ANTIBIOTIC THERAPY IN THE NEWBORN

JOHN DE LOUVOIS

In the normal course of events it is unusual for the newborn to require treatment with antibiotics. However, among babies admitted to Special Care Baby Units, as many as 60% will receive chemotherapy for suspected or proven infection. Because the presentation of infection in the newborn is obscure, subtle and nonspecific, it is difficult to distinguish infected neonates from those who are sick but not infected. The rapid course of infection in the newborn dictates that chemotherapy must be initiated as soon as infection is suspected. Because of these factors, pretreatment bacteriological cultures on many neonates who receive chemotherapy are negative. It is essential, therefore, that the antibiotics used in this situation should be totally safe.

It is convenient to distinguish between initial chemotherapy prescribed before infection is confirmed and that given to babies with established infection due to a known organism. Initial chemotherapy must provide adequate cover against the majority, if not all, common neonatal pathogens while that for an established infection can be tailored to the sensitivity of the infecting microbe. Antibiotics may be used prophylactically in the newborn, for example in babies with multiple chest drains, long line catheters or in those undergoing repeated exchange transfusions. It is inappropriate, however, to consider as prophylaxis treatment given to babies with clinically suspected sepsis. Positive bacteriological cultures will be obtained from many such babies while others will respond to chemotherapy in a way which strongly suggests that there had been an infection even though cultures were negative.

Prior to the commencement of chemotherapy, it is essential that bacteriological investigations are performed. These should consist of one or more blood cultures, swabs from the ear, umbilicus and axilla and a clean catch specimen of urine. A suprapubic aspirate should be collected if infection of the urinary tract is suspected. swabs should also be taken from any sites of obvious infection. Examination of a gastric aspirate even from newborn babies is unrewarding. In Britain where the incidence of neonatal meningitis is relatively low, it is the practice to perform a lumbar puncture only on neonates thought to be at special risk of meningitis. In neonates at special risk of intrauterine infection, a TORCH screen should be carried out at the same time as the septic screen.

In almost every respect the neonate handles antibiotics differently from older patients. In order to manage chemotherapy of the newborn satisfactorily, the clinician must have access to data on the absorption, metabolism, penetration and excretion of each antibiotic in neonates. It is not possible to extrapolate from data on older children or adults and data on term neonates is only of limited value in the management of their preterm low birthweight counterparts. Even when appropriate data are available, this will not give the full picture since, for ethical reasons, no data can be collected on healthy subjects. It is necessary also to remember not

only that the dose per kilogram body weight is different for neonates and adults but, in addition, there may be differences in the type and degree of toxic side-effects and the extent to which an antibiotic is protein bound. The interpatient variation is much wider in neonates than in older patients and because of the speed with which the physiological systems develop after birth, there is wide intrapatient variation over very short periods of time.

ROUTE OF ADMINISTRATION

Most antibiotics may be administered equally effectively to neonates by either the intravenous or intramuscular routes (Mulhall, 1984). The exception is chloramphenicol which shows poor absorption following intramuscular administration. In neonates, oral administration of chloramphenicol also results in poor absorption (Mulhall *et al.,* 1983a) in contrast to the situation in older children where the oral route is used as soon as the patient is able to swallow. There is little information on the oral absorption of other antibiotics in neonates and until such information is available, this route cannot be recommended. There is also the risk of regurgitation and aspiration if antibiotics are administered orally to small babies.

DURATION OF TREATMENT

Treatment of neonates receiving antibiotics for clinical signs of sepsis should be reassessed after 48 hours when the results of pretreatment bacteriological cultures are known. At this time, the clinical condition of many of those treated will have improved dramatically and if bacteriological cultures are negative, antibiotic therapy may be stopped. Neonates who continue to show clinical signs of infection, should be treated for at least five days whether pathogenic bacteria have been isolated or not. If chemotherapy is to continue for longer than five days, the bacteriological tests should be repeated to determine whether supra-infection or colonisation with resistant bacteria has occurred, in which case a change of therapy may be required. Neonates with meningitis must be treated parenterally for 14-21 days because of the risk of ventriculitis and recurrent infection.

CURRENT THERAPY

For a number of years gentamicin with ampicillin or penicillin has been the chemotherapy of first choice for neonatal infections, in spite of the possible risk of ototoxicity following gentamicin and its poor penetration into the cerebrospinal fluid. Ampicillin resistance is now widespread among coliforms thus further reducing the value of the current combination when the antibiotic susceptibility of the infecting organism is unknown. The potential toxicity of gentamicin is of special concern in neonates where the wide inter and intra-patient variation in response to a standard dose of 2.5 mg/kg results in 50% patients having trough serum concentrations in excess of 2 mg/l (Mulhall *et al.*, 1983b). The low mean peak concen-

TABLE 1. — *Minimal inhibitory concentration (mg/l) of some new antibiotics for neonatal pathogens.*

Pathogen	Cefuroxime	Cefotaxime	Latamoxef	Ceftazidime	Piperacillin	Ampicillin	Gentamicin
E. coli *	7.5	0.14	0.35	0.42	1.0	4.8	0.5
Klebsiella sp. *	6.9	0.18	0.1	0.38	4.0	R	0.8
Enterobacter sp.	4-30	0.1	0.1	0.5	3.0	R	0.8
Serratia sp.	8-R	0.36	0.4	0.32	3.0	8-R	0.8
Salmonella sp. *	8-6	0.12	0.28	0.38	2-4	1-4	1.0
Proteus sp.	13	0.13	0.18	0.15	0.5	R	1.0
Str. agalactiae	0.03	0.03	4	0.3		0.05	R
Staph. aureus *	0.6	1-2	8-R	6	R	R	0.06
Staph. epidermidis	0.2	1	16	8	1	0.1	8
Enterococci	R	R	R	R	2	1-2	R
L. monocytogenes	R	R	R	R	2	0.5	0.12
Ps. aeruginosa	R	16-32	16	1.3	5	R	1.5

* β-lactamase producers

tration does not allow the dose to be reduced. The risk of drug accumulation can be reduced by maintaining the same daily dose but extending the dosage interval to 18 hours. The problems with gentamicin make it desirable that an alternative non-toxic antibiotic be found for initial therapy in neonates suspected of having infection. Gentamicin plus a penicillin is likely to remain the regimen of choice for established infection due to susceptible organisms at least in the short term.

In the United Kingdom, chloramphenicol is the antibiotic most widely used for the treatment of neonatal meningitis either alone or in combination with a penicillin and/or gentamicin (Mulhall *et al.*, 1983c). There is a significant risk of toxic side-effects in neonates receiving chloramphenicol if the drug is incorrectly prescribed or inadequately monitored (Mulhall *et al.*, 1983d). In this situation also there is the need for non-toxic highly active compound which will penetrate into the cerebrospinal fluid in therapeutic concentrations.

NEW ANTIBIOTICS

A number of new antibiotics have recently been introduced which have a high level of activity against the majority of neonatal pathogens and are non-toxic (de Louvois, 1983). Preliminary results suggest that there may soon be safer alternatives to gentamicin and chloramphenicol for the treatment of infection in the newborn. The antimicrobial activity of five of these new compounds is compared to that of gentamicin and ampicillin for common neonatal pathogens in table 1. Relatively few enteric Gram-negative rods are reliably sensitive to ampicillin. However, cefotaxime, latamoxef and ceftazidime are highly active against these organisms. They have adequate activity also against the majority of Gram-positive pathogens

TABLE 2. — *Pharmacokinetic data on new antibiotics in neonates.*

	Dose (mg/kg)	Route	Peak serum level (mg/l)	Trough serum level (mg/l)	Serum half-life (h)	Volume of distribution (ml/kg)	Total clearance (ml/min/kg)
Cefuroxime *	25	i.m./i.v.	45	10.5	5.8	671	—
Cefotaxime *	50	i.m./i.v.	87	8	3.1	559	1.7
Ceftriaxone *	50	i.m./i.v.	143	41	11.8	339	0.4
Latamoxef *	50	i.m./i.v.	100	28	6.8	503	0.9
Azlocillin	50	i.m.	100-200	—	2.5	330	—
Mezlocillin	50	i.m.	80-150	—	2.1	520	—
Piperacillin	50	i.m.	115	—	3.5	400-580	—
Netilmicin	2	i.m.	5.7	2.2	—	—	—
Gentamicin **	2.5	i.m./i.v.	7.5	2.3	7.9	637	1.0

* Data from de Louvois *et al.*
** Data from Mulhall

with the exception of the enterococci, *Listeria monocytogenes* and some strains of *Staphylococcus epidermidis.*

Pharmacokinetic data on these new antibiotics in neonates is presented in table 2 and compared to that of gentamicin. Unlike earlier β-lactam antibiotics the dosage interval for these new agents can be extended to 12 hours in neonates. The concentration of antibiotic in neonatal serum 12 hours after the recommended parenteral dose exceeds that necessarry to inhibit the majority of neonatal pathogens by a factor of 5-200.

In general, the half-life of the newer β-lactam compounds in the first week of life is 3-4 times that in adults while the rate of clearance is a third of the adult value. The major factor affecting the pharmacokinetics of antibiotics during the neonatal period is postnatal age, with prematurity, birthweight and other factors having little influence. The half-life drops with increasing postnatal age. By the end of the neonatal period, higher doses, possibly at more frequent intervals, may be required to maintain adequate serum concentrations.

Studies in comparable groups of premature neonates with clinical signs of sepsis have shown new β-lactan agents to be efficacious and safe (de Louvois *et al.*, 1982a; de Louvois *et al.*, 1982b; de Louvois *et al.*, 1983). These studies failed to detect any antibiotic associated adverse effect on bilirubin/albumin binding or clotting mechanisms. When monotherapy is used colonisation by enterococci and other inherently resistant microbes is reported in 5-10% of patients. It remains to be seen whether such colonisation has any clinical significance.

In comparative studies in children and adults cefuroxime (Swedish Study Group, 1982), cefotaxime (Belohradsky *et al.*, 1980), latamoxef (Rahal, 1982) and ceftriaxone (Del Rio *et al.*, 1983) used as monotherapy have been shown to be as effective as conventional treatment for meningitis. There are no comprehensive

studies on the use of these compounds to treat neonatal meningitis. Relatively few neonates with established infection have been treated with these compounds but where they have been used the results have been good.

Netilmicin has received wide publicity as an alternative to gentamicin in the treatment of neonatal infection. Early claims that is was active against strains resistant to gentamicin have not been confirmed and the demonstration that netilmicin is inactivated by the majority of enzymes that inactivate gentamicin would indicate a high level of cross resistance (Shannon and Phillips, 1982). Also, contrary to earlier reports, the activity of the two compounds is very similar. There remains the question of toxicity. While evidence in older patients suggests that netilmicin may be less toxic than gentamicin (Lane, 1984), there are as yet no data on the comparative toxicity of these agents in neonates.

The ureido penicillins offer little advantage over ampicillin in the treatment of unconfirmed neonatal sepsis being as susceptible as ampicillin to β-lactamase degradation. They do have antipseudomonal activity however and have been used successfully to treat established infections with known susceptible organisms. On a few occasions they have been combined to good effect with gentamicin to treat life-threatening infections.

In conclusion, the innate prematurity of many of the physiological systems in the neonate and the possibility that these systems may be less efficient at eliminating antibiotics and more susceptible to their toxic side-effects, dictate that potentially toxic antibiotics should not be used if there is a suitable non-toxic alternative. This is especially so in that group of neonates who require chemotherapy but from whom an infecting organism has not been isolated. A number of compounds have been found to be effective as monotherapy in this situation. The choice will vary from centre to centre and should reflect the local infection situation and the susceptibly pattern of any persistent strains within the Special Care Baby Unit. These new compounds offer great promise for the treatment of neonatal infection and it is likely that they will gradually replace treatment regimens containing gentamicin or chloramphenicol as antibiotics of first choice.

REFERENCES

Belohradsky B. H., Bruch K., Geiss D., Kafetzis D., Marget W., Peters G.: *Lancet, 1,* 61, 1980. – Del Rio M. A., Chrane D., Shelton S., McCracken G. H., jr., Nelson J. D.: *Lancet, 1,* 1241, 1983. – Lane A. Z.: *Journal of Chemotherapy, 13* (suppl. A), 67, 1984. – de Louvois J.: *Hospital Update, 9,* 1291, 1983. – de Louvois J., Mulhall A., Hurley R.: *Archives of Disease in Childhood, 57,* 59, 1982. – de Louvois J., Mulhall A., Hurley R.: *Pediatric Pharmacology, 2,* 275, 1982. – de Louvois J., Mulhall A., James J.: Proceedings of the 13th International Congress of Chemotherapy, part 81: 41-44, Vienna, 1983. Mulhall A.: *Developmental Pharmacology and Therapeutics, 8,* 1-8, 1985. – Mulhall A., de Louvois J., Hurley R.: *Journal of Antimicrobial Chemotherapy, 12,* 629, 1983a. – Mulhall A., de Louvois J., Hurley R.: *Archives of Disease in Childhood, 58,* 897, 1983b. – Mulhall A., de Louvois J., Hurley R.: *Lancet, 1,* 284, 1983c. – Mulhall A., de Louvois J., Hurley R.: *British Medical Journal, 2,* 1424, 1983d. – Rahal J. J.: *Rexiew of Infectious Diseases, 4,* 606, 1982. – Shannon K., Phillips I.: *Journal of Antimicrobial Chemotherapy, 9,* 91, 1982. – Swedish Study Group: *Lancet, 1,* 295, 1982.