CHLORAMPHENICOL ALONE VERSUS CHLORAMPHENICOL PLUS PENICILLIN FOR BACTERIAL MENINGITIS IN CHILDREN

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Summary 367 children with cerebrospinal-fluid findings suggestive of bacterial meningitis were randomised to receive either chloramphenicol alone by intramuscular injection, or chloramphenicol plus penicillin by intravenous injection. Sequential analysis showed no difference in mortality between the two treatments. 48 (26%) of the 183 children in the chloramphenicol alone group died, and 49 (27%) of the 184 children in the chloramphenicol plus penicillin group died. In children with bacterial meningitis chloramphenicol alone given by intramuscular injection is as effective as chloramphenicol plus penicillin given intravenously.

Introduction

The clinical significance of antagonism between penicillin and chloramphenicol has been debated since the in-vitro interaction was first described in detail by Jawetz et al in 1951. If the two drugs are to be used together, two quite separate issues need to be considered: the effect of adding chloramphenicol if a sensitive organism is being treated with penicillin, and whether anything is gained by adding penicillin when a patient is receiving chloramphenicol.

In the treatment of infection with an organism, such as Streptococcus pneumoniae, that is sensitive to penicillin, what is the effect in vivo of giving chloramphenicol in addition to penicillin? A study in dogs with pneumococcal meningitis and a randomised controlled trial in patients with meningitis both suggested that penicillin (or ampicillin) alone was substantially better than penicillin plus chloramphenicol. Similarly, Leeper and Dowling demonstrated that tetracycline antagonised the action of penicillin in adults with pneumococcal meningitis. On the other hand, Bodine et al reported that chloramphenicol did not antagonise the action of penicillin in pneumococcal meningitis in rabbits. Because Haemophilus influenzae is only moderately sensitive to penicillin, and S pneumoniae often has reduced sensitivity to penicillin in Papua New Guinea, we decided that it would not be ethical to compare benzylpenicillin alone with benzylpenicillin plus chloramphenicol in children with meningitis in Papua New Guinea.

When an organism is not very sensitive to penicillin, or when the organism or the antibiotic sensitivity is not known, and chloramphenicol is used, is there any benefit from giving penicillin or ampicillin as well as chloramphenicol? A study in rabbits with H influenzae meningitis showed little difference between chloramphenicol alone, ampicillin alone, and both drugs together. There have been no prospective randomised controlled trials in man designed to answer this question. In two retrospective studies of children with H influenzae meningitis, sequelae were four times more common after treatment with ampicillin plus chloramphenicol than after chloramphenicol alone.

Chloramphenicol sodium succinate is well absorbed after intramuscular administration in children, and the injection is not particularly painful. Chloramphenicol alone, it can reasonably be given intramuscularly for 2 or 3 days, then orally when the child starts to improve. This regimen is cheap and easy to administer. On the other hand, if both chloramphenicol and penicillin are given, the large number of injections required means that an intravenous drip is usually used. Consequently, use of chloramphenicol plus penicillin is more expensive, makes greater demands on the time of staff, and carries the risks of sepsis and overhydration associated with intravenous fluid therapy.

A multicentre prospective randomised controlled trial has been carried out in children with cerebrospinal-fluid findings suggestive of bacterial meningitis to see whether chloramphenicol plus penicillin (given intravenously) is any more effective than chloramphenicol alone (given intramuscularly).

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Methods
The study was carried out in three hospitals in Papua New Guinea: Goroka Hospital (children admitted between May, 1979, and June, 1983), Kundiawa Hospital (August, 1979, to April, 1981) and Lae Hospital (October, 1979, to June, 1982). Children were admitted to the trial if bacteria grew from their CSF, or if the CSF polymorph count was >100 cells/μl, or the CSF polymorph count was >20 cells/μl with either CSF protein >1.0 g/l or CSF glucose <2.2 mmol/l. The study was approved by the Papua New Guinea Medical Research Advisory Committee.

A table of random numbers was used to prepare sealed, numbered envelopes. After a child had been admitted to the trial, the next envelope was opened to determine which treatment to be given. The investigators were aware of the treatment being given to each child. Children randomised to receive chloramphenicol alone were given 25 mg/kg chloramphenicol sodium succinate intramuscularly every 6 h at first, then 25 mg/kg of chloramphenicol palmitate orally every 6 h once clinical improvement had begun. Children who were too ill to feed were given fluid by nasogastric tube. Children randomised to receive chloramphenicol plus penicillin had an intravenous drip inserted. A solution of 4%-3% dextrose in 0.18% sodium chloride was infused at the following rates: body-weight 3-4 kg, 10 ml/h; 5-9 kg, 15 ml/h; 10-14 kg, 20 ml/h; 15-39 kg, 25 ml/h; Chloramphenicol sodium succinate was given intravenously every 6 h in a dose of 25 mg/kg, and benzylpenicillin was given intravenously every 3 h in the following doses: body-weight 3-9 kg, 500 000 U; 10-19 kg, 1000 000 U; 20-29 kg, 1500 000 U; 30-39 kg 2000 000 U. When the child began to recover, the treatment was changed to 25 mg/kg of chloramphenicol palmitate orally every 6 h, and the above dose of benzylpenicillin intramuscularly every 6 h. Antibiotic therapy was given for a total of 14 days. All children were given quinine or amodiaquine. CSF was cultured on human blood agar and chocolate agar.

Each child was paired to the next child in the other treatment group at the same hospital. Treatment was said to have failed if the child died. The preferences of untied pairs were analysed by means of Cochran's test to compare the proportion of children who died in the two treatment groups. Treatment group A was paired to the next child in the other treatment group at the same hospital. Treatment was said to have failed if the child died. The preferences of untied pairs were analysed by means of Cochran's test to compare the proportion of children who died in the two treatment groups. There was no significant difference (p>0.2, χ² test, 1 df) between the two treatment groups in the proportion of children who were male, comatose, or aged <6 months, or in the proportion who had bacteria present on CSF culture, neck stiffness, a bulging fontanelle, haemoglobin >9.0 g/dl, white blood cell count (WCC) >13 000/μl, CSF WCC <750/μl, axillary temperature >38.0°C, or weight-for-age <80% of the Harvard median (the value of each of the continuous variables chosen for comparison was midway between the medians of the two treatment groups). However, at the time of admission to the trial, the children in the chloramphenicol alone group had been ill for 5 days or more (χ² 5.747, 1 df, p<0.02), whereas children in the chloramphenicol plus penicillin group were somewhat more likely not to be feeding (χ² 3.417, 1 df, 0.1>p>0.05) and to have had a convulsion (χ² 2.239, 1 df, 0.2>p>0.1). The proportions of children who died in the two treatment groups were therefore compared by means of Cochran's test to adjust for the number who had been ill for 5 days or more, were not feeding, or had had a convulsion. Although the adjusted mortality rate was 26% (48/183) in the chloramphenicol alone group and 27% (49/184) in the chloramphenicol plus penicillin group, the adjusted mortality rate was lower in the chloramphenicol plus penicillin group by 2.1%±8.5% (±95% confidence limits).

The outcome was poor (death, discharged with brain damage, abscessed still sick) in 38% (69/183) of the chloramphenicol alone group and in 40% (74/184) of the chloramphenicol plus penicillin group (table i); the adjusted mortality rate was lower in the chloramphenicol plus penicillin group by 2.1%±8.5% (±95% confidence limits).

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<th>TABLE I-OUTCOME, BY ANTIBIOTIC TREATMENT</th>
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<td>Treatment group</td>
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<td>Chloramphenicol alone</td>
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<th>TABLE II-PROPORTION OF CHILDREN IN WHOM TREATMENT FAILED,* BY RESULT OF CSF CULTURE</th>
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*Absconded still sick, discharged brain damaged, or died.
difference was lower in the chloramphenicol alone group by 0.4% to 1.1% (±95% confidence limits). Table II shows the outcome of treatment according to the results of bacterial culture of the CSF. An organism was cultured from the CSF of 181 children: 28 (31%) of the 91 treated with chloramphenicol alone died and 28 (29%) of the 90 treated with chloramphenicol plus penicillin died; the difference in mortality is 1.8% ± 1.3% (±95% confidence limits), which is not significant.

30 children were discharged with signs suggesting that they were likely to have suffered permanent brain damage (table I). 10 of these children (4 from the chloramphenicol alone group) were comatose or semicomatose and probably died at home, 13 children (4 chloramphenicol alone) were conscious but had spasticity or unequivocal evidence of impaired motor or social functioning, and the other 7 children had hemiparesis (3 cases), frequent convulsions (3 cases), or total deafness (1 case). The 48 children who were well at the time they absconded (table I) had all had at least 5 days of antibiotic treatment. Of the 16 children who were still sick when they absconded, 9 (5 chloramphenicol alone) had had less than 4 days of antibiotic treatment, 6 (chloramphenicol alone) were semicomatose or had poorly controlled fits, and 1 child had persistent fever and irritability after 10 days of chloramphenicol alone.

Discussion

In Papua New Guinea, standard treatment regimens have been developed to guide paramedical workers and doctors in the management of the important diseases of children. The standard treatment for meningitis in children must take into account the fact that none of the health centres and only some of the hospitals in Papua New Guinea have facilities for performing bacterial cultures.

Possible Sources of Error in This Trial

Since most of the children in this trial came from rural villages with poor communications, it was not possible to follow up patients after they had left hospital, and only major sequelae such as death or gross brain damage could be detected. However, because the children presented late, the incidence of major sequelae was too low that any important difference in the effectiveness of the two antibiotic regimens would probably have been detected. The investigators knew what treatment was being given to each child in the study, but it is unlikely that this caused bias, because the endpoint in the trial was whether the patient lived or died. The results may have been affected by the high proportion of pneumococci which show reduced sensitivity to penicillin in Papua New Guinea, because this might have obscured any benefit from giving penicillin in addition to chloramphenicol. However, of 49 strains of S. pneumoniae isolated from CSF in Goroka during the trial, only 10 (20%) had a penicillin MIC over 0.1 μg/ml (6 strains 0.2–0.9 μg/ml, 2 strains 0.5–5 μg/ml, and 2 strains 1–10 μg/ml; Gratton M and Shinn F, unpublished data).

Random allocation resulted in close matching of the two treatment groups for all risk factors except length of illness, history of convulsions, and inability to feed. Cochran's test was used to adjust for the effect of these variables. The adjusted difference in the mortality rate was 2.1% ± 3.5% (±95% confidence limits), and the adjusted difference in the rate of treatment failure (death, discharged with brain damage, or absconded still sick) was 0.4% ± 0.1%. These differences are not statistically significant.

The criteria for inclusion in the trial included increased numbers of polymorphs, and increased protein or decreased glucose in the CSF; these findings are not diagnostic of bacterial meningitis. However, our study addresses the question that is of importance to clinicians: in a child with CSF findings that suggest bacterial meningitis, should the initial antibiotic therapy be chloramphenicol alone or chloramphenicol plus penicillin? Furthermore, in the 181 children whose CSF grew an organism, the mortality in the two treatment groups differed by only 1.6% ± 3.3% (±95% confidence limits), which is not a statistically significant difference.

The Combination of Chloramphenicol and Penicillin

The main reason for giving penicillin in addition to chloramphenicol in bacterial meningitis is the hope that the penicillin will cause more rapid killing of S. pneumoniae and N. meningitidis. Chloramphenicol itself is usually bacteriostatic against both these organisms (as well as H influenzae) and, when it is only bacteriostatic, chloramphenicol may antagonise the bactericidal action of penicillin anyway. After reviewing the literature on antibiotic combinations, Rahal and Simberkoff suggested that chloramphenicol plus penicillin is probably equivalent to chloramphenicol alone. Similarly, Lambert stated that there is no reason to believe that the results of combination therapy of bacterial meningitis (with penicillin, chloramphenicol, and a sulphonamide) are better than those obtained with chloramphenicol alone. One reason for giving ampicillin in addition to chloramphenicol is the risk of H influenzae being resistant to chloramphenicol. However, such organisms are very uncommon in most countries and, when they do occur, they are usually resistant to ampicillin just as well as chloramphenicol.

The results of our trial suggest that chloramphenicol alone is as effective as chloramphenicol plus penicillin in the treatment of bacterial meningitis in children. This conclusion is strengthened by the results of the comparison of chloramphenicol alone with chloramphenicol plus penicillin in children with severe pneumonia, which was carried out in the same hospital wards at the same time as the meningitis study.

Intramuscular injections of chloramphenicol sodium succinate are not very painful. Intramuscular administration of chloramphenicol, followed by oral administration, may be no more distressing to a small child than a long struggle to insert an intravenous cannula (often on more than one occasion), followed by several days of being tied down so that the drip does not come out. Intramuscular administration of chloramphenicol alone has several advantages over intravenous therapy with both chloramphenicol and penicillin, particularly in developing countries: it is much cheaper, it makes fewer demands on the time of staff, and it does not carry the risks of sepsis and overhydration associated with intravenous therapy.

We thank Dr Stephanie Germer, Dr Simon Landown, Dr Victor Linneemann, Dr Christopher Mackenzie, Dr Hilda Polumo, Dr Alphorse Rongap, Dr Benjamin Tahija, and Dr Likei Thein for their assistance.

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REFERENCES


References continued at foot of next page
CHLORAMPHENICOL ALONE VERSUS CHLORAMPHENICOL PLUS PENICILLIN FOR SEVERE PNEUMONIA IN CHILDREN

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Summary

748 children with severe pneumonia in three hospitals in Papua New Guinea were randomised to receive intramuscular injections of either chloramphenicol alone or chloramphenicol plus penicillin. Sequential analysis showed no difference between the two treatments. 48 (13%) of the 377 children in the chloramphenicol alone group died, and 3 (0-8%) were changed to different treatment. 62 (17%) of the 371 children in the chloramphenicol-plus-penicillin group died, and 6 (1-6%) were changed to different treatment. The difference in failure rates (death or withdrawal/change of treatment) was 4-8% to 5-2% (±95% confidence limits). In children with severe pneumonia, treatment with chloramphenicol alone is as effective as treatment with chloramphenicol plus penicillin.

Introduction

PNEUMONIA and diarrhoea are the commonest causes of death in children. Pneumonia accounts for more than 40% of deaths in children at Goroka Hospital, in the highlands of Papua New Guinea, and most cases are caused by Haemophilus influenzae or Streptococcus pneumoniae. Culture of lung aspirate or lung biopsy is required to determine the aetiology of bacterial pneumonia in small children. Since lung aspiration is not usually done routinely, children with severe pneumonia are often treated with both penicillin (for S pneumoniae) and chloramphenicol (for H influenzae).

When chloramphenicol is given because of the possibility of H influenzae infection, what is the effect of adding penicillin to cover S pneumoniae? A study in dogs with pneumococcal meningitis suggested that chloramphenicol plus penicillin may be superior to chloramphenicol alone for severe pneumococcal infections. However, in two retrospective studies in children with H influenzae meningitis, there were more common failures in treatment with chloramphenicol than with chloramphenicol alone.

A multicentre prospective randomised controlled trial has been carried out in children with severe pneumonia in Papua New Guinea to see whether chloramphenicol plus penicillin is any more effective than chloramphenicol alone.

Methods

Children with severe pneumonia were studied at Goroka Hospital, Kundiau Hospital, and Lae Hospital between May, 1979, and April, 1982. Children were admitted to the trial if they had cough and intercostal recession with any of the following: severe intercostal recession, pulse rate over 160/min with hepatomegaly, inability to feed, bronchial breathing, grunting, cyanosis, severe chest X-ray changes, or a total white cell count (WCC) over 30 000/μl. Children with meningitis were excluded. The study was approved by the Papua New Guinea Medical Research Advisory Committee.

A table of random numbers was used to prepare sealed, numbered envelopes. After each child had been admitted to the trial, the next envelope was opened to determine the treatment to be given. The investigators were aware of the treatment being given to each child.

Chloramphenicol sodium succinate was given intramuscularly in a dose of 25 mg/kg every 6 h until the child began to improve, and then 25 mg/kg of chloramphenicol palmitate was given orally every 6 h. Benzylpenicillin was given intramuscularly every 6 h in a dose of 250 000 units to children weighing 3-9 kg, and 500 000 units to children weighing 10-19 kg. All children were given quinine or amodiaquine.

Each child was paired with the next child in the other treatment group at the same hospital. Treatment was said to have failed if the child died or if the antibiotic therapy was changed because of deterioration in the child's condition. The preferences of unpaired pairs were analysed by sequential analysis on a repeated significance test plan with 2e-0.05, 1.8 > 0.95, 6 = 0.70, and n = 104. Thus, there was a 95% chance of obtaining a significant result (p<0.05) provided that the probability of a preference for 1 treatment group over the other was 0.70 or more.

Results

Of the 748 children admitted to the trial, 455 were in Goroka (where 1 child in the chloramphenicol alone group was unpaired), 174 were in Kundiau (2 chloramphenicol alone unpaired), and 119 were in Lae (3 chloramphenicol alone unpaired). Of the 371 pairs of results, 272 were tied, 58 favoured chloramphenicol alone, and 119 favoured chloramphenicol plus penicillin (see figure). 9 children (3 chloramphenicol alone) had their treatment changed during the trial because their condition was deteriorating (see table); the preferences of untied pairs were analysed by sequential analysis on a repeated significance test plan with 2e-0.05, 1.8 > 0.95, 6 = 0.70, and n = 104. Thus, there was a 95% chance of obtaining a significant result (p<0.05) provided that the probability of a preference for 1 treatment group over the other was 0.70 or more.

P. SHANN AND OTHERS: REFERENCES—continued


