Summar

Devices that use a spectral reflectance technique are used to non-invasively measure total bilirubin levels in neonates to monitor the development of hyperbilirubinemia.

As a screening technique for the healthy neonate population, these devices provide instantaneous information, may reduce the need of heel-pricks on neonates, and indicate which neonates will need serum bilirubin measurement.

Evidence from studies supported by the manufacturer of BiliChek™, the newest device using the spectral reflectance technique, suggests that there is a linear correlation between transcutaneous bilirubin measured by BiliChek™ and total serum bilirubin as measured by the gold standard technique (i.e. HPLC). The correlation, however, is limited by gestational age of the neonate, as well as certain pathological neonatal conditions.

Prospective cohort studies on the effectiveness of the technology in the reduction of hospital readmission, and using the incidence of morbidity and mortality from kernicterus as clinical endpoints, would be useful.

The Technology

Hyperbilirubinemia (total serum bilirubin > 17.1 SI units or 1 mg/dL) leading to a yellow discoloration of the skin (jaundice), can occur transiently in healthy neonates and is termed physiologic jaundice. However, elevated bilirubin within the first 24 hours of life or bilirubin levels that exceed 205.2 SI units (12 mg/dL) is considered pathologic jaundice, and may be due to genetic or acquired pathological conditions. Infants with very high serum bilirubin levels (>342 SI units or 20 mg/dL) may develop permanent neurological damage due to bilirubin deposits in the brain (kernicterus).

The Minolta JM-102™ (Air Shields, Inc.), the Colormate III™ (Chromatics Color Sciences International, Inc.) and the BiliChek™ device (SpectRx Inc.) measure bilirubin transcutaneously, using a reflectance spectrophotometry technique. The systems work by directing white light into the skin of a neonate and measuring the intensity of the specific wavelengths, which are reflected. JM-102™ is based upon two-wavelength data analysis, and Colormate III™ is based upon multiple wavelengths analysis. BiliChek™, the newest device using the spectral reflectance technique, converts multi-wavelength spectral reflectance into optical densities, which are analyzed by an algorithm to eliminate interference by other skin components and to yield a numerical measurement of transcutaneous bilirubin (TcB).

There is a linear correlation between serum bilirubin and readings with these techniques, but serum bilirubin cannot be predicted accurately because of errors related to factors such as skin pigmentation, gestational age, and birth weight. It is noteworthy that these reflectance instruments cannot detect different forms of bilirubin (i.e. conjugated, unconjugated, delta bilirubin) and bilirubin degradation products in the serum.

Regulatory Status

The U.S. Food and Drug Administration (FDA) approved BiliChek™, Colormate III™ and JM-102™. SpectRx and Air Shields have received approval to market BiliChek™ and JM-102™ in Canada in 1998 and 2001, respectively.
Patient Group

Neonatal jaundice occurs in 30% to 60% of full-term neonates and in nearly all premature neonates. It is a frequent reason for neonate readmission after hospital discharge.6-9 Kernicterus is rare in apparently healthy, full-term neonates without a discernible cause for jaundice,10 but is very serious. Pathologic jaundice may be associated with disorders leading to hemolysis such as Rh or ABO blood group incompatibilities, inborn error of metabolism, breast-feeding, or consequences of prematurity.11

Current Practice

The daily monitoring of bilirubin concentrations in jaundiced newborns gives information on serum bilirubin levels, and can help to distinguish physiologic from pathologic hyperbilirubinemia. Screening tests for neonatal jaundice include visual inspection and TcB measurements to identify which neonates require serum bilirubin measurement.12 Once screening tests detect neonates with a high risk of developing pathological hyperbilirubinemia, further serum tests can be carried out to detect underlying diseases.13 The management of neonates with pathological jaundice requires total serum bilirubin (TSB) to be measured. Serum samples are traditionally obtained by heel-prick, and TSB determined in a clinical laboratory on a multi-analyte automated chemistry analyzer (usually by a diazo method) or by direct spectrophotometric measurement on a bilirubinometer. HPLC analysis, the gold standard, is usually reserved for reference and research laboratories.14

The American Academy of Paediatrics (AAP) 1994 practice guidelines on management of neonatal jaundice are being updated, with publication likely in late 2002. These guidelines will include any available evidence on transcutaneous measurement although little new information is anticipated (Carla Herrerias, AAP, Elk Grove Village, IL: personal communication, 2002 Apr 24). The Canadian Paediatric Society (CPS) updated guidelines will likely be released in 2003 (Colette Laplante, CPS, Ottawa: personal communication, 2002 Apr 11).

Administration and Cost

The fibre optic probe of BiliChek™, covered by a disposable tip, is placed in contact with the forehead skin of the infant who has been placed in a supine position or cradled in a lap. Light pressure is applied, and one measurement made over one to three seconds. The light source in the unit is triggered for five measurements that are then averaged to provide one TcB measurement. In a quiet infant, the total process should take from 10 to 15 seconds.2 The BiliChek™ sells for $3,995. The cost for a test with BiliChek™ ($5.25-$7.00) is mainly attributable to the cost of the calibration tip. This cost is similar to the cost of a TSB measurement (diazo method), when all additional material for TSB (cannula, gloves, test tube etc.) and the special cost for sample transport and urgent analysis are taken into consideration.15 In Ontario, the Ontario Health Insurance Plan (OHIP) fee schedule for TSB is $2.59.

Rate of Technology Diffusion

An objective, rapid and non-invasive screening technique would be ideal to identify those neonates who require more in-depth investigation by measurement of serum bilirubin. Even though sufficient information is not available to calculate the projected rate of diffusion of transcutaneous bilirubinometry, a transcutaneous test with enhanced accuracy and low cost could be an attractive option for bilirubin measurement in neonates.

Concurrent Developments

Air Shields Inc. has released a new Jaundice Meter, the JM-103, in Japan, to measure transcutaneous bilirubin. CO-Stat Analyzer is a product manufactured by Natus Medical Inc. to measure the carbon monoxide level in the baby's...
exhaled breath, which is an indicator of hemolysis and hyperbilirubinemia. These devices have not yet received approval in Canada.

**The Evidence**

In a recent study supported by the manufacturer of BiliChek™, 490 term (37-42 weeks of gestational age) and near-term (≥36 weeks of gestation age and ≥2,000 g birth weight, or 35 weeks of gestational age and ≥2,500 g birth weight), multi-racial infants between 12 and 128 hours of age had TcB levels tested using the BiliChek™ device. These results were paired with heel-prick TSB measurements using the gold standard HPLC technique. The results showed a linear and statistically significant correlation between TcB and TSB (r=0.91, p<0.001). Similar correlations were observed when the population was categorized by race and gestational age. With the BiliChek™ device, intradevice and interdevice standard deviations were 10.1 SI units (0.59 mg/dL) and 11.6 SI units (0.68 mg/dL), respectively. The paired TcB values were above the 75 percentile track for 6.1% of the population who had predischarge TSB above the 95 percentile track. This means these infants may be considered at high risk for subsequent excessive hyperbilirubinemia. However, the probability that infants with predischarge TcB values above the 75 percentile for age will develop hyperbilirubinemia is only 32%, or in other words, BiliChek™ is capable to predict which neonates are at high risk for developing hyperbilirubinemia 32% of the time. Another study, also supported by the manufacturer, showed a similar correlation between TSB levels using the HPLC technique and TcB values using the BiliChek™ device in a total of 210 near-term, multi-racial infants.

A recent independent study reporting on 145 pre-term (26-36 weeks gestation), mostly Caucasian, neonates revealed limitations of the clinical value of the BiliChek™ assay. In this study, TSB was measured using the diazo reaction method and TcB was determined using the BiliChek™ device. The results showed there was only a strong correlation between TSB and TcB values in infants who were not receiving phototherapy (r=0.73, p<0.005), the correlation being much weaker in those who were being treated with phototherapy (r=0.59). Also, the correlations were strong only in neonates older than 30 weeks gestation who were not receiving artificial ventilation. The same trend (decreased correlation in neonates receiving phototherapy) was also found in another independent study involving pre-term and term neonates.

**Implementation Issues**

Many factors can affect the accuracy and reliability of TcB measurements such as physiological variations in the pigmentation of neonates, the site used for TcB measurement, the use of phototherapy, and increased frequency of breast-feeding. The correlation between TcB and TSB can be affected by skin thickness and variations in daylight and room illumination.

Many of the studies using the BiliChek™ device have not addressed the above factors. Even in multi-racial studies, the population distributions have been mostly Caucasian and the number of subjects from other ethnic groups was too small to produce reliable results.

In most studies to date, the correlation between TcB and TSB has been determined using regression analysis. An important study pointed out the disagreement between regression analysis and difference plots in determining the correlation. In this study, regression analysis showed a good correlation between TcB and TSB values, but difference plots showed that BiliChek™ is not reliable for TSB > 188.1 SI units (11 mg/dL), leading to an underestimation of TSB when decisions are being made for or against the use of phototherapy.

Larger studies are required to test the performance of devices using spectral reflectance technique throughout a range of serum bilirubin levels, as well as in various ethnic groups.

**References**


