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Transdermal delivery of theophylline to premature infants using a hydrogel disc system

RUTH G. CARTWRIGHT[1], P. H. T. CARTLIDGE[2], N. RUTTER[2], C. D. MELIA[1] & S. S. DAVIS[1]
[1]Department of Pharmaceutical Sciences, University of Nottingham, University Park, Nottingham NG7 2RD and [2]Department of Neonatal Medicine and Surgery, City Hospital, Nottingham

1 Preterm infants show incompletely developed skin with reduced barrier function. The possibility of transdermal delivery of theophylline from hydrogel discs swollen with choline theophyllinate has been investigated.

2 Drug loaded hydrogel discs 2 cm^2 in area were applied to the abdomen and occluded. Serum theophylline concentrations were measured in twenty-one infants of less than 31 weeks gestation.

3 Therapeutic concentrations were achieved in 18 individuals, and maintained for up to 15 days after repeated application of discs. A correlation between maximum serum drug concentration and transepidermal water loss, gestation and birthweight was demonstrated.

Keywords theophylline transdermal delivery premature infants hydrogel discs

Introduction

It is well established that preterm infants have incompletely developed skin, and in the most immature babies, the epidermis is thin and histologically almost devoid of stratum corneum (Evans & Rutter, 1986). These properties reduce the barrier function of the skin, rendering the infants vulnerable to poisoning from the inadvertent percutaneous absorption of noxious substances, for example aniline dyes (Kagan *et al.*, 1949), hexachlorophene (Curley *et al.*, 1971; Powell *et al.*, 1973) and alcohol (Harpin & Rutter, 1982). This has led us to consider the use of transdermal absorption as a route for delivery of drugs to the neonate. The advantages offered by this route over the more usual intravenous or oral delivery, might include the elimination of variations in absorption of orally administered drugs, the avoidance of gastrointestinal intolerance, reduction in first-pass liver metabolism, control of drugs with small therapeutic indices by rapid termination of drug input if needed, and removal of the need to maintain intravenous access (Shaw & Chandrasekaran, 1978).

In 1985, our group successfully exploited the enhanced permeability of preterm skin for the percutaneous delivery of theophylline from hydroxyethylmethylcellulose gels (Evans *et al.*, 1985). We were able to produce therapeutic concentrations of theophylline for up to 3 days, following a single application of drug loaded gel to the skin. However, the applied dose was impossible to measure, and moreover, the gel system was difficult to handle and leaked easily. It was therefore impractical for routine use.

Theophylline was chosen for transdermal delivery because it is widely used to treat apnoea of prematurity, and gastrointestinal intolerance or disease may preclude oral administration. Furthermore, the drug is often required for several weeks, during which time repeated intravenous cannulation may be necessary. Consequently, the transdermal route appears to be particularly suitable for theophylline administration, since it is both non-enteral and non-invasive.

In developing the transdermal delivery of theophylline further, we have investigated the use of a swollen hydrogel disc loaded with drug. Such hydrogel polymers are characteristically capable of swelling and imbibing large amounts of water without dissolving (Roorda *et al.*, 1986). Our aim was to achieve a sustained therapeutic

response using a method that could be developed into an elegant, reproducible and clinically acceptable system. Two theophylline salts were considered for the investigations. Preliminary work (Cartwright, 1989) suggested that the more soluble salt of theophylline, choline theophyllinate (CT), produced higher blood concentrations of the drug than theophylline sodium glycinate (TNaG). The studies were therefore conducted using choline theophyllinate.

Methods

Preparation of discs

The hydrogel disc used was 90/10 HEMAC, a polymer consisting of 90% w/w poly-2-hydroxyethylmethacrylate crosslinked with 10% w/w polytetramethylene oxide (Ciba-Geigy, Ardsley, New York). Sheets of the polymer were swollen in h.p.l.c. grade ethanol, punched into discs of 2 cm^2 area and 0.05 cm thickness, and vacuum dried. The discs were then loaded with drug by swelling them individually in a saturated solution of choline theophyllinate (Boehringer Ingelheim, Germany) at 37° C for a minimum of 48 h. Equilibrium swelling typically occurred at 24 h. The swelling solution used was either sterile water, or a mixture of water and USP grade propylene glycol (PG) in proportions of 10 to 80%. The cosolvent was added since *in vitro* studies had shown that it produced an increased swelling of the disc and thus increased loading of the disc with drug (Cartwright, 1989). However, *in vivo* the propylene glycol had no effect on drug delivery and so all the results will be considered together.

Clinical evaluation

Before application, the weight of theophylline base in each swollen disc was calculated using the equation

$$\text{Loading} = DS \times S$$

where DS = Degree of swelling at 70 h expressed as a fraction of 100% and S = Solubility (g ml^{-1}). On a molecular weight basis, choline theophyllinate contains 63.9% theophylline base.

After use, each spent disc was washed in distilled water until all traces of theophylline had been removed. The concentration of the resultant solution was calculated by ultraviolet absorbance at 272 nm, from which the weight of theophylline remaining in the disc after use could be calculated. From the knowledge of theophylline loading prior to clinical use, the amount of theophylline which diffused out of the disc *in vivo* was determined by subtraction.

The theophylline content ranged from 18.5 to 61.6 mg per disc. The range of theophylline content is attributable to the effect of PG content on degree of swelling and also to some extent on the variability of the dry weight of each individual disc.

Immediately before application, the swollen hydrogel disc was rinsed briefly with distilled water to remove surface drug solution. The disc was then placed onto dry, untraumatised abdominal skin and occluded with a transparent dressing consisting of a double-sided adhesive ring covered with a polythene layer and overlaid with a sheet of the film dressing, Tegaderm (3M Healthcare, Loughborough, England) (Figure 1). Blood samples for theophylline assay were taken before application, every 6 h during the first 24 h, and thereafter each day. The initial sample was taken in order to detect any theophylline already present in the neonatal serum due to maternal ingestion of xanthine-containing beverages (Van't Hoff, 1986). Blood samples of about 0.5 ml were taken from indwelling cannulae by venepuncture or by heelprick, at the same time as blood was being taken for routine clinical purposes. Measurements were made on a few microlitres of serum. The disc was left in place for up to 7 days, and removed when serum drug concentrations indicated that the disc was depleted of drug.

In each infant the barrier function of abdominal skin was assessed before the disc was applied. This was performed by measuring transepidermal water loss (TEWL) using a skin evaporimeter (Evaporimeter Epl, Servomed, Sweden), as previously described (Nilson, 1977; Rutter & Hull, 1979).

Patients

Twenty-one infants were studied (Table 1). Their gestation ranged from 24 to 30 weeks and birthweight from 0.81 to 1.68 kg. In 16 infants of between 6 h and 6 days old, a single hydrogel disc was applied. In the other five infants three or four hydrogel discs were applied consecutively. The first disc was sited when the infants were between 26 and 76 h of age. Subsequent discs were applied when the serum theophylline concentration from the preceding disc was decreasing. The infants lay supine if being ventilated; if unventilated their position varied from supine to prone to lateral. Indications for the use of theophylline were to assist weaning from mechanical ventilation or for the treatment of apnoea of prematurity. The therapeutic range for theo-

Table 1 Summary of data for single and multiple application of theophylline discs

Infant number	*Sex*	*Gestation (weeks)*	*Postnatal age (days)*	*Birthweight (kg)*	*TEWL ($g\,m^{-2}\,h^{-1}$)*	*Co-solvent (%PG)*	*Maximum serum drug concentration ($mg\,l^{-1}$)*	*Weight of base in disc (mg)*	*Weight of base released (mg)*	*Time of maximum serum drug concentration (days)*
1	M	30	0.67	1.51	9	0	4.0	18.5	11.8	2.6
2	F	30	3.00	1.43	12	0	4.1	19.2	11.8	2.6
3	M	28	0.75	1.23	32	10	7.3	25.0	21.8	1.4
4a	M	26	1.67	1.02	26	10	4.3	24.3	21.2	1.7
5a	F	26	3.67	1.09	27	20	10.0	28.2	25.7	1.1
6	M	30	3.00	1.00	14	20	5.1	30.1	24.3	1.7
7	F	29	0.67	1.23	28	40	9.6	44.8	41.5	1.1
8	M	30	0.25	1.45	7	40	1.7	45.7	38.2	3.9
9	F	28	0.92	1.23	23	60	8.6	61.6	59.2	0.6
10	M	29	4.00	1.68	20	60	3.9	58.3	55.0	1.6
11	M	29	5.00	1.15	20	80	10.8	51.3	49.3	2.6
12	M	25	6.00	0.83	30	0	12.3	19.6	15.8	1.8
13	F	26	6.00	0.98	16	0	9.0	19.3	15.6	1.3
14	M	28	3.00	1.15	20	0	5.2	19.4	15.4	2.7
15	M	30	4.00	1.48	24	0	5.9	20.2	16.6	2.1
16	F	24	0.67	0.81	100	40	41.7	48.3	47.8	
17*	F	27	1.46	1.12	43	0	11.9	23.0	21.7	2.8
							16.0	24.2	23.2	7.8
							11.0	24.6	20.3	12.8
							4.3	23.9	18.3	19.8
18*	M	29	1.08	1.50	17	0	6.3	23.5	19.9	1.7
							4.7	21.1	17.8	5.8
							5.0	22.7	19.3	10.8
19*	F	26	2.00	1.06	40	0	11.7	19.8	17.8	1.1
							10.2	20.7	18.0	5.7
							6.8	21.1	16.6	12.7
20*	F	28	2.00	1.20	17	0	8.6	20.4	17.4	1.7
							5.9	22.4	16.1	5.7
							3.3	24.3	16.9	10.8
21*	F	28	3.17	1.27	14	0	6.5	20.2	16.3	1.6
							8.1	23.6	18.9	3.7
							1.3	23.9	14.2	8.61

Key: * Multiple dosing protocol a = twins.

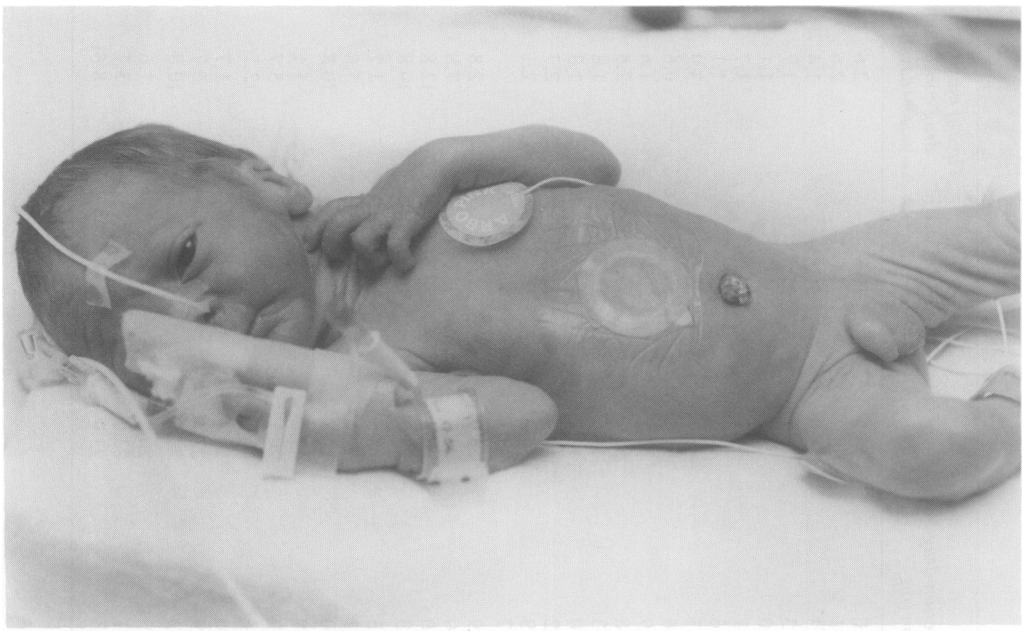

Figure 1 Hydrogel disc occluded with a transparent dressing on the abdomen of an infant of 29 weeks gestation.

phylline for the treatment of apnoea of prematurity in neonates is quoted to be from 2 to 15 mg l^{-1} (Aranda *et al.*, 1981; Jones & Baillie, 1979). (This range is different from that used for the treatment of adult asthma.) In our practice, a somewhat narrower range of 4 to 12 mg l^{-1} is employed. No infant had received theophylline prior to the study. All infants were studied with the written consent of their mothers and the protocol was approved by the hospital ethics committee.

Theophylline assay

In this work theophylline analyses were performed by substrate labelled fluorescent immunoassay (SLFIA), using a commercial kit (TDA Theophylline: Ames Company, Indiana, USA). The principle of this assay is that theophylline in a sample competes with a drug-labelled fluorogenic substrate for binding sites on the antibody. This method has been described in detail by Li *et al.* (1981). These workers note that the correlation between SLFIA and other methods is excellent.

Results

In the 16 infants treated with a single theophylline disc, all but three had serum drug concentrations within the therapeutic range of 4 to 12 mg l^{-1} (Figure 2). The time taken to reach this range was 6 to 60 h (median = 22 h) and therapeutic concentrations were maintained for between 2 and 117 h (median = 64 h). The maximum serum concentration (C_{max}) ranged from 4 to 41.7 mg l^{-1}, and the time taken to reach C_{max} (t_{max}) ranged from 15 to 65 h (median = 41 h).

Two of the 16 infants produced theophylline concentrations below the therapeutic minimum of 4 mg l^{-1}. The lowest C_{max} of 1.7 mg l^{-1} was in an infant with a low TEWL of 7 g m^{-2} h^{-1}, indicating a well matured skin. The other infant was the heaviest studied and the C_{max} of 3.9 mg l^{-1} was just outside the therapeutic range. Very rapid drug absorption was seen in one infant with a theophylline concentration of 41.7 mg l^{-1} after only 8 h. She was born at 24 weeks gestation and had a high TEWL of 100 g m^{-2} h^{-1}, indicating very limited skin barrier function. The only toxic manifestation was a mild tachycardia. The disc was immediately removed so the true C_{max} is unknown.

All five infants treated with repeated application of theophylline loaded discs achieved serum concentrations within the therapeutic range. These concentrations were first attained between 8 to 25 h after the initial application, and were maintained within the therapeutic range for 6 to 15 days (Figure 3). The amount of theophylline absorbed was usually greatest after

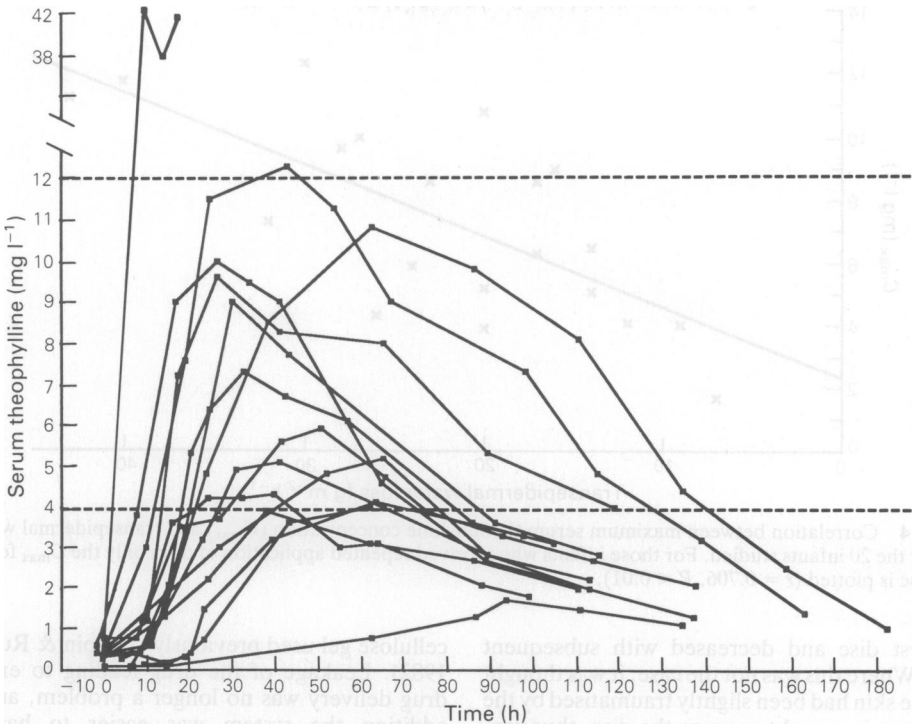

Figure 2 Serum theophylline concentrations in 16 infants, after application of choline theophyllinate swollen hydrogel disc to the skin. Therapeutic range (4–12 mg l^{-1}) is indicated.

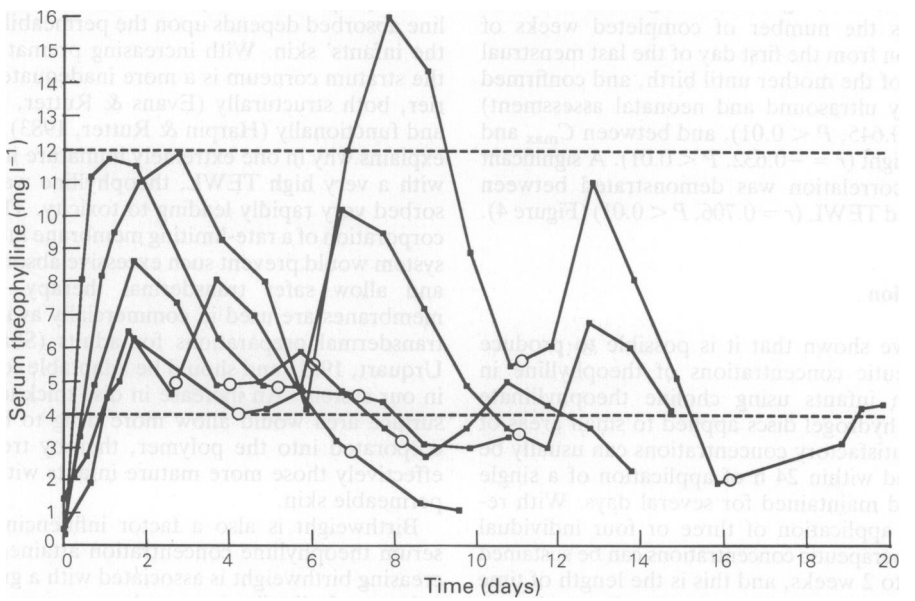

Figure 3 Serum theophylline concentrations in five infants, after repeated application of choline theophyllinate swollen hydrogel discs to the skin. O represents time of removal of preceding disc and application of subsequent disc.

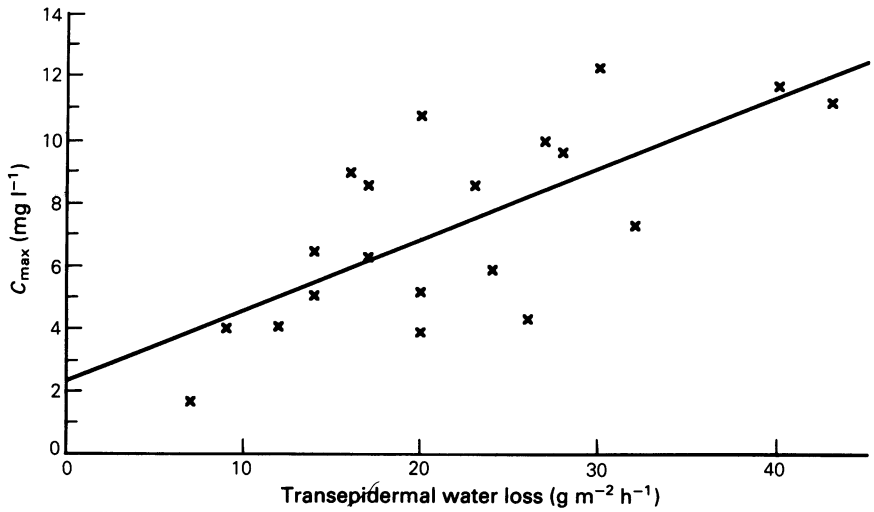

Figure 4 Correlation between maximum serum theophylline concentration (C_{max}) and transepidermal water loss for the 20 infants studied. For those infants who received repeated application of discs only the C_{max} for the first disc is plotted ($r = 0.706$, $P < 0.01$).

the first disc and decreased with subsequent discs. Where this was not the case, it was thought that the skin had been slightly traumatised by the adhesive ring used to secure the disc, thus rendering the skin more permeable. No skin damage was caused by the drug loaded hydrogel discs.

A significant inverse linear correlation was demonstrated between C_{max} and gestation (gestation is the gestational age in weeks, defined as the number of completed weeks of gestation from the first day of the last menstrual period of the mother until birth, and confirmed by early ultrasound and neonatal assessment) ($r = -0.645$, $P < 0.01$), and between C_{max} and birthweight ($r = -0.632$, $P < 0.01$). A significant linear correlation was demonstrated between C_{max} and TEWL ($r = 0.706$, $P < 0.01$) (Figure 4).

Discussion

We have shown that it is possible to produce therapeutic concentrations of theophylline in preterm infants using choline theophyllinate loaded hydrogel discs applied to small areas of skin. Satisfactory concentrations can usually be achieved within 24 h of application of a single disc and maintained for several days. With repeated application of three or four individual discs, therapeutic concentrations can be sustained for up to 2 weeks, and this is the length of time for which theophylline therapy is usually required. The hydrogel disc was a more effective drug reservoir than the hydroxyethylmethylcellulose gel used previously (Harpin & Rutter, 1982). Leakage of the drug leading to erratic drug delivery was no longer a problem, and in addition the system was easier to handle. Furthermore, use of the hydrogel polymer has allowed us to measure the amount of drug applied and delivered, which will be essential if the system is to be practical for clinical use.

The proportion of topically applied theophylline absorbed depends upon the permeability of the infants' skin. With increasing prematurity, the stratum corneum is a more inadequate barrier, both structurally (Evans & Rutter, 1986) and functionally (Harpin & Rutter, 1983). This explains why in one extremely immature infant, with a very high TEWL, theophylline was absorbed very rapidly leading to toxicity. The incorporation of a rate-limiting membrane into the system would prevent such excessive absorption and allow safer transdermal therapy. Such membranes are used in commercially available transdermal preparations for adults (Shaw & Urquart, 1981) and should be adaptable for use in our system. An increase in disc thickness or surface area would allow more drug to be incorporated into the polymer, thereby treating effectively those more mature infants with less permeable skin.

Birthweight is also a factor influencing the serum theophylline concentration attained. Increasing birthweight is associated with a greater volume of distribution, and consequently in larger infants serum theophylline concentrations were lower. An additional factor is the matu-

ration of the various body systems responsible for drug elimination (particularly liver function). Older infants would have a greater systemic clearance and consequently a lower theophylline concentration.

The effect of gestation on serum theophylline concentration showed generally higher levels in infants of earlier gestation. This might be expected since these infants would tend to have more immature skin, lower birth weights and lower clearance than those born at later gestations.

Transdermal administration does not allow rapid drug loading to the infant. This is usually of little consequence, since the need for theophylline therapy is seldom urgent and can often be anticipated. If, however, the occurrence of frequent or severe apnoeas demanded rapid drug loading, this could be achieved intravenously and the levels maintained transdermally.

There were no particular toxic effects observed, although a mild sinus tachycardia was sometimes seen. Preterm infants tolerate theophylline very well, and many studies have shown that the incidence of side effects is low even when higher blood levels are obtained. This is discussed in the review by Aranda *et al.* (1981).

The transdermal administration of theophylline avoids the various problems associated with conventional approaches to the medication of preterm infants. It presents a simple and clinically effective means of maintaining serum drug concentrations over prolonged periods and is potentially useful for other drugs. The beneficial effects were not correlated with blood levels since our aim was to achieve blood levels of theophylline in the accepted therapeutic range which has been shown to produce clinical benefit (Jones & Baillie, 1979). Babies in our study appeared to respond to theophylline in the same way as if the drug had been given orally or intravenously.

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References

Aranda, J. V., Grondin, D. & Sasynuik, B. I. (1981). Pharmacologic therapy of neonatal apnoea. *Pediatric Clinics of North America*, **28**, 113–133.

Cartwright, R. G. (1989). *Some aspects of percutaneous absorption in the neonate*, Ph.D. Thesis, University of Nottingham.

Curley, A., Hawk, R. E., Kimbrough, R. D., Nathenson, G. & Finberg, L. (1971). Dermal absorption of hexachlorophene in infants. *Lancet*, **ii**, 296–297.

Evans, N. J. & Rutter, N. (1986). Development of the epidermis in the newborn. *Biol. Neonate*, **49**, 74–80.

Evans, N. J., Rutter, N., Hadgraft, J. & Parr, G. (1985). Percutaneous administration of theophylline in the pre-term infant. *J. Pediatr.*, **107**, 307–311.

Harpin, V. & Rutter, N. (1982). Percutaneous alcohol absorption and skin necrosis in a preterm infant. *Arch. Dis. Child.*, **57**, 477–479.

Harpin, V. A. & Rutter, N. (1983). Barrier properties of the newborn infant's skin. *J. Pediatr.*, **102**, 419–425.

Jones, R. A. K. & Baillie, E. (1979). Dosage schedule for intravenous aminophylline in apnoea of prematurity based on pharmacokinetic studies. *Arch. Dis. Child.*, **54**, 190–193.

Kagan, B. M., Mirman, B., Calvin, J. & Lundeen, E. (1949). Cyanosis in premature infants due to aniline dye intoxication. *J. Pediatr.*, **34**, 574–578.

Li, T. M., Benovic, J. L., Buckler, R. T. & Burd, J. F. (1981). Homogeneous substrate-labelled fluorescent immunoassay for theophylline in serum. *Clin. Chem.*, **27**, 22–26.

Nilson, G. E. (1977). Measurement of water exchange through skin. *Med. Biol. Eng. Comput.*, **15**, 209–218.

Powell, H., Swarner, O., Glock, L. & Lampert, P. (1973). Hexachlorophene myelinopathy in premature infants. *J. Pediatr.*, **82**, 976–981.

Roorda, W. E., Bodde, H. E., de Borer, A. G. & Junginger, H. E. (1986). Synthetic hydrogels as drug delivery systems. *Pharm-Weekbl.* (Sci. Ed.), **8**, 165–189.

Rutter, N. & Hull, D. Water loss from the skin of term and preterm babies. *Arch. Dis. Child.*, **54**, 858–868.

Shaw, J. E. & Chandrasekaran, S. K. (1978). Controlled topical delivery of drugs for systemic action. *Drug Metab. Rev.*, **8**, 223–233.

Shaw, J. E. & Urquart, J. (1981). Transdermal drug administration – a nuisance becomes an opportunity. *Br. med. J.*, **283**, 875–876.

Van't Hoff, W. G. (1986). The maternal ingestion and transplacental passage of caffeine. *Early Hum. Dev.*, **13**, 346–347.

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