

# Continuous intravenous infusion of ampicillin and gentamicin during parenteral nutrition in 88 newborn infants

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**SUMMARY** Ampicillin and gentamicin were dissolved once a day in an L-amino acid solution especially prepared for parenteral nutrition of newborn infants and infused continuously to 88 infants in whom septicaemia was suspected or had been proved. The mean dosages were 162 and 5.3 mg/kg per 24 hours respectively, and the 95% limits for the serum concentrations were 11-133 and 1.3-7.4 µg/ml. The treatment results were at least as good as with intermittent intramuscular or intravenous administration. This new mode of giving antibiotics is less painful to the babies and easier for the nurses.

In many cases intramuscular (IM) injections of antibiotics are a safe mode of administration. However, in small, sick newborn infants with reduced muscle mass, induration of the muscles after previous injections, or poor blood circulation intravenous (IV) administration is preferable. During parenteral nutrition (PN) of newborn infants a closed infusion system is used to avoid contamination of the solutions. Intermittent IV administration of antibiotics via the PN infusion system may be hazardous to such infants since the closed system will be broken 4 to 6 times a day. We therefore decided to combine continuous infusion of antibiotics with parenteral nutrition. It is well documented that penicillins dissolved in a variety of parenteral solutions are rendered inactive. We therefore tested the stability of ampicillin in combination with gentamicin dissolved in three common parenteral solutions: Invertose Darrow, vamin with fructose (Vitrum, Stockholm), and vamin especially prepared for newborns.<sup>1</sup> We found that inactivation of this combination of antibiotics was least in the third solution so this was chosen for clinical use. By continuous IV infusion of antibiotics it is possible to maintain a steady state serum concentration higher than the minimal inhibitory concentration for most bacterial strains. Aminoglycosides administered in this way have been shown to give a high cure rate in adults, and nephrotoxic and ototoxic side effects are no more frequent than after intermittent injections.<sup>2-4</sup>

The aim of the present study was to evaluate the practical, pharmacokinetic, therapeutic, and toxicological aspects of this treatment, which has not been used in newborn infants before.

## Patients and methods

**Patients.** Between January 1978 and January 1980, 2354 newborn infants were admitted to the Neonatal Department, Rigshospitalet, Copenhagen. Eighty-eight infants receiving PN (39 girls and 49 boys) to whom antibiotics were prescribed were allocated to a prospective study in which PN plus ampicillin and gentamicin were given by continuous IV infusion as described earlier.<sup>5</sup> We told the parents that in case of suspected or proved infection antibiotics would be given to their infants. Gestational ages ranged from 27 to 42 (median 34) weeks. Birthweights ranged from 805 to 4850 (median 1975) g. Fifty-one of the 88 patients had mainly surgical problems, 22 had respiratory distress syndrome as their principal problem, and 13 had very low birthweight only. One patient had Fallot's tetralogy and one had myotonic dystrophy. Nine died, 3 of whom had signs of bacterial infection.

**Administration of PN.** PN with 10% invertose, 20% Intralipid (Vitrum, Stockholm), and an L-amino acid solution based upon vamin (Vitrum, Stockholm) especially prepared for newborns (vamin for newborns)<sup>1</sup> was started between the 1st and 48th

day of life. In 72 patients PN was started within the first week of life. The indications for PN described by Heird and Winters<sup>6</sup> were used. PN was administered via a peripheral vein as described earlier.<sup>5,7</sup> The duration of PN ranged from 2 to 78 (median 10) days. The mean weight gain during PN was 9 g/kg a day.

**Administration of antibiotics.** Antibiotic treatment was initially given intermittently (IM or IV) for 0–16 (median 2) days. When PN was begun the intermittent administration of antibiotics was changed to continuous IV antibiotic treatment which was started between the 1st and 53rd (median 5) day of life. The duration of this treatment ranged from 2 to 20 (median 5) days. The infused amounts of ampicillin and gentamicin chosen for the first 24 hours were the same as the dosages normally given by IM injection—that is 200 mg/kg per 24 hours of ampicillin and 5 mg/kg per 24 hours of gentamicin. Assuming that clearance did not change from one day to the next and aiming at a serum concentration of 4 µg/ml for gentamicin the daily amount of gentamicin (mg) to be added to the bottle could be calculated by using the equation:  $y=4 \times A \times D / C \times B$ . A is ml vamin for newborn infants given during the period 48 hours to 24 hours before, and D is mg gentamicin added to that bottle.

C is the serum concentration of antibiotic measured 24 hours before (µg/ml), and B is ml vamin for newborn infants to be given during the next 24 hours. The ampicillin dosage was calculated using the same equation inserting 40 as the steady state concentration instead of 4. The ampicillin dosage was not changed when the serum concentration was found to be between 40 and 60 µg/ml. For the first 34 infants, the serum concentration of gentamicin was measured the same day and inserted in the equation together with ml vamin given during the previous 24 hours. For the last 58 infants, the same daily dosages of the antibiotics were generally planned for the first 3 days. Nineteen of the infants with intestinal perforation or necrotising enterocolitis also received clindamycin 15 mg/kg per 24 hours diluted in 5.5% glucose given IV over 30 minutes 3 times daily.

**Specimens.** Blood samples for antibiotic assay were obtained by heel puncture at 0900 hours, and in the first 26 newborn infants also at 2100 hours. Blood urea nitrogen, serum electrolytes, leucocyte and platelet counts were performed together with blood, spinal fluid, tracheal, stool, peritoneal, and urine cultures for anaerobic or aerobic bacteria and fungi.

**Assay methods.** Serum concentrations of antibiotics were measured microbiologically using a paper disc

Table 1 Mean administered dosages of vamin for newborn infants, ampicillin and gentamicin, and serum concentrations of antibiotics in relation to gestational age, weight, and postnatal age during a total of 776 treatment days

	No of treatment		Initial treatment weight (g)	Postnatal age (days)	Vamin (ml/kg per 24 h)	Dosage (mg/kg per 24 h)		Ampicillin		Gentamicin	
	Days	Courses				Ampicillin	Gentamicin	No of measurements	Serum concentration (µg/ml)	No of measurements	Serum concentration (µg/ml)
<b>Gestational age (weeks)</b>											
≤ 32	274	42	1217	20	88	161	5.6	205	45	219	3.2
33–36	153	23	1677	8	93	159	5.2	124	43	133	3.4
≥ 37	332	43	2730	15	91	164	5.0	265	33*	287	2.9†
<b>Initial treatment weight (g)</b>											
≤ 1000	88	13		16	87	147	5.5	72	47	73	3.3
1001–1500	220	32		17	87	164	5.5	171	41	182	3.1
1501–2000	150	23		12	97	163	5.0	111	45	124	3.4
2001–2500	104	15		11	86	150	5.2	80	35	89	3.1
2501–3000	116	13		16	98	182	5.6	92	33	99	3.0
≥ 3001	98	14		19	90	162	4.6	82	30*	86	2.6*
<b>Postnatal age (days)</b>											
≤ 7	242	67	1862		89	166	4.7	149	48	158	3.1
8–14	278	77	2058		92	155	5.3	260	38	279	3.1
15–21	95	24	1950		90	150	5.2	72	41	83	3.2
≥ 22	161	26	2026		91	178	6.1*	128	31†	134	2.9
Mean			1977	15	91	162	5.3		39‡		3.1‡
SD within the individual treatment courses (% of mean)			3.4	20	24	45	43		82		53

\*P<0.001, †P<0.005, ‡geometric mean.

method as described previously.<sup>1,8</sup> The bacterial sensitivity was assessed by a disc diffusion method (AB Biodisk, Stockholm).

**Statistical methods.** A logarithmic transformation was required to obtain normal distribution for the serum concentrations of the antibiotics. Because of differences between treatment courses within the groups defined by gestational age and the initial treatment weight—that is weight at the beginning of continuous IV antibiotic treatment—initial treatment weight, and postnatal age comparisons were made using an unbalanced 2-way nested classification model for gestational age and initial treatment weight, the observations within the 110 treatment courses being nested within groups.<sup>9</sup> Comparisons between the postnatal age groups were made using an unbalanced 2-way analysis of variance classified by treatment courses and postnatal age. It should be noted that the comparisons between postnatal age group 4 ( $\geq 22$  days) and the other postnatal age groups (Table 1) are based upon only 9 of the treatment courses because 17 infants were  $\geq 22$  days old during the entire treatment course.

## Results

In Table 1 the mean dosages of vamin for newborn infants, ampicillin and gentamicin, plus the mean serum concentrations of ampicillin and gentamicin are presented in relation to gestational age, initial treatment weight, and postnatal age during all 776 treatment days (110 treatment courses). The gestational age of one child who was treated for 17 days is not known. The differences in serum concentrations of antibiotics (Table 1) cease to be significant if the statistical analysis is restricted to 109 and 150 of the 776 treatment days during which 80–110% of the planned volume of vamin and 90–110% of the planned amount of ampicillin (mean dosage 145 mg/kg per 24 hours) and gentamicin (mean dosage 6.1 mg/kg per 24 hours) had actually been given. The corresponding mean serum concentrations were 40 and 3.3  $\mu\text{g/ml}$  (data not shown).

The results were the same whether the calculations of the daily amount of gentamicin to be added to the bottle were based on the same day (34 infants) or the previous day (54 infants) serum concentration measurements.

The serum concentrations of antibiotics during the first three treatment days during which most of the first 30 and all of the last 58 infants were given the same daily dosage did not differ significantly from the results for all 776 treatment days.

In Table 2 the mortality rates are given in relation

to the type of infection. Of the 3 infants who died with signs of bacterial infections caused by strains resistant to ampicillin and sensitive to gentamicin Case 1 weighed 960 g. Ampicillin and gentamicin had been given intermittently from day 5 to day 8 and continuously IV thereafter. All treatment, including antibiotics, was stopped after a conference decision on day 12—that is 30 hours before death—because of his desperate clinical condition. At necropsy a subphrenic abscess was found and *Escherichia coli* was cultured from heart blood and all organs. In Case 2, who weighed 1720 g, a septostomy was made on day 1 because of transposition of the great vessels. On day 5 signs of necrotising enterocolitis developed. The child was hemicolectomised on day 41 because of necrosis and perforation of the colon. Antibiotics were given as intermittent injections on days 41 and 42 and as continuous IV infusions from day 43 until she died 4 days later. At necropsy, *E. coli* and *Klebsiella oxytoca* were cultured from all organs except the brain. Case 3, who weighed 1080 g, developed necrotising enterocolitis on day 7 with perforation and was operated on day 11 and continuous IV infusions of antibiotics were given until death 6 days later, shortly after reoperation. At necropsy *Klebsiella pneumoniae* was cultured from heart blood and all organs.

Gram-negative rods, sensitive to gentamicin, were isolated from 11 of the 14 surviving patients among the 17 with bacteraemia or peritonitis (Table 2). Six of these strains were resistant to ampicillin. Of the remaining 3 patients one had bacteraemia with *Staphylococcus aureus* and the other two had peritonitis, verified during operation. Furthermore, in one case a *Bacteroides* species and in two cases a *Clostridium* species were isolated from the peritoneum. From 3 of the 16 patients with necrotising

Table 2 Mortality rates in relation to type of infection for 88 newborn infants

	Number of patients	Fatal	
		Without bacterial infection	With bacterial infection
Peritonitis and bacteraemia	2	0	1*
NEC, peritonitis, and bacteraemia	3	0	1
NEC, peritonitis, bacteraemia, and meningitis	1	0	1
Pneumonia and bacteraemia	1	0	0
Bacteraemia only	4	1	0
NEC and peritonitis	3	0	0
Peritonitis only	3	0	0
NEC only	9	1	0
Bacteraemia suspected but not verified	62	4	0

\*Death occurred 30 hours after treatment had been stopped. NEC=necrotising enterocolitis.

enterocolitis a *Clostridium* species was isolated from peritoneum or stool.

### Discussion

Many studies have shown that penicillins are inactivated in a variety of parenteral solutions. We in an earlier study<sup>1</sup> found as much as 69% loss of ampicillin in vamin with fructose (Vitrum, Stockholm) after 24 hours. In a vamin-solution especially prepared for newborns<sup>1</sup> however, the inactivation of ampicillin was only 22% and gentamicin was fully stable. Earlier studies have shown that the half-lives of ampicillin and gentamicin are correlated to gestational age, weight, and postnatal age in newborn infants.<sup>10 11</sup> Extensive experience with the currently recommended dosage of gentamicin indicates that gentamicin given either by IM injections or IV infusion over a 20-minute period is neither ototoxic nor nephrotoxic for newborn infants if used for periods of 7–10 days.<sup>10</sup> Recently, it has been shown that using the recommended dosage the mean predosage gentamicin serum concentration is about 3 µg/ml for newborns with a gestational age less than 35 weeks and a postnatal age less than 1 week.<sup>12</sup> Concern for possible accumulation associated with predose concentrations greater than 1.0 µg/ml has led to recommendations to monitor gentamicin serum concentrations and to tailor individual dosage regimens in neonates.<sup>12 13</sup> For ampicillin it has been shown that the mean predosage serum concentration is about 40 µg/ml.<sup>14</sup> The reason why the mean serum concentration of antibiotics, especially gentamicin, was lower than aimed at in this study was due to the fact that the whole amount of antibiotics calculated for the next 24 hours was not always given. This was mainly caused by subcutaneous infiltration of the scalp with vamin for newborn infants to which the antibiotics had been added. A new scalp vein line could not always be established at once, thus causing a delay in the planned infusion. This problem of giving less than planned during PN to newborn infants in a busy intensive care unit is being increasingly recognised.<sup>15</sup> The only way to resolve the problem is by meticulously observing that the IV fluids do not infiltrate subcutaneously and if they do that the IV line is re-established at once. In some cases the doctors had incorrectly calculated the amount of antibiotics. The differences between treatment courses and the three criteria, gestational age, initial treatment weight, and postnatal age, were small compared with the random variation within the individual treatment courses, and disappeared when the planned amount of antibiotics had been correctly calculated and actually given.

Using the formula for infusion rate as described earlier,<sup>5</sup> the mean values of the elimination rate constant for ampicillin and gentamicin were 0.26 and 0.11 per hour respectively. Further evaluation of the kinetics of the antibiotics and calculations of the elimination rates will be presented in detail in a subsequent paper.

In the present study the 95% limits for serum concentrations of ampicillin and gentamicin were 11–133 and 1.3–7.4 µg/ml respectively. For ampicillin this is more than 10 × minimal inhibitory concentration for sensitive strains, and for gentamicin above the minimal inhibitory concentration for sensitive strains but below the toxic value.

For the 64 infants receiving PN and intermittent injections of antibiotics in our department during 1976 and 1977, the mortality rate was 17%. About half (7.8%) of these patients had bacterial infections. Some of these patients received kanamycin instead of gentamicin. In this study the mortality rate was 10% and bacterial infection was found in 3.4% (Cases 1, 2, and 3). In Cases 2 and 3, the strains isolated from the peritoneal cavity during operation and from blood were resistant to ampicillin but sensitive to gentamicin as assessed by Biodisk—that is minimal inhibitory concentration <2 µg/ml. The range of their gentamicin serum concentrations was 1.9–5.2 µg/ml. From both patients *Klebsiella* sp. was isolated. It has been shown that infection with *Klebsiella* sp. is a risk factor related to dying from necrotising enterocolitis.<sup>16</sup> Furthermore, it has been shown in adults that the response rate for *Klebsiella* sp. infections is significantly lower than for infections with other Gram-negative bacilli using continuous IV infusion.<sup>3</sup> Therefore, as regards Case 2, ampicillin should have been changed to cephalosporin and Case 3, who had meningitis, should have been treated with chloramphenicol.

No nephrotoxic reactions were seen in the patients. The assessment of ototoxicity will have to be deferred until the infants are older.

In conclusion, the study has shown that it is possible to maintain serum concentrations of ampicillin and gentamicin above the minimal inhibitory concentration for sensitive bacterial strains by continuous IV infusions in combination with parenteral nutrition using individually calculated dosages. The results are at least as good as our results with intermittent antibiotic treatment. However, if the isolated strains are resistant to ampicillin the treatment should be changed. From two practical points of view the continuous IV infusion of antibiotics is superior to intermittent administration. Injections into the often small muscles of low birthweight infants are avoided and only one dose needs to be calculated and injected

