Intravenous Magnesium in Acute Paediatric Asthma

Clinical Topic Review for FFAEM Examination

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INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways associated with widespread but variable and reversible airflow obstruction, affecting both adults and children. During an acute asthma attack the inflammatory reaction in the bronchial wall causes oedema and contraction of smooth muscle cells leading to bronchoconstriction. As flow through the bronchioles is related to the fourth power of the radius small changes in the cross-sectional area can result in dramatic changes in air flow. In children the proportional change in flow is greater still as the bronchioles are smaller to start off with.

1.5 million children in the United Kingdom are currently receiving treatment for asthma.[1] The prevalence of children ever diagnosed with asthma is 21%. Acute exacerbations of asthma are a major cause of morbidity and sometimes mortality in children. In the year 2000-01 there were over 27000 children aged 0-14 were admitted to hospital in England with a diagnosis of asthma[2]. Many more present to Emergency Departments (EDs) and Paediatric Emergency Departments (PEDs).

The mainstays of treatment for acute asthma are bronchodilators, usually $beta_2$-agonists that act rapidly to reverse smooth muscle contraction within the airways and corticosteroids, which reduce mucosal inflammation in the airways over a period of hours.

For patients who present with severe symptoms and in those who do not respond to initial treatments additional therapies are required. Traditional second line treatments such as intravenous aminophylline or intravenous salbutamol have been the subject of much debate[3].While shown to be individually better than placebo there have been few trials of good design comparing them head to head. The small numbers of patients involved mean that while showing a trend towards greater efficacy for aminophylline this has not been statistically significant.[4] Both intravenous salbutamol and in particular intravenous aminophylline have major side effects and toxicity. Side effects of salbutamol include tremor, headache, tachycardia and hypokalaemia. Aminophylline has a very narrow therapeutic index and toxic effects include nausea, headache, dysrrhythmias and convulsions.[5]

In recent years there has been growing interest in the use of another treatment for acute asthma. Pabon et al first described the use of magnesium sulphate infusions in children with status asthmaticus in 1994[6] . Intravenous magnesium sulphate was incorporated into the British Thoracic Society (BTS) guidelines for acute asthma in 2003, to be used at a dose of 1.2-2g over 20 minutes in adults with moderate to severe asthma failing to respond to nebulized $beta_2$-agonists or in those with life-threatening or near fatal asthma. However in the paediatric population the BTS guidelines state that “Intravenous magnesium sulphate is a safe treatment for acute asthma although its place in management is not yet established… Studies of efficacy for severe childhood asthma unresponsive to

more conventional therapies have been inconsistent in providing evidence of benefit."[7]

Magnesium is the second most abundant intracellular cation and is a cofactor in many enzymatic reactions. It antagonises the influx of calcium into cells needed for smooth muscle contraction thereby producing smooth muscle relaxation and bronchodilation. Magnesium is also thought to reduce the breakdown of mast cells, reducing the release of histamine and other inflammatory mediators such as leukotrienes that can cause bronchoconstriction.

Reported side effects of magnesium include flushing, hypotension, CNS and myocardial depression.

While children are not simply small adults, the pathological processes that occur in acute asthma are similar across age groups and other pharmacological treatments used are the same in both the adult and paediatric population. Why then has intravenous magnesium sulphate not been widely adopted or recommended for the treatment of acute asthma in children? Is there evidence that magnesium is not beneficial, or indeed even harmful to this group of patients, or is there simply a lack of evidence?

3-part question

In [children with acute asthma presenting to an Emergency Department] does

[the addition of intravenous magnesium to conventional treatment] lead to

[improved clinical outcome]?

METHODS

Search strategy

Medline database using Ovid interface 1966-present

[exp MAGNESIUM SULFATE/ or exp MAGNESIUM/ or magnesium.mp or MAGNESIUM COMPOUNDS]

AND [exp ASTHMA/ or asthma$.mp or exp Status Asthmaticus]

AND [paediatric filter[a]]

LIMIT to human AND English

Embase database using Ovid interface 1980-present

[exp MAGNESIUM/ or exp MAGNESIUM SULFATE/ or exp magnesium derivative or magnesium.mp]

AND [exp ASTHMA/ or asthma$.mp or exp Asthmatic State/]

AND [paediatric filter[a]]

The Cochrane Database of Systematic Reviews was searched for relevant studies.

References of all papers identified were scrutinised for any other possibly relevant trials

Trials were included which looked at children with acute asthma in an ED or PED setting or equivalent in which they were randomized to intravenous magnesium or placebo, or meta-analyses of these groups. Case reports and series were not included in this review.

RESULTS

Nine relevant papers were identified and are tabulated below

Randomised Controlled Trials

Author, date and country	Patient Group	Intervention	Study Type	Outcome Measures	Key Results	Study Weaknesses
Ciarallo L et al USA 1996[8]	31 children in urban PED aged 6 to 18 years	25mg/kg IV MgSO4 vs placebo	PRCT	PEFR	Percentage improvement in PEFR at 110 mins 59% Mg group vs 20% placebo (p=0.05)	Power study performed but insufficient numbers enrolled due to change in policy regarding iv access Magnesium group had significantly lower FEV1 at baseline
				FEV_1	Improvement in FEV_1 at 110 mins 75% Mg group vs 5% placebo (p=0.01)	
				FVC	Improvement in FVC only significant at 80 mins	
				Admission to hospital	4/15 Mg patients discharged vs 0/16 placebo (p=0.03)	
Devi PR et al India 1997[9]	47 children aged 1-12 years in PED	IV MgSO4 0.2ml/kg of 50% solution vs placebo (equivalent to 100mg/kg)	PRCT	PEFR	PEFR >70% predicted at 11hrs in 8/15 Mg group vs 2/16 placebo (p<0.05)	No power study Little detail about other drugs given

				Asthma Score[c]	Asthma scores lower in Mg group at 1,2,3 and 11 hrs (p<0.01)	
Gurkan F et al Turkey 1999[10]	20 children aged 6-16 in PED with acute severe asthma	40mg/kg IV MgSO4 (maximum 2g) vs placebo	PRCT	PEFR	At 90 mins PEFR in Mg group improved by 43% vs 14.6% (p<0.0002)	Small numbers No power study
				Asthma score	Asthma score at 90 minutes better in magnesium group 2.5 vs 5.8 (p=0.005)	
Scarfone et al USA 2000[11]	54 children aged 1-18 yrs in PED with moderate to severe asthma	75mg/kg IV MgSO4 (maximum 2.5g) vs placebo	PRCT	Pulmonary Index Scores[b]	No significant difference in change in pulmonary index score between groups or in time to meet discharge criteria (p=0.39)	Entry criteria changed during winter months to over 2 yrs Magnesium group significantly older (p=0.04)
				Hospitalisation rates		
				Time to discharge		
Ciarallo L et al USA 2000[12]	30 children aged 6 to 17.9 years in 2 urban PEDs	40mg/kg IV MgSO4 (maximum 2g) vs placebo	PRCT	PEFR	Mg group at 110 mins improvement in PEFR 25.8% vs 1.9% (p<0.001)	Patients unable to perform spirometry excluded
				FEV_1	FEV_1 improvement in Mg group at 110 mins 24.1% vs 2.3% (p<0.001)	
				FVC	FVC improvement in Mg group at 110 mins 27.3% vs 2.6% (p<0.001)	

				Admission to hospital	Mg group 8/16 discharged vs 0/14 placebo (p<0.00)	

The placebo treatment used in all studies was normal saline

Systematic Reviews

Author, date and country	Patient Group	Intervention	Study type	Outcome Measures	Key Results	Study Weaknesses
Rowe et al Canada 1999[13]	Adults and children presenting to ED with acute asthma	Magnesium vs placebo	Systematic review	Admission to hospital Pulmonary function tests Vital signs Adverse outcomes and side effects	No statistically significant benefit of magnesium found overall Sub-group analysis suggested benefit in severe group. No difference between adult and paediatric results	Heterogenous study groups of both adults and children.
Alter et al USA 2000[14]	Adults and children in ED with acute bronchospasm	Adjuvant bolus iv magnesium therapy	Meta-analysis	PEFR	Overall improvement in PEFR of 16% of a SD	Adults and children included. COPD included. Error in converting reported dosage of magnesium from ml/kg to mg/kg
Markowitz USA[15]	Children with status asthmaticus	Administration of iv magnesium sulphate	Short-cut review	Hospital admission	¾ studies found had significant reduction in hospital	Search strategy missed paper

					admission rate	

DISCUSSION

There have been several double-blinded prospective randomised controlled trials comparing the use of intravenous magnesium with placebo in children. All have used small numbers of patients with a total of 182 children aged from 1 to 18 years studied. Of the 5 papers found, four showed benefit from IV magnesium[8-10,12] while one found no difference[11]. Of particular note, none of the studies described any harm or major side effects from the administration of magnesium.

Enrolment Criteria

The enrolment criteria varied between the studies. Four papers attempted to confine the study group to children with severe asthma by recruiting children who had not had a satisfactory response to nebulized beta-2-agonists but this was done in different ways. Devi et al[9] included children who had an “inadequate or poor response” (unspecified) to 3 doses of nebulized salbutamol every 20 minutes for 1 hour. Ciarillo in 1996[8] enrolled children who after 3 nebulized beta-2-agonists (unspecified) had PEFR less than 60% predicted. In 2000 the entry criteria used by her team[12] were PEFR less than 70% predicted after 3 nebulized beta-2-agonists (salbutamol or ipratropium or both). Gurkan et al[10] randomised children who had PEFR less than 60% predicted after 3 doses of nebulized salbutamol 0.15mg/kg per dose (max 5mg/dose). All 4 of these studies showed significant improvements in PEFR in patients treated with magnesium.

Using PEFR as part of the enrolment criteria may introduce selection bias as very young children and those with the most severe asthma will be able unable to perform the test.

The one study in this review (Scarfone et al[11]) which did not show any significant improvement in the magnesium group enrolled children with moderate to severe asthma, defined as a pulmonary index score of 8 to 13 and intravenous magnesium sulphate was commenced at the end of the first nebulized salbutamol (0.15mg/kg) treatment. All patients then got either iv magnesium or placebo plus nebulized salbutamol every 30 minutes until 5 nebulized treatments had been administered. Therefore this study included children who may have responded well to inhaled bronchodilators and not required any further treatment. It may be that the benefits of magnesium are confined to that subgroup of children who do not have a good response to nebulized beta-2-agonists and in whom an additional route of bronchodilation is necessary and this is masked in this study.

The exclusion criteria varied slightly between the studies but all excluded patients with significant pyrexia, hypotension or chronic cardiac, renal or pulmonary disease other than asthma. Unfortunately none of the studies included a CONSORT diagram[14] or other details of the patients who were not included which makes it hard to assess if there was any recruitment bias.

Sample size

Scarfone et al[11] described performing a power calculation and needed to recruit 34 patients to have 80% power to detect an improvement of 2 in the Pulmonary Index score. The investigator felt from previous experience that an improvement of 2 in PI score was clinically significant. They in fact recruited 54 patients.

Ciarillo et al[8] in 1996 performed a power calculation and needed 40 children to have 80% power in finding a 25% difference in PEFR. They only recruited 31 patients thus underpowering their work. The explanation they give is that IV access was used less frequently in the PED during the course of the study and so impaired the rate at which eligible patients were enrolled. In 2000 her team again calculated that they needed 40 patients. This time an interim analysis of the first 30 patients suggested clinically important differences between the two groups and so enrolment was stopped after 38 patients.

Gurkan[10] and Devi[9] did not report any power calculations but did find statistically significant treatment effects.

Dose of magnesium

Different doses of magnesium were used in these studies from 25mg/kg to 100mg/kg. The greatest improvement compared with the control group was at a dose of 40mg/kg, used by both Gurkan[10] in 1999 and Ciarillo[12] in 2000. The study

by Scarfone[11] that failed to show a difference between IV magnesium and placebo used a higher dose of 75mg/kg. However the study which used 100mg/kg by Devi[9] found significant benefit from magnesium. It would be interesting to see the results of a trial which randomised patients to different doses of intravenous magnesium sulphate to try and ascertain the optimum dose.

Other drugs used

All the studies used nebulized beta-2-agonists in addition to magnesium or placebo and steroids (Ciarillo 1996 and 2000 2mg/kg iv methylprednisolone if not already on steroids, Scarfone 1mg/kg iv methylprednisolone, Gurkan[10] 2mg/kg methylprednisolone, Devi[9] type, route and dosage unspecified). In Devi's study[9] all patients also received iv aminophylline. The other studies excluded patients taking theophyllines. There are no studies comparing iv magnesium sulphate with iv aminophylline (the current recommended first line intravenous treatment) so while magnesium appears to be beneficial it is not possible to state whether it should be in addition to or instead of aminophylline.

Outcome measures

A variety of outcome measures were used in the different studies. Because there is a relatively small amount of work published on this topic all outcome measures used by investigators were considered. Peak expiratory flow rate (PEFR) is a

commonly used test in Emergency departments and if performed properly is a good indicator of severity of asthma but as mentioned above cannot be used in the very young or the very severe cases.

Other spirometry measures such as forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) are not routinely used in clinical practice in the assessment of asthmatic children in the ED in the UK.

The need for hospital admission is certainly a relevant clinical outcome. However asthma can be very labile and in current UK practice I think there are few that would advocate sending home children with acute severe asthma who have failed to respond to several salbutamol nebulizers no matter how effective a second line treatment is. It may be that in the PEDs where these studies have been carried out there are facilities to observe and manage children for longer than the four hours available in most UK Emergency Departments.

Reviews and meta-analyses

Rowe et al[13] performed a systematic review of the use of magnesium sulphate in the treatment of acute exacerbations of asthma in the ED. They found no difference overall in hospital admission rates between magnesium and placebo but sub-group analysis suggested benefit in the group with severe asthma. They looked at both adults and children and while age was one of the sub-groups

examined there is little detail given, just a comment that for pooled admission rates children improve similarly to adults who have severe asthma. This review was carried out in 1999, therefore excluding the 2000 studies by Ciarillo[12] and Scarfone[11] and missed the study by Gurkan[10] published during 1999. Its findings are of limited utility in light of this.

In Alter's meta-analysis[14] a thorough search strategy was employed which included both adult and paediatric patients. However their inclusion criteria was bronchospasm rather than asthma, because they felt it can be difficult for the clinician to identify the cause in an emergency situation and so chronic obstructive pulmonary disease (COPD) patients were considered together with asthmatics. It is debatable whether results of studies in adults with asthma can be extrapolated to children with asthma, but certainly adults with COPD are a very different group of patients from asthmatic children. They found a pooled post-treatment effect size of 0.162 for patients treated with intravenous magnesium sulphate. A sensitivity analysis suggested that the findings in adults were robust when the paediatric studies were excluded but there was no sub-group analysis done for paediatric patients. This meta-analysis was published in 2000 and only looked at the two earliest studies in children by Ciarillo[8] in 1996 and Devi[9] in 1997. They made a mistake in reporting the dose of magnesium sulphate used in Devi's study as 10mg/kg. The study used 0.2ml/kg of 50% magnesium sulphate solution which is equivalent to 100mg/kg.

Markovitz[15] in his short-cut review tried to address the question of whether administration of iv magnesium reduced hospital admission in patients with status asthmaticus and found 3 out of 4 studies had significant reduction in need for admission. His search strategy was limited and it missed the paper by Gurkan[10]. All the studies looked at need for admission as either a primary or secondary outcome. As mentioned above this has some limitations when applied to UK practice.

Implications for Practice

Most ED physicians in the UK are familiar with using intravenous magnesium sulphate to treat adults with acute severe asthma, dysrhythmias or eclamptic seizures. In contrast for most paediatricians it will be an unfamiliar drug. Most children with acute severe asthma are managed jointly by emergency physicians and paediatricians. If the use of intravenous magnesium in these patients is to be introduced it will need to be led by emergency physicians for whom the change in practice will not seem as great. The evidence will need to be presented to clinicians to support the change and ultimately incorporated into national guidelines such as those produced by the British Thoracic Society.

Conclusion

There are several small but well conducted studies examining the use of intravenous magnesium in children with acute asthma. There is a definite

evidence of benefit from this treatment in terms of statistically significant improved pulmonary function tests and reduced hospital admissions. Importantly there is no suggestion of harm from this treatment. Larger studies of children which are adequately powered and a formal meta-analysis of paediatric studies are needed. In addition further work is needed to clarify the optimum dosage of intravenous magnesium sulphate and whether it should be used in place of or in addition to currently recommended treatment. However given the current evidence available I feel that intravenous magnesium is a treatment worth using in children with acute severe asthma who are failing to respond to nebulized beta-2-agonists.

Appendix A

Paediatric filter

BestBETs Paediatric filter (maximally sensitive) 2003 updated version for MEDLINE OVID interface. [15]

1 exp Adult Children/
2 exp Adolescent/
3 exp Child/
4 exp Child, preschool/
5 exp Infant/
6 exp Infant, newborn/
7 exp Infant, low birth weight/
8 exp Infant, small for gestational age/
9 exp Infant, very low birth weight/
10 exp Infant, postmature/
11 exp Infant, premature/
12 exp Child of impaired parents/
13 exp Child, abandoned/
14 exp Child, exceptional/
15 exp Child, gifted/
16 exp Child, unwanted/
17 exp Minors/
18 exp Adolescent hospitalized/
19 exp Adolescent institutionalized/
20 exp Child hospitalized/
21 exp Child institutionalized/
22 exp Homeless youth/
23 exp Disabled children/
24 exp Pediatrics/
25 or/1-24
26 child$.mp.
27 paediatric$.mp.
28 pediatric$.mp.
29 perinat$.mp.
30 neonat$.mp.
31 newborn$.mp.
32 infan$.mp.
33 bab$.mp.
34 toddler$.mp.
35 boy$.mp.
36 girl$.mp.
37 kid$1.mp.
38 schoolage.mp.
39 juvenil$.mp.
40 underage$.mp.
41 teen$.mp.
42 offspring.mp.

43 youth$.mp.
44 pubescen$.mp.
45 adolescen$.mp.
46 or/26-45
47 25 or 46
48 infan$.jw.
49 child$.jw.
50 pediatric$.jw.
51 paediatric$.jw.
52 adolescen$.jw.
53 or/48-52
54 47 or 53

Appendix B

Pulmonary Index Scores

Score	Respiratory Rate (breaths/min)*	Wheezing	Inspiratory / Expiratory Ratio	Accessory Muscle Use	Oxygen Saturation %
0	<= 30	none	2:1	none	99-100
1	31-45	End expiration	1:1	+	96-98
2	46-60	Entire expiration	1:2	++	93-95
3	>60	Inspiration and expiration without stethoscope	1:3	+++	<93

Appendix C

Clinical Asthma Score

Score	RR*	Wheeze	Accessory Muscle Use	Dyspnea
0	<30	nil	nil	nil
1	31-45	mild	mild	mild
2	46-60	moderate	moderate	moderate
3	>61	severe	severe	severe

*For patients >6 <=20 score 0, 21-35 score 1, 36-50 score 2, .50 score 3

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