AUDIT, RESEARCH AND GUIDELINE UPDATE

Which 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 10-week assessment period, 3238 children aged 1–16 years presented with acute wheeze to Paediatric Emergency Research in the UK and Ireland centres. 110 (3.3%) received intravenous bronchodilators. Intravenous magnesium sulfate ($MgSO_4$) 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 $MgSO_4$, then aminophylline. Overall, 30 different intravenous treatment regimens were used varying in drugs, dose, rate and duration.

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, but that for second-line agents including intravenous salbutamol, aminophylline or magnesium sulfate ($MgSO_4$) is less clear.[2]

Our aim was to evaluate the management of acute wheezing illness in EDs in the UK and Ireland by determining the frequency and demographic details of presentations of wheeze and examining the use of intravenous bronchodilators.

METHODS

This was a prospective observational multicentre service evaluation of the management of acute severe wheezing in EDs within the Paediatric Emergency Research in the UK 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 (see the Acknowledgements section). A continuous data set was collected at each site across a 10-week period commencing in March 2013 which were:

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 treatment

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

Data were double entered and errors addressed and analysed using SPSS V.21.

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 was able to provide detailed data on those children who received intravenous 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.

Screening denominator data

During the evaluation 3238 children presented with acute wheeze (2008 male; 62%) with a median (IQR) age of 3 (1–5) years. It was the first episode of wheeze for 692 (21.3%) children. A total of 110 (3.3%) children received intravenous treatment. Intravenous rate varied among sites between 0% and 19.4% (table 1). Children who received intravenous treatment had significantly lower mean O_2 saturations (91.5% (SD 5.5)) compared with those who did not (95.8% (SD 3.3), mean difference 4.3% (95% CI for the difference 3.2%–5.4%), $p<0.001$; figure 1). Females (5.5%) were more likely to receive intravenous treatment compared with males (2.6%; χ^2 6.5; $p<0.001$). No nebulised $MgSO_4$ was reported being used.

Those receiving intravenous treatment

The 110 children had a median age of 4 years, 63 (57.3%) were females and 13 11.8% presented with wheezing for the first time. $MgSO_4$ 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.

Drugs used

$MgSO_4$ was only administered as a bolus (n=67); there was no use of a continuous infusion. Repeated doses of $MgSO_4$ were given in 4 cases;

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Table 1 Type of emergency department with annual attendance rates along with numbers seen during the data collection period and rate (%) of intravenous treatment administered per centre

ED type	Attendances per year (n)	Numbers screened (n)	Intravenous rate (n)	Intravenous rate (%)
Stand alone CED	47 500	335	13	3.9
Stand alone CED	24 500	93	18	19.4
Stand alone CED	35 000	245	4	1.6
Stand alone CED	31 500	138	6	4.3
Stand alone CED	30 000	109	3	2.8
Stand alone CED	34 000	181	7	3
Stand alone CED	41 000	246	4	1.6
Stand alone CED	45 000	204	9	4.4
Stand alone CED	58 500	204 (no data collected)	No data capture	Not known
Stand alone CED	30 000	96	3	3.1
Stand alone CED	45 000	107	6	2.8
Stand alone CED	50 000	180	3	1.7
Mixed ED with AVS	36 000	117	3	2.6
Mixed ED with AVS	33 500	166	5	3
Mixed ED with AVS	24 000	86 (no data collected)	2 (data collected)	2.3
Mixed ED with AVS	23 000	89	5	5.6
Mixed ED with AVS	26 500	141	10	4.1
Mixed ED with AVS	18 000	6	0	0
Within mixed ED with AVS	25 500	43	1	2.8
Within mixed ED with AVS	24 000	17	1	2.8
Within mixed ED with AVS	20 000	60	1	1.7
Within mixed ED with AVS	35 000	104	5	4.8
Fully separate department adjacent to adult unit but shares resuscitation facilities	38 000	141	2	1.4
General ED with CED open 10.00–22.00	19 500	130	0	0
TOTAL		3238	110	3.33

AVS, audiovisual separation; CED, children's emergency department; ED, emergency department.

one immediately after the first load and the others 2, 8 and 12 h later.

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

The most common 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).

Treatment regimen

A total of 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. $MgSO_4$ was used with other agents in 53 of 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 $MgSO_4$ 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, $MgSO_4$ and then aminophylline in 10/18 (55.6%) cases.

Weaning off intravenous treatment

Where infusions were used their duration varied from 4 to 72 h. 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.

Disposition

A total of 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 where seven children were intubated and one child died. Non-invasive ventilation was used in 7/110 (6.4%). Most patients who received $MgSO_4$ alone were managed on an inpatient or observation ward, whereas 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 of the choice of treatment strategy in terms of drug combinations, dosing and weaning strategies. 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 intravenous treatment. However, those children

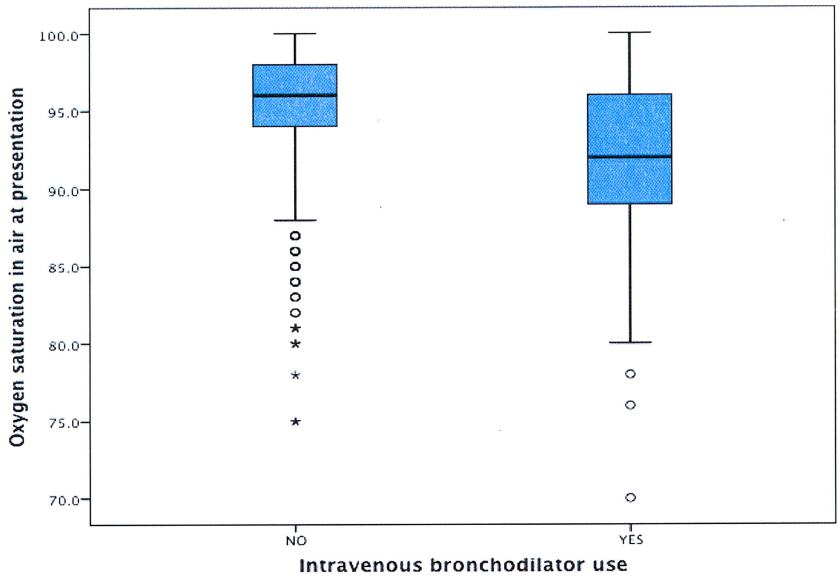

Figure 1 Oxygen saturation in air at presentation for the children presenting with wheeze and administration of intravenous bronchodilator therapy.

receiving intravenous treatment had lower oxygen saturations in air at presentation, compared with those who did not get intravenous treatment thus reflecting their severity (figure 1).

It is well recognised that clinicians vary in their practice when treating acute wheezing. While practice in mild to moderate disease is broadly similar, marked differences for treating more severe cases are recognised.[3] This is likely due to the paucity of evidence and conflicting literature underlying the management of severe wheeze in childhood.

Cochrane reviews considering the benefit of intravenous salbutamol included few good-quality studies in children, and there was insufficient evidence to support the use of intravenous β_2 agonists in acute asthma. Despite its common use, the safest and most effective doses for intravenous salbutamol are unknown. In our study, the greatest variation in management was in doses of salbutamol administered.[2] Cochrane reviews of intravenous 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 intravenous aminophylline should be reserved for the most severe cases unresponsive to maximal bronchodilators and steroids.[2] Current UK recommendations acknowledge that intravenous $MgSO_4$ is safe, although 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.[4]

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 differences in disposition for intravenous drug administration and monitoring. While 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 limitation of the evaluation was that we were unable to obtain data from some of our participating centres but the majority of presentations of wheeze were males, under the age of 5years, and many were recurrent attendees. There was a preponderance of girls receiving intravenous bronchodilators. This accords with previous BTS audits of paediatric wheeze[5] suggesting face validity of our data. We did not collect data on complications of treatment. This was a pragmatic evaluation examining what actually happened; we did not define severe wheezing nor was the study designed to decide 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 randomised trials to determine the efficacy, safety profile and optimal dosing for commonly used intravenous therapies, aiming for a clear evidence base for the management of acute severe wheeze in children.

Table 2 Intravenous treatments (n=110)

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

Correction notice This article has been corrected since it was published Online First. The group 'the PERUKI network' has been added to the end of the author list.

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