Research

Parenteral penicillin for children with meningococcal disease before hospital admission: case-control study

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Abstract

Objective To explore the impact on mortality and morbidity of parenteral penicillin given to children before admission to hospital with suspected meningococcal disease.

Design Retrospective comparison of fatal and non-fatal cases.

Setting England, Wales, and Northern Ireland; December 1997 to February 1999.

Participants 158 children aged 0–16 years (26 died, 132 survived) in whom a general practitioner had made the diagnosis of meningococcal disease before hospital admission.

Results Administration of parenteral penicillin by general practitioners was associated with increased odds ratios for death (7.4, 95% confidence interval 1.5 to 37.7) and complications in survivors (5.0, 1.7 to 13.0). Children who received penicillin had more severe disease on admission (median Glasgow meningococcal septicaemia prognostic score (GMSPS) 6.5 v 4.0, \(P = 0.002\)). Severity on admission did not differ significantly with time taken to reach hospital.

Conclusions Children who were given parenteral penicillin by a general practitioner had more severe disease on reaching hospital than those who were not given penicillin before admission. The association with poor outcome may be because children who are more severely ill are being given penicillin before admission.

Introduction

General practitioners in the United Kingdom are currently expected to carry benzyl penicillin in their emergency bags and to administer it parenterally before hospital admission whenever they suspect a diagnosis of meningococcal disease. This guidance reflects the potential of the disease to cause death in a matter of hours and the excess morbidity and mortality associated with delays in treatment. Observational studies that have attempted to assess the impact of such use in clinical practice, however, have reported conflicting results. In 1992 Cartwright et al reported a 40% reduction in case fatality in children given parenteral penicillin before admission. In contrast, two more recent studies from Denmark report a twofold to threefold increase in mortality associated with antibiotics given before admission. We report data that allow further exploration of this important issue.

Methods

From 1997 to 1999 the Royal College of Paediatrics and Child Health (RCPCH) and the paediatric department at Imperial College London conducted a study of 190 fatal cases of meningococcal disease in children in England, Wales, and Northern Ireland. For each case, researchers approached three children who survived meningococcal disease as controls matched by age group (four strata) and region. The parents of 544 children (114 who died, 430 who survived) consented to participate (fig 1). We restricted our analysis to the subset of 158 children (26 who died, 132 who survived) in whom meningococcal disease was diagnosed by general practitioners before admission to hospital and who were therefore eligible to receive penicillin before admission.

We collected and corroborated data from six sources: questionnaires with parents, telephone interviews with general practitioners (conducted by NN), copies of primary care records (including notes made by deputising services), hospital referral letters, and records of complaints made to health authorities. We obtained information about progression of symptoms (from the parent); the severity of the illness and the provisional diagnosis at the general practice consultation at which the referral decision was made (from the medical record or telephone interview with the general practitioner, or both); the severity of the illness at hospital admission (from the hospital case record); and the time delays involved at each stage. When the information from each source differed, we used contemporaneous medical records rather than questionnaires completed after the event.

Severity of illness in general practice was dichotomised and categorised as "severe" if one or more of the following items were present:

- Glasgow meningococcal septicaemia prognostic score (GMSPS) ≥ 6.5
- Complications
- Glasgow coma score (GCS) ≤ 8
- Parenteral penicillin given before admission
- Hospital stay of more than 24 hours
- Death after admission

We report data that allow further exploration of this important issue.
recording in the medical record: 999 or blue light ambulance call; circulatory collapse (on basis of vital signs or statement such as “shocked;” “shut down”); or loss of consciousness. Severity of ill-
ness on hospital admission was assessed by calculating the Glas-
gow meningococcal septicaemia prognostic score (GMSPS) on the
basis of data extracted from the hospital admission record; this
was available for 116 children. Data on complications (renal,
cardiovascular, or respiratory failure; neurological complication;
tissue necrosis requiring excision or amputation) among survivors
were ascertained from hospital records and parents for 108
children.

We used general practice records or the parental question-
naire, or both, to ascertain whether parenteral penicillin was
administered before admission in 152 children. We have
expressed the effects of penicillin and the other factors
considered as odds ratios rather than risk ratios because of
the case-control approach used to identify the cohort. Adjustment of
true odds ratios was done by logistic regression using SPSS
version 12. The factors included in the logistic model were sex,
previous use of oral antibiotics, duration of illness, meningococ-
ral serotype, presence of haemorrhagic rash, presentation with
septicaemia, and severity assessed by the general practitioner.

**Results**

Parenteral penicillin was given to 105 children and not given to
47 children. In six children we could not determine whether
penicillin had been given. The most common reason given by
the general practitioner for not giving penicillin was uncertainty
in the diagnosis (27/47, 57%), mainly because the rash was not
haemorrhagic. Other reasons included penicillin allergy (seven)
and to avoid any delay in hospital admission (six). We could not
ascertain the reason for seven children.

The table shows that penicillin given before admission was
associated with a sevenfold increase in risk of death, after adjust-
ment for identified confounding factors (odds ratio 7.4, 95%
confidence interval 1.5 to 37.7). Fifty seven children (see
methods) who survived experienced complications. The children
who had received penicillin had a higher rate of complications
(5.0, 1.7 to 15.0), as did those children with serogroup C (3.3, 1.9
to 10.4), and those rated by the general practitioner as having
severe disease (2.9, 1.1 to 7.5).

Figure 2 shows the severity of disease when the children
reached hospital according to the time taken to get there and
whether or not the child had already received penicillin.
Children who had received penicillin had more severe disease
(median GMSPS score $6_{4}$, Mann-Whitney U test $P = 0.002$)
than those who did not receive penicillin. In both groups severity
decreased with the time taken to reach hospital. There was no
significant difference, however, in the slope of the regression
lines between children who did and did not receive antibiotics
(test of equal slopes in linear regression, $P = 0.503$).

**Discussion**

Our data confirm results from previous retrospective studies
from Denmark in showing an association between penicillin
treatment in the community and poor outcome. Penicillin is
more likely to be given if the child is extremely unwell, and the
authors of one of the Danish papers explicitly drew attention to
the likelihood of unadjusted confounding by severity. Though
we had more data on severity before admission, the general
practitioner’s assessment of severity was not strongly predictive
of mortality (odds ratio 1.8). This may have been because we had
only two groups classified by severity and vital signs were seldom
recorded by the general practitioner. So one likely explanation
for the high odds ratio we obtained for mortality is that there is a
strong residual selection bias towards giving penicillin to the
most severely ill children. This is supported by the finding that
children who received penicillin had more severe disease as
measured by GMSPS on admission.

An alternative explanation to the increased severity of
disease in the children treated with penicillin is that penicillin
precipitates shock by liberating endotoxin during bacteriolysis
before the child reaches hospital. Though the previous studies
by Brandzaeg et al did not show a rise in plasma endotoxin
concentrations after administration of either penicillin or
chloramphenicol,4 we explored this alternative explanation by
looking at the relation between severity on admission and transit
time. We reasoned that if penicillin increased severity by liberat-
ing endotoxin during bacteriolysis, the severity of disease on
admission would increase with the time taken for the child to
arrive at hospital. We found no evidence of this. There was no
change in the severity of the disease on hospital presentation
with increasing time up to three hours after administration of
penicillin. Furthermore, severity was not increased in children
who did not receive penicillin in periods up to three hours taken
only
to reach hospital. This suggests that a short delay without penicillin is not deleterious.

Why did the original paper by Cartwright et al (and a contemporaneous paper by Strang and Pugh) suggest a positive benefit from penicillin when we and our Danish colleagues show such a clear association with poor outcomes? One contributory explanation for the difference lies in the inclusion or exclusion of children in whom the general practitioner did not make the diagnosis of meningococcal disease and who were therefore unlikely to receive penicillin before admission. If we had included the 166 children who were seen but not diagnosed by general practitioners and who reached hospital at a median of 12 hours later without having parenteral penicillin before admission, the estimated crude odds of death after penicillin would be reduced from 5.96 to 1.45, at the upper limit of the 95% confidence interval of the estimate by Cartwright et al.1

The current discrepancies can be answered only by a randomised controlled trial.

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Research

Amendment

This is version 2 of this article. It incorporates various proofreading changes, none of which alters the findings of the study.

Robert Booy contributed substantially to the design of the original study. Clare Phillips assisted with the data collection.

Contributors: ML designed and oversaw the original study. NN recruited the parents, collected the data and interviewed parents and general practitioners. DM, AH, and RMW obtained funding for the Oxford research team. AH wrote the primary care protocol for this study. RP and MT performed the data analysis. AH and DM wrote the manuscript. RMW, ML, MT, RP, and NN all made contributions to the redrafting. AH is guarantor for the paper.

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Ethical approval: South Thames multi-research ethics committee and all local research ethics committees in England, Wales, and Northern Ireland.


What is already known on this topic

Current guidance to UK general practitioners is to give penicillin to children with suspected meningococcal infection before they are admitted to hospital

What this study adds

Children who receive penicillin before admission have more severe disease on reaching hospital

Children given penicillin may have had more severe disease when they were first seen by a general practitioner

An adverse effect of penicillin in the first hour cannot be excluded, though this cannot be explained by our current understanding of biological mechanisms

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