, on oxygen, intravenous infusions in botharms, ichthyosis, and limbs too small for electrodes.
Seventeen centres used an Electro Medical Supplies power supply, and in house methodology. Nine centres used a Wescor power supply, operated according to the manufacturer’s instructions, and marketed with Macroduct collectors. Two used in house power supplies, one an Orion system, and the remainder did not specify. All centres stimulated sweating by pilocarpine iontophoresis. The nine Wescor users applied agarose discs containing 5 g/l pilocarpine at both electrodes. Others used anode pilocarpine concentrations varying from 2 to 5 g/l on gauze, lint, or filter paper and a variety of cathode electrolyte solutions. A current of 1.5 to 4 mA was applied for four to 10 minutes.

Twenty six centres had observed reddening/urticaria on the stimulated site, while blistering or burns was reported by nine centres, including two where operators carried out more than 100 sweat tests per year. Several centres commented that they had observed burns on a single occasion over many years testing. Sweat was collected onto filter paper with a median area of 15.0 cm² (range 7–38.5) or into Macroduct collectors of area 7 cm². Collection time was usually 20–30 minutes, but varied from 10 to 60 minutes, and was not always accurately timed. Definition of an insufficient collection varied from 7 µl from a Macroduct user to 200 mg from a laboratory collecting over 38 cm² for 60 minutes. Because of the lack of information on sweat collection times, minimum sweat rates could not be compared across centres. Insufficient collections varied from 2% to 25% of the total and did not correlate with minimum sweat weight/area (r = 0.18, p = 0.43; two tailed test).

In practice most laboratories analysed and reported results on weights below their specified minimum. Patients especially likely to produce insufficient sweat included neonates/small infants (four centres), those with eczema or other skin conditions (n = 4), and Asian patients (n = 2). Laboratories also commented on particular “difficult” patients who repeatedly failed to sweat.

Twenty eight laboratories analysed sodium by flame photometry (n = 23), ion specific electrode (n = 4), or unspecified (n = 1). Twenty four laboratories measured chloride using six different methods. Twenty four centres measured sodium and chloride, four sodium alone, and two chloride alone. One laboratory measured sodium, chloride conductivity, and osmolality. Many in house and commercial standards and internal quality control (IQC) solutions were in use at different concentrations. IQC specimens should be handled in exactly the same way as patient samples. All 15 specialist centres, but only three workshop participants, added QC samples to weighed filter paper, and reweighed, diluted, and extracted them in parallel with patient samples.

Reference ranges (fig 1) were based on literature reports (n = 15), in house data (n = 5), manufacturer’s quoted values (n = 1), not known (n = 2), or not specified (n = 6). Fifteen centres quoted an equivocal range, and two used a graph of sodium versus chloride to aid equivocal result interpretation. When a sweat test gave an abnormal result, 20 centres would repeat it, one by a different technique, and one by referral to their regional centre. One centre suggested fludrocortisone suppression. Eight centres would carry out DNA mutation testing, three pancreatic function assessment (by stool trypsin or chymotrypsin, plasma immunoreactive trypsin, or stool fat globules), and one nasal potential measurements.

Discussion

A recent NEQAS questionnaire identified more than 170 UK laboratories that measured sweat electrolytes. The 30 centres whose experience is reviewed here revealed wide variability in almost all aspects of sweat testing. Because they were a self selected group, with particular expertise and interest in sweat testing, even greater variability is likely if all testing centres were investigated. Some evidence for this is available from subsequent use of the questionnaire by regional audit groups, whose results suggest that more centres carry out very small numbers of tests, or use the Orion electrode, than would be extrapolated from the selected group reported here.

Sweat collection depends on care and skill in avoiding evaporation and contamination, both of which lead to artefactually raised electrolyte concentrations. The operator must assess when it would be inappropriate to test a child. This requires experience, and it is of concern that some individuals carry out fewer than 10 sweat tests annually, which occurs because of staff organisation in larger centres, as well as in centres with a small workload. Sporadic case reports document burns caused by iontophore-
Inconsistencies in sweat testing in UK laboratories

Inconsistencies in sweat testing in UK laboratories

427

than the sweat rate (1 g/m² weight quoted was often considerably greater
tion area and time used. The minimum sweat
sweat weights. Often these were literature
the model of their system.

the iontophoresis current applied, depending on
variables actually affect the result or the
safety of the test. The group of laboratories using
the commercial Macroduct system, which
presumably follow the manufacturer's instructions,
show less variability. However, even they differ in
the iontophoresis current applied, depending on
the model of their system.

Centres accepted a wide range of minimum
sweat weights. Often these were literature
derived and inappropriate for their
sweat collection area and time used. The minimum sweat
weight quoted was often considerably greater
than the sweat rate (1 g/m²/min) necessary for
adequate results. Extending sweat collection
time, particularly for the Macroduct coil where
the yield is readily visible, cannot increase the
sweat rate, and may not even increase sweat
weight, while increasing the possibility of evapo-
ration. The minimum volume required for
analysis is a separate issue, and with modern
technology should be achievable down to the
minimum sweat rate. As the percentage of insuf-
cient tests did not correlate with the minimum
weight required, it appeared that patients who
failed to sweat adequately usually failed com-
pletely, rather than representing the lower end of
the normal distribution of sweat production.

The great majority of centres surveyed
measured sodium and chloride. Increasingly
laboratories use elderly flame photometers
almost solely for sweat sodium samples, and
therefore may have difficulty in funding their
replacement. There is a greater range of chloride
methods in use. The two most popular are a
dedicated chloride meter with the same replace-
ment problems as for a flame photometer, or
a colorimetric method using standard laboratory
equipment. For both sodium and chloride
virtually all laboratories have entirely separate meth-
ods for the analysis of sweat and plasma, with
only the plasma method monitored by EQA.
Sweat conductivity and osmolality are not
popular. The single centre measuring both also
analysed sodium and chloride and had extensive
in house data on all four parameters. There was
wide variation in standardisation and internal
quality control. Ideally both should be at a clini-
cally important concentration, and should differ
from each other. Large centres were more likely
to make these solutions in house and to assess
quality control in the equivocal range, while
smaller centres were more likely to use commer-
cial sources.

More centres used literature reference ranges
than in house data to interpret results. About
half used a “grey” or equivocal range. Ongoing
local audit will determine whether literature
ranges are appropriate for the patient popula-
tion. For example, the first Welsh sweat standard
set a chloride cut off of 50 mmol/l. After
introduction of two tier neonatal screening by
immunoreactive trypsin (IRT) and a mutation
analysis panel, the population tested was pre-
dominantly infants aged about 6 weeks with an
abnormal IRT result and a single disease
causing mutation identified. To achieve the
maximum diagnostic rate in this pop measure it
proved necessary to lower the chloride cut off to
40 mmol/l. Local audit should also identify any
change in the percentage of tests yielding insuf-
cient sweat, or abnormal or equivocal results
that are not confirmed when repeated. Such a
change, without a change in the population
referred, indicates that a significant variable has
been inadvertently introduced into the sweat
collection or analysis procedure.

Sweat testing organisation has changed over
the last decade with recognition of the
importance of restricting testing to experi-
enced staff. For example, the sweat collection
was almost solely for sweat sodium, and
chloride. However, these improvements have
been matched by increasing complexity in
result interpretation. DNA analysis, nasal
potential measurements, and pancreatic
function assessment provide additional diag-
nostic information. The sweat test still occupies
an important place but until centres standard-
ise their methodology, particularly in defining
insufficient sweat rates, identifying analytical
problems, and using reference ranges appropri-
ate to their patient populations, it will fail to
achieve its full diagnostic potential across the
disease spectrum of cystic fibrosis.

For this to occur a threefold effort is recom-
mended:

- Ongoing local audit of sweat test perform-
ance
- Development of a national EQA scheme to
assess analytical variability and recommend
optimal methods
- Dialogue between clinicians and laboratory
specialists to produce UK guidelines on
standardised procedures for sweat collect-
analysis, and interpretation.

1 Gibson LE, Cooke RE. A test for concentration of
electrolytes in sweat in cystic fibrosis of the pancreas util-
2 Pollitt RJ, Dalton A, Evans S, Hughes HN, Curtis D. Neo-
natal screening for cystic fibrosis in the Trent region (UK):
two stage immunoreactive trypsin screening compared with
a three-stage protocol with DNA analysis as an inter-
3 Augerten A, Kerem B, Yahav Y. Mild cystic fibrosis and
normal or borderline sweat test in patients with the 3849+
4 National Committee for Clinical Laboratory Standards.
Sweat testing: sample collection and quantitative analysis;
approved guideline. NCCLS document C34-A (ISBN
5 Welsh Scientific Advisory Committee (Welsh office). *Welsh
Standard—the sweat test*. All Wales Clinical Biochemistry
Audit Group, 1996.
6 Rattenbury JM, Worthey E. Is the sweat test safe? Some
instances of burns received during pilocarpine electro-
7 Williams J, Griffiths PD, Green A, Weller PH. Sweat tests
Inconsistencies in sweat testing in UK laboratories

J M Kirk

Arch Dis Child 2000 82: 425-427
doi: 10.1136/adc.82.5.425

Updated information and services can be found at:
http://adc.bmj.com/content/82/5/425

These include:

References
This article cites 4 articles, 2 of which you can access for free at:
http://adc.bmj.com/content/82/5/425#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
Dermatology (377)
Immunology (including allergy) (2018)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/