Towards evidence based medicine for paediatricians

Edited by Bob Phillips

ARCHIMEDES

In order to give the best care to patients and families, paediatricians need to integrate the highest quality scientific evidence with clinical expertise and the opinions of the family. Archimedes seeks to assist practising clinicians by providing “evidence based” answers to common questions which are not at the forefront of research but are at the core of practice. In doing this, we are adapting a format which has been successfully developed by Kevin Macaway-Jones and the group at the Emergency Medicine Journal—“BestBets”.

A word of warning. The topic summaries are not systematic reviews, through they are as exhaustive as a practising clinician can produce. They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature. What Archimedes offers are practical, best evidence based answers to practical, clinical questions.

The format of Archimedes may be familiar. A description of the clinical setting is followed by a structured clinical question. (These aid in focusing the mind, assisting searching and gaining answers.) A brief report of the search used follows—this has been performed in a hierarchical way, to search for the best quality evidence to answer the question. A table provides a summary of the evidence and key points of the critical appraisal. For further information on critical appraisal, and the measures of effect (such as number needed to treat, NNT) books by Sackett and Moyer may help. To pull the information together, a commentary is provided. But to make it all much more accessible, a box provides the clinical bottom lines.

The electronic edition of this journal contains extra information to each of the published Archimedes topics. The papers summarised in tables are linked, by an interactive table, to more detailed appraisals of the studies. Updates to previously published topics will be linked to the original article when they are available.

Readers wishing to submit their own questions—with best evidence answers—are encouraged to review those already proposed at www.bestbets.org. If your question still hasn’t been answered, feel free to submit your summary according to the Instructions for Authors at www.archdischild.com. Three topics are covered in this issue of the journal.

- Does early administration of dexamethasone improve neurological outcome in children with meningococcal meningitis?
- Should nifedipine be used to counter low blood sugar levels in children with persistent hyperinsulinaemic hypoglycaemia?
- Do steroids help children with acute urticaria?

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References

1 Oscar London. Kill as few patients as possible: and 56 six other essays on how to be the world’s best doctor. Ten Speed Press, 1987.
3 Haynes RB. Of studies, syntheses, synopses and systems. EBM J 2001;6(2):34.

REFERENCES


www.archdischild.com
Does early administration of dexamethasone improve neurological outcome in children with meningococcal meningitis?

Report by
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A 6 month old boy was admitted to the paediatric ward with history of fever, non-blanching petechial rash, shrill cry, and poor capillary refill. He required 20 ml/kg of fluid bolus. After a full sepsis screening including a lumbar puncture, he was started on intravenous cefotaxime for a presumed diagnosis of meningococcal meningitis. Next day on the ward around the specialist registrar wondered if a short course of dexamethasone should have been started with the first dose of antibiotic to improve neurological outcome in this child.

Structured clinical question
In children with meningococcal meningitis [patient group] does early treatment with dexamethasone [intervention] reduce the frequency of sensorineural hearing loss or other neurologic sequelae [outcome]?  

Search strategy and outcome
Cochrane Database and Medline using PubMed interface.  
Search words: “meningitis” AND “steroids”; “meningo-coccal” AND “steroids”; “meningitis” AND “dexamethasone”.


Search outcome: 32 hits; four directly relevant to the question; one metaanalysis. See table 1.

Commentary
There appears to be a paucity of studies on the effects of adjunctive therapy with steroids in children specifically with meningococcal meningitis. Earlier studies done in children with bacterial meningitis, suggest improved neurological outcome with dexamethasone. However, the majority of children in these studies had *H. influenzae* meningitis and hence these could not be considered as being representative studies for meningococcal meningitis. These results were reflected in a meta-analysis of randomised control trials assessing improved neurological outcome with dexamethasone in bacterial meningitis. The later study on adults by Thomas and colleagues, which had a mix of patients with pneumococcal and meningococcal meningitis, was inconclusive regarding systematic use of dexamethasone as an adjunctive therapy for bacterial meningitis. Meningococcal meningitis appears to have the lowest risk of major neurological sequelae compared with pneumococcal and *H. influenzae* meningitis. In a multicentre prospective study on 124 children with meningococcal meningitis by Richardson and colleagues, the children treated with steroids actually had a higher incidence of hearing loss (relative risk 1.70). In this population of children, hearing loss was more common in children who had been ill for more than 24 hours (relative risk 2.72; 95% CI 0.93 to 7.98) and hence the authors hypothesise that there is a critical period around second day of illness, during which hearing loss can be reversed, provided appropriate antimicrobial and supportive treatment is commenced.

Pollard and colleagues recommend a two day course of dexamethasone as an adjunctive treatment for children with bacterial meningitis, but admit that no data were available for meningococcal meningitis. None of the studies have stratified their results according to serotype of the causative organism or age group of patients, but the subjects in the paediatric studies were outside the neonatal period. It appears, hence, from the review of current best evidence, that use of dexamethasone as an adjunctive therapy could improve neurological outcome in children with suspected *H. influenzae* meningitis and possibly pneumococcal meningitis. However, its use cannot be routinely recommended in cases of suspected meningococcal meningitis or in any case where the aetiology is uncertain.

**CLINICAL BOTTOM LINE**
- Currently there is not sufficient published evidence to recommend early use of dexamethasone in order to improve neurological outcome in children with meningococcal meningitis. In fact, there is some evidence that its use in such a situation might be disadvantageous as far as hearing is concerned.

**REFERENCES**
Table 1  Dexamethasone in meningococcal meningitis

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type (level of evidence)</th>
<th>Outcome</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>McIntyre et al (1997)</td>
<td>848 children with bacterial meningitis with mean age in studies 1.2 to 7 y</td>
<td>Meta-analysis of 11 randomised controlled trials. Non-randomised studies assessed for adverse effects (1a)</td>
<td>Hearing loss and neurological outcome other than hearing loss</td>
<td>In H influenzae meningitis dexamethasone reduced severe hearing loss (OR 0.31, 95% CI 0.14 to 0.69). Pneumococcal meningitis OR 0.52 (95% CI 0.17 to 1.46). Protection against other neurological deficits was not statistically significant (OR 0.59, 95% CI 0.34 to 1.02)</td>
<td>Authors do not report a method for assessing validity. Difference between subgroups may be observed by chance. Potential publication bias.</td>
</tr>
<tr>
<td>Thomas et al (1999)</td>
<td>60 adult patients with bacterial meningitis</td>
<td>Multicentre, double blind, randomised trial (1b)</td>
<td>Rate of patients cured without clinical neurologic sequelae at 30 days</td>
<td>Rate of cured patients without neurological sequelae was not significant (p = 0.071) between the 2 groups. RRR of severe neurologic sequelae following dexamethasone therapy was 44% (95% CI –57 to 100)</td>
<td>Adult patient groups. First dose of dexamethasone was given within 3 h of first antibiotic dose rather than with or before the dose</td>
</tr>
<tr>
<td>Syrogiannopoulos et al (1994)</td>
<td>118 children aged 2.5 mth to 15 y with suspected or proven bacterial meningitis</td>
<td>Single blind randomised control trial (1b)</td>
<td>Neurological and audiologic assessment at 6 weeks and 4-24 months</td>
<td>No difference in the rate of neurologic and/or audiologic sequelae between 2 groups; RRR –135% (95% CI –11 to 100)</td>
<td>Both groups received dexamethasone</td>
</tr>
<tr>
<td>Schaad et al (1993)</td>
<td>115 children (age 3 mth to 16 y) with suspected or confirmed bacterial meningitis</td>
<td>Double blind randomised control trial (1b)</td>
<td>Neurologic and audiologic test at 3, 9, and 18 months</td>
<td>16% of 55 placebo recipients and 5% of 60 dexamethasone recipients had 1 or more neurologic/audiologic sequelae (p = 0.066); the relative risk of sequelae was 3.27 (95% CI 0.93 to 11.47)</td>
<td>55% of children in control group and 62% in experimental group had H influenzae meningitis</td>
</tr>
<tr>
<td>Odio et al (1991)</td>
<td>101 children aged 6 weeks to 13 years with suspected or proven bacterial meningitis</td>
<td>Double blind randomised controlled trial (1b)</td>
<td>Neurological follow up to 12 months, audiologic follow up to 24 months</td>
<td>Favourable neurological outcome in dexamethasone treated group; RRR 68% (95% CI 11 to 100) with NNT 6. No difference in audiologic sequelae between two groups. RRR 63% (95% CI –13 to 100)</td>
<td>Only 2 patients (4%) in dexamethasone group and none in control group had meningococcal meningitis</td>
</tr>
</tbody>
</table>


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Charles Christoph Roehr, Department of Neonatology, Charité Campus Mitte, Humboldt University, Berlin, Germany; christoph.roehr@charite.de

Should nifedipine be used to counter low blood sugar levels in children with persistent hyperinsulinaemic hypoglycaemia?

Report by Dominik Müller, Department of Pediatric Nephrology, Charité, Humboldt University, Berlin, Germany

A 5 year old boy, suffering from hyperinsulinaemic hypoglycaemia since infancy and arterial hypertension secondary to polycystic kidney disease, was given nifedipine (0.3 mg/kg three times a day) to treat his high blood pressure. Normotension was restored and his blood sugar levels normalised. We wondered whether nifedipine could be used safely as long term treatment to counter hypoglycaemia in persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI)?

Structured clinical question
In a child with persistent hyperinsulinaemic hypoglycaemia of infancy [patient], can nifedipine [intervention] safely be given to treat hypoglycaemia [outcome]?
Search strategy and outcome

Search terms: “persistent hyperinsulinemic hypoglycaemia of infancy” and “hyperinsulinism” and “nifedipine” and “safety” and “calcium antagonist”.

Cochrane Library (nifedipine or persistent hyperinsulinaemic hypoglycaemia of infancy): no relevant study found. PubMed (limits: language English; age 0–18 years): one practice guideline,1 six case reports or patient series of PHHI (persistent hyperinsulinemic hypoglycaemia of infancy): no relevant study found.

Aims to answer our question regarding the medical treatment of PHHI by searching the Cochrane Collaboration’s internet archive of systematic reviews led to no positive result. A search of PubMed revealed no relevant controlled clinical studies. One consensus statement (evidence level 5) by Aynsley-Green and colleagues1 discussed the treatment options for hyperinsulinism in childhood and was available in electronic form: among the standard treatments of PHHI were diazoxide, chlorothiazide, and somatostatin; Ca2+ channel blockers were not regarded a routine treatment due to lack of convincing studies. Since the time of publication of the consensus statement, however, several case reports and case series of nifedipine for PHHI have been published which showed encouraging results.2 4–7

In these studies, nifedipine (either alone or in combination with other drugs or dietary measures) was introduced to avoid complications of diazoxide or somatostatin treatment (abdominal discomfort, vomiting, or anorexia).11 No severe episodes of hypoglycaemia or side effects to nifedipine (hypotension, nausea, dizziness) were reported; the longest period of follow up was eight years. 47 The author of the largest case series7 was contacted and asked about his experience with nifedipine beyond the published cases. No complications in maintaining treatment were reported. A comprehensive review on the use of Ca2+ channel blockers in children convincingly illustrated the safety of nifedipine as long term treatment in childhood.12

Nifedipine has been successfully used to treat PHHI and increasing evidence from case reports suggests that it can safely be given as long term treatment without serious adverse effects. Facing the varied clinical severity of PHHI, it promises to become a valuable treatment option for some children. The mounting evidence from the quoted case reports suggests that nifedipine could be tried in patients failing the standard treatment before pancreatectomy is considered. A large, multicentre, randomised clinical trial

Table 2 Nifedipine in persistent hyperinsulinaemic hypoglycaemia

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type (level of evidence from the Oxford CEBM)</th>
<th>Outcome</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bas et al (1999)</td>
<td>3 infants. Intervention: nifedipine 0.7, 0.5, and 0.8 mg/kg/day</td>
<td>Case series (level 4)</td>
<td>Glycaemic control</td>
<td>Normoglycaemia on therapy, hypoglycaemia after tapering of nifedipine</td>
<td>Challenge–dechallenge–rechallenge studies. Follow up 12 months, side effects not reported (see ref 7)</td>
</tr>
<tr>
<td>Lindley et al (1996)</td>
<td>1 preterm baby. Intervention: nifedipine 0.7 mg/kg/day</td>
<td>Case report (level 4)</td>
<td>Glycaemic control</td>
<td>Blood sugar increased (from 3.5 to 4.8 mmol/l), fasting tolerance from 3 to 10.5 h</td>
<td>Nifedipine introduced after diazoxide, glucagon, steroids, ACTH, and pancreatectomy were unsuccessful</td>
</tr>
<tr>
<td>Suprasongsin et al (1999)</td>
<td>2 infants. Intervention: nifedipine 0.5 and 0.7 mg/kg/day plus raw corn starch 8 g/kg/day</td>
<td>Case series (level 4)</td>
<td>Glycaemic control</td>
<td>Persistent rise in blood sugar from baseline 1.5 mmol/l and 1.9 mmol/l</td>
<td>Follow up of 8 years and 14 months, side effects not reported</td>
</tr>
<tr>
<td>Eichmann et al (1999)</td>
<td>2 infants. Intervention: diazoxide and nifedipine 0.7 mg/kg/day and nifedipine 2 mg/kg/day</td>
<td>Case series (level 4)</td>
<td>Glycaemic control</td>
<td>One patient stable on nifedipine monotherapy, the other stable while diazoxide could be reduced</td>
<td>Very low baseline blood sugar levels: 0.78 mmol/l and 0.96 mmol/l, no side effects to nifedipine reported</td>
</tr>
<tr>
<td>Shanbag et al (2002)</td>
<td>1 infant. Intervention: nifedipine 0.5 mg/kg/day</td>
<td>Case report (level 4)</td>
<td>Glycaemic control</td>
<td>Blood sugar stable on nifedipine monotherapy</td>
<td>Follow up 9 months, no side effects reported</td>
</tr>
<tr>
<td>Darendeller et al (2002)</td>
<td>4 children. Intervention: nifedipine at a median of 0.65 mg/kg/day</td>
<td>Case series (level 4)</td>
<td>Glycaemic control</td>
<td>All stable on nifedipine monotherapy</td>
<td>Follow up 4 mth to 7.3 years. 3 children from previous report included</td>
</tr>
</tbody>
</table>

Commentary

Persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) is the most common cause of persistent hypoglycaemia in infancy.1 In Central Europe it is a rare disorder, occurring sporadically (incidence approx. 1:50000), but has much higher incidences (1:2500 due to a familial form) in parts of the world with high consanguinity (for example, Arabian peninsula or Scandinavia). The majority of cases present in the neonatal period with pronounced hypoglycaemia. Severe long term neurological complications due to prolonged hypoglycaemia are common, hence treatment needs to be commenced immediately. Genetic abnormalities of intracellular metabolic pathways or membrane transport are thought to be the cause of the disorder,1 9 11 and includes constant insulin secretion through abnormally stimulated ATP-sensitive potassium channels and voltage-gated Ca2+ channels of the pancreatic β cell.1 12 Initially, high doses of glucose infusions are required to establish euglycaemia, traditionally followed by a treatment with either diazoxide or long acting somatostatin (octreotide), sometimes combined with dietary measures (high in starch, glucose, or protein).10 Partial to complete pancreatectomy is pursued in patients refractory to medical treatment, but complicated by high incidences of secondary diabetes mellitus later in life.11

Aims to answer our question regarding the medical treatment of PHHI by searching the Cochrane Collaboration’s internet archive of systematic reviews led to no positive result. A search of PubMed revealed no relevant controlled clinical studies. One consensus statement (evidence level 5) by Aynsley-Green and colleagues1 discussed the treatment options for hyperinsulinism in childhood and was available in electronic form: among the standard treatments of PHHI were diazoxide, chlorothiazide, and somatostatin; Ca2+ channel blockers were not regarded a routine treatment due to lack of convincing studies. Since the time of publication of the consensus statement, however, several case reports and case series of nifedipine for PHHI have been published which showed encouraging results.2 4–7
REFERENCES


Do steroids help children with acute urticaria?

Report by
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A 4 year old girl presents with an itchy urticarial rash. There were no other symptoms. Her general practitioner has prescribed an oral antihistamine but the rash has persisted. You wonder if there is a role for oral steroids in this otherwise well child.

Structured clinical question
In a child with acute urticaria [patient], does the addition of oral steroids to antihistamines [intervention] lead to more rapid resolution of symptoms [outcome]?

Search strategy and outcome
Cochrane Database of Systematic Reviews using search term “urticaria”: no relevant results.
Medline 1966 to October 2002 using the OVID interface. (“exp urticaria OR urticaria$.mp” AND “exp steroids OR steroid$.mp OR exp adrenal cortex hormones OR corticosteroids$.mp”) LIMIT to [human AND RCT]. Search results – 21 articles, of which two were relevant.
A further search of Medline without the RCT filter and of SUMsearch using search terms “steroids” and “urticaria” yielded no further relevant results.
See table 3.

Commentary
There are no studies specifically aimed at children with acute urticaria. These limited trials show improvement in symptoms when prednisolone is prescribed, but larger studies are needed. The decision to treat with steroids should be based

Table 3: Steroids in children with acute urticaria

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type (level of evidence)</th>
<th>Outcome</th>
<th>Key result</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollack et al (1995)</td>
<td>43 adult outpatients with acute urticaria given i.m. diphenhydramine then randomised to oral hydroxyzine plus either 20 mg prednisolone 12 hourly for 4 days or placebo</td>
<td>RCT (level 1b)</td>
<td>10 point visual analogue itch score at 48 hours. Itch score at 5 days. Description of rash at 48 hours and 5 days.</td>
<td>Mean 48 hour itch score 1.3 in prednisone group v 4.4 in control group. 5 day itch score 0 in prednisone group v 1.6 in control group.</td>
<td>Adult patients only. Small study, no power calculation. Rash not described at 5 days in control group</td>
</tr>
<tr>
<td>Zuberbier et al (1996)</td>
<td>109 adult and paediatric patients with acute urticaria treated with loratadine 10 mg daily or prednisolone 50 mg daily for 3 days followed by loratadine 10 mg daily until remission of symptoms</td>
<td>Non-randomised prospective cohort study (level 2b)</td>
<td>Days until cessation of whealing</td>
<td>65.9% of had cessation of whealing by 3 days and a further 15.9% by 7 days in loradidine group, compared with 93.8% by 3 days and a further 3.1% by 7 days in the prednisone group. Resolution in all patients after &gt;21 days. NNT with prednisolone for resolution of symptoms by 3 days = 4</td>
<td>Number of children unstated. Different exclusion criteria between groups (potentially pregnant women)</td>
</tr>
</tbody>
</table>
on the potential benefit of decreasing symptom duration in this often self-limiting illness, weighed against the potential adverse effects of therapy. However, no side effects were observed in either study.

REFERENCES
