Short reports

Percutaneous absorption of chlorhexidine in neonatal cord care

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SUMMARY The percutaneous absorption of chlorhexidine during its routine use in topical antiseptic preparations used in umbilical cord care was investigated by determining plasma chlorhexidine concentrations at ages 5 and 9 days. These showed that percutaneous absorption of chlorhexidine occurred in preterm neonates treated with a 1% solution of chlorhexidine in ethanol, but not in term infants similarly treated, or in preterm infants treated only with a dusting powder containing 1% chlorhexidine and 3% zinc oxide.

Chlorhexidine (CHD) (1, 6-di (4-chlorophenyl-diguanido) hexane) (Hibitane ICI Ltd UK) is a topical antiseptic which has a wide activity against Gram-positive and Gram-negative bacteria and some yeasts.¹ Its ability to disinfect skin² and reduce newborn staphylococcal infection³ is comparable with that of hexachlorophane (HCP). The demonstration of percutaneous absorption of HCP, of its neurotoxicity in man and animals, and the subsequent realisation of the risk incurred by its excessive application to injured skin or to the intact skin of preterm newborn babies has been reviewed.^{4,5} Restrictions on the routine use of HCP led to an increased incidence of staphylococcal infections in neonatal intensive care units which indicated the efficacy of topical antiseptics in routine neonatal care, and necessitated the cautious reintroduction of HCP.⁵

CHD is an alternative antiseptic agent to HCP. However, an earlier investigation suggested that the daily use of a CHD preparation for bathing newborn infants might result in percutaneous absorption of the antiseptic.⁶ The two studies described in this paper were undertaken to investigate plasma CHD levels in term and preterm newborn babies who were exposed to applications of CHD preparations for umbilical cord care.

Patients and methods

In the first study (Study A) 25 term (mean birthweight

3.34 kg; range 2.13-4.22) and 23 preterm babies with gestational ages between 31 and 36.5 weeks (mean birthweight 2.08 kg; range 1.29-2.79) were investigated. Three term and 4 preterm infants were black, one preterm infant was Asian, and the remainder were white. At delivery, the umbilical cord was cut and ligated 4 cm from the skin and treated with a solution of 1% CHD in ethanol, and a 1% CHD and 3% zinc oxide dusting powder. This treatment was repeated 4-hourly thereafter for at least 9 days. With the sole exception of venepunctures the CHD solution was also used for topical antiseptics during all invasive procedures, such as lumbar punctures and umbilical catheterisation.

A second study (Study B) was performed because Study A had shown detectable plasma concentrations of CHD in preterm infants; in this, only the dusting powder was used for cord care but otherwise the procedure was identical with that used in the first study. The alcoholic CHD solution was used exclusively for invasive procedures as described above. The group comprised 29 preterm infants admitted consecutively to the intensive care nursery. Their mean gestational age was 32.5 weeks (range 26-36.5) and their mean birthweight was 1.870 kg (range 1.0-2.53). These infants included one Asian and two black babies, and one set of triplets.

Gestational age was estimated by neurological and morphological examination^{7,8} and, where possible, from serial antenatal ultrasonography.

One preterm infant in Study A and 9 in Study B had umbilical catheters inserted during their initial management; in addition in Study B, one 4-day-old infant had an exchange transfusion and 4 others had phototherapy for at least 3 days.

Venous blood was taken from an antecubital vein on days 5 and 9 after birth. Samples were taken with others needed either for clinical care or for screening for inborn errors of metabolism. The skin site was cleansed twice with alcohol, once with water, and then dried before venepuncture. In Study A cord blood was also collected. The plasma CHD content

was determined by gas liquid chromatography.⁹ Calibration curves were fitted by the method of least squares and 95% confidence limits were determined. The data from Study A were non-normally distributed and plasma CHD values from term and preterm infants were compared using the non-parametric Wilcoxon's rank sum test (single sided); the median value being used as a measure of location rather than the mean.

Both these studies were approved by the hospital's ethical committee and the informed consent of both parents was obtained whenever possible.

Results

The results of Study A (Table 1) show no significant difference in the cord blood plasma CHD levels of term and preterm neonates at birth. Whereas plasma CHD levels were constant in the term infants, there was a progressive increase in plasma CHD concentrations in the preterm neonates and their values on days 5 and 9 were significantly higher than those in term infants. However, no correlation between birthweight or gestational age and plasma CHD was apparent in either study.

In Study B, 13 samples of plasma from 10 infants produced measurable peaks of gas liquid chromatography and 5 of these (from 4 infants) exceeded the limit of detection as judged by peak ratios (which could not be allied to specific values due to variations

in blood volumes measured) (Table 2). Three of these infants (of 30 weeks' gestation, or less) had had umbilical catheters and in 2, both plasma samples gave signals. The fourth infant of 33 weeks' gestational age had had phototherapy.

Discussion

These results confirm the earlier observation that percutaneous absorption of CHD may occur in the newborn⁶ and demonstrate that it does so to a greater extent in preterm than in term infants.

Studies in animals indicate that the epidermal barrier matures during the last quarter of gestation;¹⁰ the cutaneous permeability of the human newborn decreases with gestational age.¹¹ The principal cutaneous permeability barrier is the stratum corneum but organic solvents (especially those—such as ethanol—which are miscible in both lipid and water) increase its porosity and greatly reduce its efficiency.¹² The preterm infant would therefore be at an even greater risk of increased cutaneous permeability if its skin were exposed to ethanol.

The increasing plasma CHD levels in the preterm infants of Study A and the absence of this feature in those infants from Study B, who were only exposed to CHD zinc oxide dusting powder for routine cord care, suggests that the repeated use of the ethanol CHD solution was responsible for percutaneous absorption of CHD by the preterm babies in the first study.

The humidity within an incubator and exposure to phototherapy may increase cutaneous vascular perfusion thereby enhancing skin permeability. These factors were more prevalent in the second study and were probably therefore of less significance than ethanol in influencing percutaneous absorption of CHD, but we cannot exclude the possibility that such factors might have contributed to the presence of detectable plasma CHD in one of the infants from Study B. The significant plasma CHD concentrations in the other 3 infants from the second

Table 1 Median plasma chlorhexidine concentrations (ng/ml) in term and preterm infants in Study A

Sample	Time taken	Median CHD concentration (ng/ml)		Significance Wilcoxon's rank sum test
		Term	Preterm	
Cord blood	Day 0	—9	1	Not significant
Venous blood	Day 5	—9	10	P < 0.01
Venous blood	Day 9	—9	32	P < 0.0001

The estimated negative value is included rather than setting this to zero to avoid bias in the statistical comparisons being made.

Conversion: traditional to SI units—CHD 1 ng/ml = 1.98 nmol/l.

Table 2 Plasma chlorhexidine concentrations in Study B infants

Case	Sex	Birthweight (g)	Gestational age (weeks)	Chlorhexidine peak ratio† and concentrations (ng/ml)		Procedures
				Day 5	Day 9	
1	M	1500	33	(0.0049) 23	ND	Nil
2	M	1560	30	(0.0199) *23	(0.0176) *92	Umbilical catheter
3	F	1740	33	ND	(0.0065) 17	Nil
4	F	1900	33	(0.0185) *48	ND	Nil
5	M	2100	34	(0.0095) 16	(0.0104) 15	Nil
6	M	1320	29	(0.0148) *16	ND	Umbilical catheter
7	M	2210	34	(0.0039) 6	ND	Phototherapy
8	M	1830	33	ND	(0.0591) 9	Phototherapy
9	F	1565	29	(0.0055) 9	(0.0053) 7	Umbilical catheter
10	F	1240	28	ND	(0.0121) *45	Umbilical catheter, parenteral nutrition, ventilated

†Limit of detection for peak ratio: 0.0106.

* Ratio above limit of detection.

ND = none detected.

study could have resulted from inadvertent introduction of CHD during umbilical catheterisation. However, the absence of such levels in other infants from Study B, who underwent invasive procedures, suggests that accidental introduction of CHD can be avoided and that the occasional use of an ethanol CHD solution for topical antiseptics in preterm infants need not result in high plasma CHD concentrations such as those encountered with prophylactic use.

There is no evidence that the presence of CHD in plasma is indicative of possible toxicity. In one study, designed to match one which demonstrated HCP neurotoxicity, CHD was detected in the liver, kidneys, and adipose tissue of newborn rhesus monkeys bathed regularly for 90 days in an 8% CHD detergent-based solution, but there was no clinical or histological evidence of toxicity and there was no detectable CHD in their brains.¹³ Four cases of accidental intravenous administration have been reported in human adults¹⁴ but with the exception of extensive haemolysis which occurred in 3 of them there were no toxic effects.

CHD would therefore appear to be of fairly low toxicity and of proved efficacy in reducing umbilical colonisation in the neonate.^{3 15} This study shows that significant percutaneous absorption of CHD is unlikely in term infants but may occur in preterm neonates treated with an ethanol solution of the antiseptic for cord care. This may however, be considerably reduced by avoiding the use of ethanol in the routine cord care of preterm infants.

Miss Lesley Cooper died on 15 April 1977.

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Device for continuous urine collection in the newborn

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SUMMARY A device for the continuous collection of urine from newborn infants is described. This apparatus replaces the nursing tray of the Vickers 59 incubator.

Collection of urine in the newborn infant is notoriously difficult, especially if prolonged collection is required for either diagnostic or research purposes. Various methods previously used depend on modifications of urine or colostomy bags, which tend to