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Original Article

Feasibility and normal values of an integrated conductivity (Nanoduct™) sweat test system in healthy newborns

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Abstract

Background: Nanoduct™ is a simple and practical sweat analysis system measuring conductivity in situ. It requires only three microlitres of sweat, making it especially applicable to newborns.
Methods: We measured conductivity in 260 healthy term infants at the age of four days, and again at four weeks to determine the proportion of successful tests, test duration, and normal values for sweat conductivity in newborns.
Results: Sufficient sweat was collected in 159/260 of four-day olds (61%), and in 225/239 of four-week olds (94%). Mean (sd) test duration was 27 (5) and 25 (5) min. Mean (sd, range) conductivity was 53 mmol/l (16, 8–114) at age four days, and 36 (9, 12–64) at four weeks.
Conclusions: Determination of sweat conductivity using Nanoduct™ cannot be recommended for four-day old newborns. However, at the age of four weeks the success rate is high (94%), and conductivity values at that age are comparable to older healthy children.

Keywords: Sweat test; Conductivity; Cystic fibrosis; Newborn screening

1. Introduction

The sweat test is a key component for establishing a diagnosis of cystic fibrosis (CF) in infants with a positive result in newborn screening (NBS) [1,2]. Collecting sufficient sweat for analysis is a challenge in small infants and some guidelines recommend delaying the test until the infant is more than two weeks of age or weighs more than 3 kg [3–5]. Although for infants below three months of age test failure rates of up to 40% have been reported [6–10], North American recommendations aim for a failure rate of 10% or less for sweat tests in NBS programs [2,6].

Since the invention of the sweat test based on the pad method by Gibson and Cooke 60 years ago [11,12], sweat testing has evolved. The nowadays widely accepted Macroduct™ collection system needs 15 µl of sweat to analyze chloride concentration [2–4], while the sweat flow sensor of the Nanoduct™ sweat test system requires only 3 µl. This makes it especially applicable to newborns. However, it does only measure conductivity [13].

Studies using Nanoduct™ discriminated well between children with and without CF [13–17]. This is also true for other sweat tests that measure conductivity instead of chloride concentration, for instance the Sweat-Check™ [18–22]. Despite this, the European practice guidelines for neonatal screening and the US guidelines

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for diagnosis of CF do not recommend measuring sweat conductivity to diagnose CF [1,2].

This study assessed the feasibility of sweat testing with the Nanoduct™ system in healthy newborns at the age of four days and four weeks, by determining the duration of the tests and the proportion of tests that were successful. We also wanted to determine the normal values of sweat conductivity for Nanoduct™ in this age group.

2. Methods

2.1. Subjects and study design

We conducted this single-center study from June 2013 to December 2014 with 260 healthy term infants born in the maternity unit of the Department of Gynaecology at the Cantonal Hospital St. Gallen in Switzerland. Each infant was tested twice with the Nanoduct™ (Wescor, Utah, USA) sweat system, at age 3–4 days and 3–4 weeks. We chose these age groups because in Switzerland NBS with the Guthrie test is performed at the age of 3–4 days, before infants leave the birth clinic [23,24]. When they are 3–4 weeks old, children with a positive NBS result are recalled to a CF center for sweat testing. We asked all parents of healthy infants born in the hospital during this period to participate, except those whose infants were born prematurely (gestational age <37 weeks), had a birth weight below 3000 g, or were sick, presenting symptoms such as oedema, hyperbilirubinemia, signs of dysmaturity, malnourishment, or a systemic disease. We also excluded children whose parents did not speak German, and all those who were discharged on a weekend.

2.2. Nanoduct™ sweat test analysis system

The Nanoduct™ sweat test is a micro-flow conductometric device, which induces and analyzes the conductivity of sweat in situ while attached to a patient. The procedure is described in detail elsewhere [13,20]. In brief, iontopheresis using small Pilogel™ iontophoretic discs and direct current supplied by the Nanoduct™ inducer/analyzer is followed by a continuous-flow analysis of sweat conductivity using a conductivity sensor. The continuous-flow principle allows display of the initial sweat rate in grams per square meter of skin surface per minute, which is important in accepting sweat test results (valid results: ≥ 1 g/m^2/min). Its continuous sweat flow sensor requires only 3 μl of sweat. The value of conductivity is expressed as mmol/l eq NaCl. This is not equal to a quantitative chloride measurement; its displayed equivalent is approximately 20 mmol/l higher than the sweat chloride concentration because of additional anions such as lactate and bicarbonate [18,19,21].

The sweat tests at the age of four days were carried out in the Department of Gynaecology of the Cantonal Hospital St. Gallen by two trained and experienced persons (Agnieszka Mazur and a research nurse). The sweat tests at the age of four weeks were performed at infants' homes or in the Children's Hospital in St. Gallen by the same two persons. The Nanoduct™ device was placed on a forearm or a leg. The sweat test was considered valid (that is, a successful test) if the sweat rate was ≥ 1 g/m^2/min, and as not valid if the sweat rate was lower (<1 g/m^2/min) or zero (no sweat rate displayed on Nanoduct™).

The parents were told by the technician that the test results needed to be interpreted by the doctor, and were then informed by the investigator after the end of the two tests only if the result was regarded as ambiguous or not normal. If the second sweat test at the age of 4 weeks was above an upper limit of 60 mmol/l, we offered the parents another sweat test at the Children's Hospital, followed by a chloride measurement using the Macroduct™ method, if the conductivity value was still elevated.

2.3. Statistical analysis

We calculated the proportion of successful tests as the number of tests with valid results divided by the total number of tests performed. We compared the proportion of successful tests across quintiles of body weight at the day of the test, and across quintiles of weight loss between birth and the test day, in percent of birth weight, using tests for trend to assess statistical significance. We checked the distribution of quantitative data (duration of tests, conductivity) using histograms, Q–Q plots, and Shapiro–Wilk and Shapiro–Francia tests for normality. Since data were normally distributed, we described sweat conductivity (mmol/l) and test duration (minutes) as mean values and standard deviations (sd), and determined 95% (99%) reference intervals for sweat conductivity as the mean ± 2 (±3) standard deviations. For infants with paired data, we compared agreement with a Bland Altman plot, displaying the mean of the two values on the x axis versus the difference between the two measurements on the y axis. We analyzed the data using STATA version 13.1 (StataCorp. 2005. Stata Statistical Software: Release 13.1 StataCorp LP, College Station, TX, USA).

3. Results

Between July 1, 2013 and Dec 31, 2014, 2231 infants were born in the maternity unit in St. Gallen. Of these, 366 were excluded because of preterm birth, 707 because of low birth weight and 898 for different reasons (discharge at weekends, parent's insufficient knowledge of the German, clinical symptoms such as hyperbilirubinemia, or no parental consent). None of the children born in this unit had a positive CF-NBS result . Parents of 260 newborns agreed to participate (Table 1). In total, 239 infants had two sweat tests (Table 2). Twenty-one infants were lost to follow-up at four weeks, twelve due to parental refusal, six due to no answer to repeated phone calls, and three because of unavailability of the sweat test equipment on the test day. The time needed to perform the sweat test was on average 27 min (5–40, sd 5 min) at the age of 4 days, and 25 min (14–40, sd 5 min) at the age of 4 weeks.

The proportion of successfully conducted sweat tests was 61% at age 4 days, and 94% in four-week olds (Table 2). At age four days, 159 of 260 infants (61%) produced enough sweat (≥ 3 μl), while 23 (9%) had an insufficient quantity and 78 (30%) produced no sweat at all (Table 2). The proportion of successful tests was positively associated with body weight,