Double blind, randomised, placebo controlled study of oral vancomycin in prevention of necrotising enterocolitis in preterm, very low birthweight infants

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Abstract

***Aims*—To evaluate the effectiveness of oral vancomycin in the prophylaxis of necrotising enterocolitis in preterm, very low birthweight infants.**

***Methods*—A prospective, double blind, randomised, placebo controlled study in a tertiary referral centre of a university teaching hospital was conducted on 140 very low birthweight infants consecutively admitted to the neonatal unit. The babies were randomly allocated to receive oral vancomycin (15 mg/kg every 8 hours for 7 days) or an equivalent volume of placebo solution. Prophylaxis was started 24 hours before the start of oral feeds. All suspected cases of necrotising enterocolitis were investigated with a full sepsis screen and serial abdominal radiographs. Necrotising enterocolitis was diagnosed and staged according to modified Bell's criteria.**

***Results*—Nine of 71 infants receiving oral vancomycin and 19 of 69 infants receiving the placebo solution developed necrotising enterocolitis (p=0.035). Infants with necrotising enterocolitis were associated with a significant increase in mortality (p=0.026) and longer duration of hospital stay (p = 0.002).**

***Conclusions*—Prophylactic oral vancomycin conferred protection against necrotising enterocolitis in preterm, very low birthweight infants and was associated with a 50% reduction in the incidence. However, widespread implementation of this preventive measure is not recommended, as it would only be effective in necrotising enterocolitis caused by Gram positive organisms and could increase the danger of the emergence of vancomycin resistant or dependent organisms. Its use should be restricted to a high prevalence nursery for a short and well defined period in a selected group of high risk patients.**

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Keywords: necrotising enterocolitis; oral vancomycin; prophylaxis

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Necrotising enterocolitis (NEC) is predominantly a disease of premature neonates. It has become the most serious and common gastrointestinal emergency in very low birthweight (VLBW) infants.[1–3] Although its exact pathophysiology is not fully understood, three essential elements have been implicated in pathogenesis: (1) immature and/or hypoxic–ischaemic bowel injury, resulting in the loss of the intestinal mucosal barrier integrity; (2) enteral feeds providing food substrates for intraluminal bacterial growth; and (3) translocation of bacteria or their toxic products across the intestinal mucosal barrier.[4–6]

As bacterial translocation is considered to be a graded phenomenon[4] and only likely to occur if enteric bacteria exceed a critical population level ($>10^{9-10}$/g of stool in an animal model),[7] therapeutic approaches to lower the intraluminal bacteria density should theoretically decrease the incidence of NEC.[8–11] Oral vancomycin has been tried[10 11] because of its activity against coagulase negative staphylococci, *Clostridium* spp, and Gram positive anaerobes, and also because it does not completely sterilise the bowel which could promote colonisation by unwanted pathogens.

Vancomycin is poorly absorbed and so a high drug concentration can be achieved in the gut lumen with minimal risk of systemic toxicity.[10] Although we have shown that the use of prophylactic oral vancomycin was associated with a significant reduction in the incidence of NEC, the study was unable confidently to determine whether late introduction of enteral feeding was also a contributory factor.[10] This prospective randomised trial was undertaken to evaluate the effectiveness of oral vancomycin in the prophylaxis of NEC in a high prevalence neonatal intensive care unit, and the adverse effects of this treatment on individual infants and in the neonatal unit.

Methods

Neonates were eligible for inclusion in the study if their birthweight was less than 1500 g and did not have: (1) lethal congenital anomalies; (2) major gastrointestinal abnormalities such as oesophageal atresia, intestinal stenosis or atresia, or Hirchsprung's disease; (3) major gastrointestinal surgery before enteral feeding; and (4) congenital cyanotic heart disease.

Around 70 infants weighing less than 1500 g are admitted to our neonatal intensive care unit each year. All consecutive admissions were considered for the study if they fulfilled the entry criteria. Eligible infants were randomly assigned by computer at 48 hours of postnatal age to receive either vancomycin or placebo

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treatment. The attending team caring for the infants were unaware of the random assignments.

Infants in the treatment group received oral vancomycin (vancomycin hydrochloride, Abbott Laboratories, Chicago, IL, USA) 15 mg/kg/dose every 8 hours; those in the placebo group received an equivalent volume of placebo solution. The placebo solution was prepared by diluting one drop of a yellow coloured, sugar free, multivitamin preparation, Vimax (MediPharma Ltd., Tsuen Wan, Hong Kong) into 20 ml of sterile water to simulate the colour of vancomycin. Prophylaxis was begun 24 hours before the start of oral feeds. All infants received a 7 day course of treatment. In infants who developed NEC while receiving the study drug, medication was suspended. The prophylactic drug was not restarted when enteral feeding was introduced after the infant had recovered. During the trial period, all other experimental prophylaxis for NEC, such as oral immunoglobulins or other oral antibiotics, were excluded.

All VLBW infants were started on parenteral nutrition, 6% TrophAmine (McGaw Inc., Irvine, CA, USA) and 20% Intralipid (Kabi Pharmacia AB, Stockholm, Sweden), on day 3. Oral milk feeds were usually started in the first week of life at the discretion of the attending neonatologist and were given as intermittent boluses via an oro-gastric tube starting at 1 ml/hour. Oral intake was gradually increased at a rate of 0.5–1 ml/hour/day according to tolerance. Infants were fed mother's milk whenever possible and a number of preterm commercial milk formulas were also used.

All infants were examined at least twice a day and closely observed for gastrointestinal problems including abdominal distension, vomiting, gastric retention, signs of peritonitis and blood in the stools. All suspected cases of NEC were investigated with a full sepsis screen which included cerebrospinal fluid, blood, urine, endotracheal aspirate (intubated infants) and stool (daily sample for three consecutive days) cultures for bacteria and fungi; removal of indwelling umbilical lines; and culture of surgical specimens and specific sites such as peritoneal swab or fluid. Serial abdominal radiographs were routinely performed in these infants and screened for evidence of pneumatosis intestina-

Table 1 Comparison of clinical characteristics and incidence of NEC between oral vancomycin and the placebo groups

Clinical features	*Oral vancomycin group (n=71)*	*Placebo group (n=69)*
Gestational age (weeks)	29.6 (27.7 to 31.1)	28.6 (27.0 to 30.1)
Birthweight (g)	1180 (935 to 1350)	1170 (939 to 1325)
Sex (female:male)	35 (50):36 (50)	29 (42):40 (58)
Inborn:outborn	68 (96):3 (4)	67 (97):2 (3)
Antenatal corticosteroid treatment	50 (70)	45 (65)
Mode of delivery		
Vaginal	32 (45)	26 (38)
Caesarean section	37 (52)	42 (61)
Ventouse	1 (1.5)	1 (1)
Forceps	1 (1.5)	0 (0)
Apgar scores		
1 min < 3	12 (17)	7 (10)
5 min < 3	1 (1)	1 (1)
First arterial blood gas after delivery		
pH	7.37 (7.29 to 7.46)	7.36 (7.31 to 7.43)
Base excess	−2.5 (−6.1 to −1.0)	−2.6 (−5.4 to −0.6)
Temperature on admission (°C)	36.1 (35.8 to 36.5)	36.2 (35.6 to 36.7)
First venous haematocrit after delivery	0.52 (0.47 to 0.57)	0.51 (0.46 to 0.54)
Lowest mean arterial blood pressure (mm Hg)	28 (23 to 32)	27 (21 to 30.5)
Exchange transfusion	2 (3)	0 (0)
Umbilical arterial catheterisation	42 (59)	38 (55)
Umbilical venous catheterisation	55 (77)	59 (86)
Aminophylline treatment	49 (69)	46 (67)
Respiratory distress syndrome		
Stage 0-2	45 (63)	51 (74)
Stage 3-4	26 (37)	18 (26)
Periventricular haemorrhage		
Stage < 2	63 (89)	57 (83)
Stage 3-4	8 (11)	12 (17)
Patent ductus arteriosus		
Indomethacin closure	35 (49)	37 (54)
Surgical ligation	3 (4)	2 (3)
Age started on enteral feeds (days)	5 (3 to 9)	6 (5 to 9)
Age received full enteral feeds (days)	27 (20 to 36)	28 (19 to 45)
Type of milk feeds		
Breast	12 (17)	8 (12)
Formula	28 (39)	33 (48)
Mixed	31 (44)	28 (41)
Incidence of NEC*	9 (13)	19 (28)
NEC stages	25 (16 to 42)	26 (17 to 33)
0-1	62 (87)	50 (72)
2	4 (6)	12 (17)
3	5 (7)	7 (11)
Stool culture (fungus: Gram (−): Gram (+))		
Before prophylaxis	1 (1):2 (3):13 (18)	2 (3):6 (9):12 (17)
Immediately after prophylaxis	8 (11):10 (14):1 (1)	9 (12):12 (17):2 (3)
Four weeks after prophylaxis	4 (6):16 (23):2 (3)	1 (1):14 (20):0 (0)
Duration of mechanical ventilation (days)	6 (2 to 14)	8 (3 to 24)
Duration of O_2 dependency (days)	10 (3 to 29)	13.5 (4.5 to 50.5)
Duration of hospital stay (days)	84 (55 to 112)	90.5 (66 to 126)
Died	11 (15)	13 (19)

Continuous variables are expressed in median (interquartile ranges) and proportions in number of patients (%).
* $p<0.05$.

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Table 2 Comparison of infants with and without necrotising enterocolitis

Clinical features	*With NEC (n=28)*	*Without NEC (n=112)*
Gestational age (weeks)	28.1 (26.3 to 30.4)	29.0 (27.7 to 30.9)
Birthweight (g)	1095 (873 to 1348)	1195 (960 to 1330)
Sex (female:male)	14 (50):14 (50)	50 (45):62 (55)
Inborn:outborn	26 (93):2 (7)	109 (97):3 (3)
Antenatal corticosteroid treatment	17 (61)	78 (70)
Mode of delivery		
Vaginal	18 (64)	43 (38)
Caesarean section	10 (36)	66 (59)
Ventouse	0 (0)	2 (2)
Forceps	0 (0)	1 (1)
Apgar scores		
1 min < 3	5 (18)	14 (13)
5 min < 3	1 (4)	1 (1)
First arterial blood gas after delivery		
pH	7.37 (7.32 to 7.45)	7.36 (7.30 to 7.44)
Base excess	−2.4 (−5.0 to −0.80)	−2.6 (−5.6 to −0.9)
Temperature on admission (°C)	36.0 (35.8 to 36.8)	36.2 (35.6 to 36.6)
First venous haematocrit after delivery	0.52 (0.47 to 0.55)	0.51 (0.45 to 0.57)
Lowest mean arterial blood pressure (mm Hg)	27.5 (22.5 to 31.5)	27 (22 to 32)
Exchange transfusion	1 (4)	1 (1)
Umbilical arterial catheterisation	18 (64)	62 (55)
Umbilical venous catheterisation	24 (86)	90 (80)
Aminophylline treatment	20 (71)	57 (51)
Respiratory distress syndrome		
Stage 0-2	20 (71)	86 (77)
Stage 3-4	8 (29)	26 (23)
Periventricular haemorrhage		
Stage < 2	26 (93)	94 (84)
Stage 3-4	2 (7)	18 (16)
Patent ductus arteriosus		
Indomethacin closure	15 (54)	57 (51)
Surgical ligation	2 (7)	3 (3)
Age started on enteral feeds (days)	6.5 (4 to 14.5)	6 (4 to 9)
Age received full enteral feeds (days)	36 (23 to 61)	26 (19 to 37)
Type of milk feeds		
Breast	3 (11)	17 (15)
Formula	11 (39)	50 (45)
Mixed	14 (50)	45 (40)
Stool culture (fungus: Gram (−): Gram (+))		
Before prophylaxis	0 (0):0 (0):5 (18)	3 (3):8 (7):20 (18)
Immediately after prophylaxis	4 (14):6 (21):0 (0)	13 (12):16 (14):3 (3)
Four weeks after prophylaxis	2 (7):6 (21):1 (4)	3 (3):24 (21):1 (1)
Duration of mechanical ventilation (days)	9.5 (2 to 31)	6.5 (3 to 16)
Duration of O_2 dependency (days)	16 (3.5 to 47.5)	10 (3 to 34)
Duration of hospital stay (days)*	115 (90 to 144)	81 (55 to 110)
Died*	9 (32)	15 (13)

Continuous variables are expressed in median (interquartile ranges) and proportions in number of patients (%).
* $p<0.05$.

lis, portal venous gas, ascites and pneumoperitoneum. The suspected cases were staged according to the modified Bell's criteria[12] by two of the investigators who had no knowledge of the randomisation assignments. Stages II and III disease were considered diagnostic of NEC.

Stool samples for microbiological culture were collected in all studied infants immediately before treatment, immediately after, and 4 weeks after the completion of the prophylaxis. All specimens were cultured on to a wide range of selective media including: (1) deoxycholate citrate (DC) agar, thiosulphate citrate bile sucrose agar, MacConkey agar and selenite-F enrichment broth (further subcultured onto DC agar after incubation), incubated aerobically at 37°C for 18 to 24 hours; (2) blood agar supplemented with vitamin K1 and cycloserine cefoxitin fructose agar incubated anaerobically at 37°C for 48 hours; (3) Skirrow agar incubated under microaerophilic conditions at 42°C for 48 hours; and (4) Sabouraud dextrose agar incubated aerobically at 30°C for 48 hours.

Stool pathogens including *Salmonella* spp, *Shigella* spp, thermophilic *Campylobacter* spp and *Vibrio* spp were identified using standard biochemical tests, the API systems (bioMérieux, Marcy-l'Etoile, France) and serological tests where appropriate. Heavy predominant growth or pure growth of aerobes, *Clostridium* spp, and yeast were recorded. The microbiologists who performed the stool cultures were also unaware of the randomisation assignments.

Our statistics revealed a consistently high prevalence of NEC during the five consecutive years before the study. Most cases occurred in preterm neonates (> 95%) and the incidence ranged from 18–25% (mean 21%) in VLBW infants. Using the previously detected rate of occurrence and our experience of using prophylactic oral vancomycin,[10] it was determined that 68 infants would be required in each arm of a randomised controlled study to detect a significant difference at the 5% level with a power of 80%, if the incidence of NEC was to decrease from 21% to 5%. Fisher's exact test was used to compare proportions and the Wilcoxon rank sum test for comparison of continuous variables.

This study was approved by the Ethics Committee of the Chinese University of Hong Kong. Written informed consent for participation was obtained from the parents before enrolment.

Results

One hundred and seventy five VLBW infants were admitted to the neonatal intensive care

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unit between February 1994 and August 1996. Sixteen infants died from extreme prematurity and respiratory diseases before 48 hours of age, 19 parents did not give consent, leaving 140 infants who were successfully recruited to the study.

Seventy one infants received oral vancomycin and 69 received the placebo solution. Table 1 compares the clinical characteristics and incidence of NEC between the two groups. Significantly more infants developed NEC in the placebo group (19 of 69 infants)than in the oral vancomycin group (9 of 71 infants; $p = 0.035$). All other variables including: gestational age; birthweight; mode of delivery; perinatal asphyxia indices; umbilical catheterisation; drug treatment such as antenatal corticosteroids, aminophylline, and indomethacin; feeding patterns; stool cultures; severity of respiratory distress syndrome and periventricular haemorrhage; duration of mechanical ventilation, oxygen dependency, and hospital stay; and mortality did not differ significantly between the two groups.

A significant decrease in the incidence of stool cultures with pure or heavy predominant growth for Gram positive organisms ($p < 0.001$) and a significant increase in the incidence of stool cultures for Gram negative organisms ($p < 0.05$)was observed immediately and 4 weeks after treatment with oral vancomycin when compared with the pre-treatment incidence. Similarly, a significant increase in the incidence of stool culture with pure or heavy predominant growth for yeast ($p < 0.05$) was also detected in infants immediately after oral vancomycin treatment. In contrast, only the incidence of stool culture for Gram positive organisms was significantly decreased after receiving the placebo solution when compared with the pre-treatment incidence ($p < 0.01$).

Table 2 compares the clinical characteristics between infants with and without NEC. NEC was associated with a significant increase in mortality ($p = 0.026$) and longer duration of hospital stay ($p = 0.002$) in VLBW infants. Although there was a trend towards longer duration of mechanical ventilation and oxygen dependency in affected infants, neither variable reached significance.

Pathogens were isolated from blood and/or peritoneal specimens in six of nine (67%) and nine of 19 (47%) NEC infants treated with oral vancomycin and placebo, respectively. *Enterobacter* spp (3 cases), methicillin resistant *Staphylococcus aureus* (MRSA 2 cases), and *Serratia* spp (1 case) were isolated in the oral vancomycin group. In contrast, coagulase negative staphylococci (4 cases), MRSA (2 cases), *Enterobacter* spp (1 case), *Klebsiella* spp (1 case), and *Serratia* spp (1 case) were isolated in the placebo group.

Discussion

The most common pathogen for late onset (> 48 h of birth) neonatal sepsis is coagulase negative staphylococci[13–16] which mainly affects infants weighing less than 1500 g,[14–16] and accounts for over 70% of all septicaemias in neonatal intensive cares.[13 16] Furthermore, coagulase negative staphylococci have been implicated as the single most frequent group of organisms recovered from infants with NEC who died, and from peritoneal specimens taken at the time of surgery.[17 18] In recent years these organisms have also become the commonest group responsible for systemic infection in our unit, and the bacteria most frequently isolated from blood and peritoneal cultures in those infants with NEC (>50% of NEC infants with positive cultures). Oral vancomycin was therefore tried in an attempt to lower the incidence of NEC in the unit.

One of the most important risk factors of NEC is prematurity. Although the infants in the treatment group were on average one week more mature than those in the placebo group, this was not significant. Furthermore, their birthweight were more closely matched and hence, it would be very unlikely that the difference in gestation would have contributed to such a striking difference in incidence between the two groups. More importantly, our results show that prophylactic oral vancomycin conferred protection against NEC in preterm, VLBW infants and was associated with a 50% reduction in its incidence.

The mechanism is likely to be a decrease in the colonisation and multiplication of Gram positive organisms in the gut lumen which results in the decrease of bacterial translocation or invasion across the immature or injured intestinal mucosa.[4] Our findings also suggest that infants with NEC had 2½ times the risk of mortality of infants without NEC (table 2). Furthermore, affected infants required a significantly longer period of hospital stay and also tended to require prolonged mechanical ventilation and oxygen supplementation. These results suggest that the morbidity and mortality were associated with development of long term complications,[3] such as bronchopulmonary dysplasia, as a consequence of severe and prolonged ventilation during the acute phase of the illness, septicaemia,[19] cholestatic jaundice and liver failure secondary to prolonged hyperalimentation.[19]

No increase in the incidence of systemic infections caused by fungi or Gram negative organisms was observed, nor were vancomycin resistant or dependent organisms isolated from routine microbiological surveillance or specimens obtained for sepsis screening during the study. No serious adverse effects such as impaired renal function, diarrhoea, or toxic serum drug concentration associated with the use of oral vancomycin were encountered. However, a clinically significant change in the stool flora, with heavy predominant growth of yeast and Gram negative organisms after treatment with oral vancomycin, was worrying, and may indicate the replacement of the normal gut flora by unwanted virulent pathogens.

Although this study supports the prophylactic use of oral vancomycin for prevention of NEC in preterm VLBW infants, we do not recommend widespread implementation of this preventive measure. There are great variations in the pattern of bacterial colonisation and the incidence of NEC among different neonatal

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intensive care units. The risks associated with routine use of oral prophylactic antibiotics probably outweigh the benefits in nurseries with a low incidence or in those colonised predominantly with Gram negative organisms. It is also worrying to note a significant change in the stool flora with heavy predominant growth of yeast and Gram negative organisms after treatment with oral vancomycin. Although the development of organisms resistant to vancomycin was not detected in our study, vancomycin resistant staphylococci,[20] enterococci,[21] and vancomycin dependent enterococci[22 23] have been reported. As only five infants in the unit received oral vancomycin at any one time, and the duration of our study was limited to 31 months, the proportion of infants exposed to this treatment was relatively small and the study period might have been too short to allow resistant strains to develop. In our opinion, oral vancomycin treatment should be restricted only to treating an NEC outbreak caused by Gram positive organisms[11] or use in a high prevalence nursery for a short and well defined period in a selective group of high risk infants. In all circumstances, vigilant microbiological surveillance for vancomycin resistant organisms is mandatory. Until the question of safety can be adequately addressed, the use of oral vancomycin for routine prophylaxis of NEC in VLBW infants should remain experimental.

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