What intravenous bronchodilators are being administered to children presenting with acute severe wheeze in the UK and Ireland?

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ABSTRACT

During a prospective ten-week assessment period 3,238 children aged 1-16 years presented with acute wheeze to Paediatric Emergency Research in the UK and Ireland (PERUKI) centres. 110 (3.3%) received intravenous bronchodilators. Intravenous (IV) magnesium sulphate (MgSO4) was used in 67 (60.9%), salbutamol in 61 (55.5%) and aminophylline in 52 (47.3%) of cases. In 35 cases (31.8%), two drugs were used together, and in 18 cases (16.4%), all three drugs were administered. When used sequentially the most common order was salbutamol, then MgSO4, then aminophylline. Overall, thirty different IV treatment regimens were used varying in drugs, dose, rate and duration.

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What is the key question?

How are children managed, when presenting with acute severe wheeze in Emergency Departments around the UK and Ireland when it is deemed they need intravenous bronchodilator therapy?

What is the bottom line?

These children are managed with an unacceptable variation in treatment regimen, which highlights the lack of an evidence base.

Why read on?

This paper establishes current practice in the UK and Ireland in this very sick group of children and will be the foundation for the development of further randomised controlled studies to address this paucity of evidence.

INTRODUCTION

Episodes of acute severe wheezing represent a significant proportion of Emergency Department (ED) presentations and hospital admissions. [1] Initial strategies of inhaled β_2 agonists, ipratropium bromide and corticosteroids have a good evidence base [2], but the evidence for second line agents including intravenous (IV) salbutamol, aminophylline, or magnesium sulphate (MgSO4) is less clear. [2] There is conflict in the literature and in practice for the efficacy and optimal treatment regimens [2,3,4], reflected in differences in recommended management between national guidelines.

Our aim was to obtain a snapshot of management of acute wheezing illness in ED to determine: a) the frequency and demographic details of presentations of wheeze to EDs in the UK and Ireland; and b) a detailed assessment of the use of intravenous bronchodilators in each patient.

METHODS

This was a prospective observational multi-centre service evaluation of the management of acute severe wheezing in EDs within the Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI) network. PERUKI is a research collaborative of paediatric-specific and mixed adult and paediatric EDs with an annual census of over 1 million childhood visits. [5] A continuous data set was collected at each site across a 10-week period commencing in March 2013. There were two stages to the data collection:

1) Screening denominator data.

All children aged from 12 months to 16 years who presented with wheeze were screened, and a proforma was completed for all patients.

2) Those receiving intravenous (IV) treatment.

For all presentations resulting in IV therapy, a more detailed proforma exploring severity of illness and management decisions was completed.

Data were double entered and errors addressed, and analysed descriptively using Microsoft Excel 2010 and SPSS V21.

RESULTS

Twenty-four centres contributed to the evaluation. Two sites were unable to collect detailed screening data of all those presenting other than the numbers presenting, and one of those centres were able to provide detailed data on those children who received IV treatment (Table 1). The remaining centres delivered 100% capture rate of data for all those children presenting with acute wheeze during the data collection period.

1) Screening denominator data

During the evaluation 3,238 children presented with acute wheeze (2,008 male; 62%) with a median (IQR) age of 3 (1-5) years. It was the first episode of wheeze for 692 (21.3%) children. 110 (3.3%) children received IV treatment. IV rate varied amongst sites between 0% and 19.4% (Table 1). Children who received IV treatment had significantly lower mean O_2 saturations [91.5% (SD 5.5)] compared to those who did not [95.8% (SD 3.3), mean difference 4.3% (95%CI for the difference 3.2% to 5.4%), p <0.001] (Figure 1). Females (5.5%) were more likely to receive IV treatment compared to males (2.6%) [Chi Squared 6.5; p<0.001]. No nebulised MgSO4 was reported to have been used.

2) Those receiving IV treatment

The 110 children had a median age of 4 years, 63 (57.3%) were female and 11.8% presented with wheezing for the first time. MgSO4 was the most commonly used intravenous bronchodilator, followed by salbutamol and then aminophylline. Details of the most common doses, and dose ranges for each agent are presented in Table 2. The terms 'load' and 'bolus' appeared to have been

used interchangeably, so we used the term 'bolus' if it was not followed by an infusion and used the term 'load' (whatever the dose) if it was followed by an infusion.

(i) Drugs used

MgSO4 was only administered as a bolus (n=67); there was no use of a continuous infusion. Repeated doses of MgSO4 were given in 4 cases; one immediately after the first load and the others 2, 8 and 12 hours later.

For salbutamol (n=61), a load followed by an infusion was the commonest regimen, occurring in 40/61 (65.7%) of cases. 10 (16.4%) children had an infusion only and 11 (18%) only a bolus. There were 22 variations of bolus/load dose and duration.

The commonest aminophylline regimen was a load followed by an infusion 44/52 (85%); 5 (9.6%) children had a bolus only and 3 children received an infusion with no load (Table 2).

(ii) Treatment regimen

57/110 (52%) were managed with one agent only, 35/110 (32%) with two agents and 18/110 (16%) were managed with all three agents. MgSO4 was used with other agents in 53/110 (48.2%) cases and was administered concurrently in 10/53 (18.9%). When used sequentially it was the first drug given in 19/43 (36%) cases. Salbutamol was used with other agents in 43/110 (39%) and was used concurrently in 7/43 (16.3%) cases. When used sequentially it was the first drug of choice in 18/36 (50%) of cases. Aminophylline was used with other agents in 28/110 (25.5%) cases and was used concurrently in 5/28 (17.9%) cases. When used sequentially it was the first drug given in 10/23 (43.5%) cases. When all three drugs were used, the first line agent was most commonly salbutamol 9/18 (50%), others used MgSO4 first line 7/18 (38.8%), with aminophylline being the least common

first line choice in 2/18 (11.1%). The most common order of agents used was salbutamol, MgSO4 and then aminophylline in 10/18 (55.6%) cases.

(iii) Weaning off intravenous treatment

Where infusions were used their duration varied from four to 72 hours. Weaning involved halving the dose before stopping in half the cases, the remainder simply stopped directly from the initial dose when deemed to be clinically unnecessary.

(iv) Disposition

35/110 (31.8%) were managed on an inpatient or observation ward, 66/110 (60.0%) on a Paediatric High Dependency Unit (PHDU), and nine (8.2%) on a Paediatric Intensive Care Unit (PICU) where seven children were intubated and one child died. Non-invasive ventilation was used in 7/110 (6.4%). Most patients who received MgSO4 alone were managed on an inpatient or observation ward, while most who received either aminophylline or salbutamol alone were managed on a PHDU.

DISCUSSION

We have demonstrated wide variation in the clinical management of acute severe wheeze across the UK and Ireland, with variability in the treatement strategies in terms of drug combinations, dosing, and weaning. The small numbers in our study did not allow direct comparison between individual units, nor could we explore the thresholds and rationale behind the initiation of IV treatment. However, those children receiving IV treatment had lower oxygen saturations in air at presentation, compared to those who did not get intravenous treatment thus reflecting their severity (Figure1).

It is well recognised that clinicians vary in their practice when treating acute wheezing. [3,4,6] Whilst practice in mild to moderate disease is broadly similar, marked differences for treating more severe cases are recognised and we have demonstrated that these differences haven't changed over recent years and actually practice appears to have become more varied since the increased use of IV MgSO4. [4] This is likely due to the lack of evidence and conflicting literature underlying the management of severe wheeze in childhood.

This paucity of evidence clearly exists for IV salbutamol. Cochrane reviews considering the benefit of IV salbutamol instead of and in addition to inhaled delivery included few good quality studies in children, and there was insufficient evidence to support the use of intravenous β2 agonists in acute asthma. Despite its common use, the safest and most effective doses for IV salbutamol are unknown. In our study the greatest variation in management was in the doses of salbutamol administered. [2]

There is also conflicting evidence for the use of IV aminophylline. Cochrane reviews of IV aminophylline in adults and children fail to demonstrate any clinical benefit over intravenous β_2 agonists. However, paediatric studies have suggested hastened recovery, a reduced need for ventilation in severe cases, significant reduction in length of hospital stay and improvements in pulmonary function. UK guidelines state that IV aminophylline should be reserved for the most severe cases unresponsive to maximal bronchodilators and steroids. [2]

Current UK recommendations acknowledge that IV MgSO4 is safe, though its efficacy in children has not been established. [2] Meta analyses suggest improvements in short-term pulmonary function and clinical symptoms when used in combination with inhaled bronchodilators and steroids with a greater effect in children than in adults. [7] The evidence for the effectiveness of IV MgSO4 treatment in adults is poor with even the most severe exacerbations gaining only minimal benefit. [8]

Single agents were used in 52% of cases, two agents in 32%, and all three in 16%. There is currently no evidence to inform an optimal approach, and at present none of the widely used guidelines offers direction for practice in terms of combinations and sequences of administration of these agents.

There were marked differences in disposition for IV drug administration and monitoring. Whilst most patients received care on PHDU, one third were managed in observation or inpatient wards. This may have reflected the severity of the exacerbation but it may be that boluses of drugs with no infusion allow children to be nursed on a ward, whereas continuous infusions require higher level care.

A potential limitation of the questionnaire design of this study was ambiguity relating to loading versus bolus dosing, and weaning strategies. Additionally, we were unable to obtain data from some of our participating centres. However, in our study the majority of presentations of wheeze were male, under the age of 5, and many were recurrent attendees. There was a preponderance of girls receiving intravenous bronchodilators. This accords with previous BTS audits of paediatric wheeze [9] and other studies, suggesting face validity of our data. We did not collect data on complications of treatment such as lactic acidosis or hypokalaemia and this is clearly an important area for future studies. [4] This study was a pragmatic examination of what actually happened and we did not define what we meant by severe wheezing nor was the study design planned to evaluate whether it was appropriate to administer the intravenous treatment.

Our study has demonstrated variation in practice across the UK and Ireland in the management of children with acute severe wheeze. There is an urgent need for good quality randomised trials to determine the efficacy, safety profile, and optimal dosing and weaning strategies for commonly used IV therapies, aiming for a clear evidence base for the management of acute severe wheeze in children.

Contributorship: CP and ML conceived the evaluation. CP, ML, ID, ROS, NS, IM developed the methodology and protocol and collected the data. Analysis and initial draft was by IM, CP and ML. ROS, ID, NS provided further comment on the analysis and editing for the final submitted paper.

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Table 2: Intravenous treatments (n = 110)

Drug	Cases used	Most common dose	Dose ranges
$MgSO_4$	67 (60.9%)	Bolus: 40mg/kg over 20 mins (50.7%) Infusion: N/A	Bolus: 5 to 54mg/kg over 20-30 mins Infusion: N/A
Salbutamol	61 (55.5%)	Bolus/Load: 250µg (33.3%) over 5 -15 mins Infusion: 1µg/kg/min (68%)	Bolus/Load: 2µg/kg to 15µg/kg over 5-40 mins Infusion: 0.3 to 5µg/kg/min
Aminophylline	52 (47.3%)	Bolus/load: 5mg/kg over 20-30 mins (96.2%) Infusion: 1mg/kg/hr (62%)	Bolus Load: 10mg/kg to 200mg (total) over 30 mins Infusion: 0.5 to 1.0 mg/kg/hr