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IN SILICO ADMET PROFILING AND CLINICAL COMPARISON OF MAGNESIUM SULFATE ADMINISTRATION ROUTES IN PEDIATRIC ACUTE SEVERE ASTHMA

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Abstract

Purpose: *Intravenous (IV) magnesium sulfate (MgSO4) is used as adjunct therapy to treat acute asthma exacerbations. Despite its clinical use, there is a limited understanding of the disposition of magnesium in children.*

Methods: *To explore the pharmacokinetics (PK) of IV MgSO4 in this population, we collected retrospective data from 154 children who received IV MgSO4 for treatment of an acute asthma exacerbation at Primary Children's Hospital in THQ hospital Yazman, Bahawalpur, Punjab, Pakistan. These data were analyzed using population PK modeling techniques in Swiss ADME, PKCSM to determine sources of variability affecting the disposition of magnesium, as well as to predict the dose of IV MgSO4 needed to achieve clinical benefit. Results The covariate analysis found that only weight was a significant predictor of magnesium concentrations in children. Estimated model parameters suggested that magnesium ex hibits a short serum half-life (2.7 h) in children. The average endogenous magnesium concentration (priortoadministration of IV MgSO4) was estimated to be 21 mg/L. Simulated data suggested that doses between 50 and 75 mg/kg are required to achieve concentration-time profiles within a hypothesized target therapeutic range between 25 and 40 mg/L.*

Conclusions: *Both intravenous (clinical) and pharmacokinetics (ADMET) $MgSO_4$ resulted in clinically meaningful improvement in children with acute severe asthma when used as adjuncts to guideline-based therapy. IV $MgSO_4$ demonstrated stronger clinical efficacy but was associated with more systemic side effects, whereas nebulized $MgSO_4$ offered a more favorable safety profile. These findings contribute critical local evidence to support context-appropriate guideline development for the management of paediatric ASA in Pakistan.*

INTRODUCTION

The prevalence of asthma is rising and the number of deaths from asthma has increased.[1] Asthma affects 1 in 12 US children aged up to 17 years of age.[2]In Pakistan, asthma is a common respiratory disease in all age groups. Recent decades have seen lots of improvement in asthma care in the

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shape of inhalers and better delivery of medications but local data suggests that hospitalizations have increased 8-folds in that time.[3] A two-stage community-based representative cross-sectional survey conducted in Karachi from March 2012 to April 2013 among children revealed that prevalence of asthma among study participants was 10.2%.[4] Acute severe asthma (ASA) is a life-threatening medical emergency characterized by episodes of increasing cough, wheezing, chest recession and inability to speak or drink, resulting in respiratory failure if not managed in time.[5] ASA in children is the 3rd most common cause of hospital admission and one of the most common causes of Paediatric intensive care unit (ICU) admission.[6] Common triggers of ASA are viral infections, allergens (cockroaches, dustmites, pollens and molds), air pollution and tobacco smoke.[7,8]

Standard treatment of ASA is use of inhaled short-acting β2 agonists (salbutamol), systemic corticosteroids and supplemental oxygen.[8] The standard therapies initially performed to relieve bronchial obstruction and reduce inflammation include oxygen, nebulized β2- agonists, anticholinergic agents and systemic corticosteroids, which are usually adequate for many patients. However, a limitation of these therapies is that between 19-50% of patients exhibit only a partial response and require additional treatment.[9] For critically ill patients, a smooth muscle relaxant, such as aminophylline or MgSO4, may be necessary to alleviate bronchospasm. For several decades, aminophylline has been a popular agent for the treatment of serious acute asthma attacks in developing countries. However, due to its narrow therapeutic range, aminophylline is not recommended in the asthma relief Global Initiative for Asthma (GINA) report. Instead, nebulized MgSO4 is recommended as an optional therapy for severe acute asthma exacerbation.[10]

Currently, $MgSO_4$ is available in two forms, intravenous and aerosolized, for the treatment of acute asthma. Shan reported that, combined with β2-agonists and systemic steroids, intravenous $MgSO_4$ improved pulmonary function and reduced hospital admission rates in children.[11] However, magnesium infusion increases blood magnesium levels, and therefore, can cause adverse effects, which has diminished the popularity of intravenous $MgSO_4$. In order to reduce magnesium toxicity, nebulized $MgSO_4$ was developed. Although this regimen has been confirmed to be effective in adults with severe asthma, little research has been conducted on the effects of nebulized MgSO4 in pediatric patients.[12-15] A study from Thailand analyzing efficacy of nebulized magnesium sulfate and intravenous magnesium sulfate in children with severe acute asthma revealed that there was no statistically significant difference between nebulized magnesium sulfate (n=15) versus intravenous magnesium sulfate (n=13) in terms of asthma severity score at 4-hours (2.73+0.70 vs. 2.92+1.04, p=0.572).[16] Alter HJ et al[17] found intravenous $MgSO_4$ to results in improvement in spirometry airway functions by 16% in severe acute asthma while Zannat-ul-Sarmin et al from Bangladesh[18] found increase in peak expiratory flow rate (PEFR) by 35.1% with nebulized $MgSO_4$. A metal analysis comparing intravenous and magnesium sulfate for the treatment of acute asthma in children revealed that Intravenous magnesium sulfate treatment was associated with significant effects on respiratory function (standardized mean difference, 1.94; 95% confidence interval [CI], 0.80-3.08; P = 0.0008) and hospital admission (risk ratio, 0.55; 95% CI, 0.31-0.95; P = 0.03) while nebulized magnesium sulfate treatment showed no significant effect on respiratory function (standardized mean difference, 0.19; 95% CI, -0.01-0.40; P = 0.07) or hospital admission (risk ratio, 1.11; 95% CI, 0.86-1.44; P = 0.42).[19]

Due to the benefits in patients that present early, the GINA guidelines recommend the use of $MgSO_4$ in children aged over 2 years with very severe illnesses.[10] However, there is still inadequate information on the use of $MgSO_4$ therapy for the treatment of acute asthma in Pakistan. To the best of our knowledge, no previous research has been done in Pakistan to compare the efficacy of nebulized versus intravenous $MgSO_4$ in children

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with severe acute asthma. The findings of my study are thought to help clinicians decide that which drug is better in our Pakistani population so that it can then be opted in routine practice for management of acute severe asthma in children in order to reduce the morbidity and mortality of the patients.

Asthma is the most common chronic illness in children, affecting >6 million children in the United States.[20] In 2014 to 2015, of all emergency department (ED) visits in the United States, 9.5% had an asthma diagnosis documented in the medical record; the largest proportion of these patients were children aged 5 to 17 years (13%).[21] 2 Each year, asthma accounts for >700,000 ED visits by children and 2% to 5% of all pediatric hospitalizations.[22,23]

In this study, we provide an up- to- date overview of the ED diagnosis and treatment of children with acute asthma exacerbations. Optimal treatment in the ED can improve patient outcomes, including both reducing ED length of stay and hospital admission rates.[24-27] The study focuses on ED treatment and reflects the literature and guideline recommendations through 2019. We begin with a brief discussion of the clinical presentation of asthma in children, the differential diagnoses, and the scoring tools available to aid in the assessment of severity. We then review the ED treatment of asthma, with a focus on the most well-supported therapies. We conclude with general guidelines to determine patient disposition.

Asthma is a chronic lower respiratory tract disease characterized by a combination of airway inflammation, bronchoconstriction, bronchial hyperresponsiveness, and variable outflow obstruction. In patients with asthma, inflammatory cell activation leads to airway edema and hypersecretion of mucous, and, if sufficiently chronic and severe, may progress to airway remodeling and persistent narrowing.[28] An acute, severe asthma exacerbation unresponsive to repeated administration of inhaled β- agonists may be life- threatening if untreated.

Young children can be particularly difficult to diagnose with asthma because wheezing can be caused by a variety of etiologies, most commonly respiratory viral infections. Rather than formally diagnosing children with asthma, ED clinicians are tasked with determining when to initiate treatment for a possible or likely asthma exacerbation. ED clinicians must use a combination of history and physical exam findings to determine when to start treatment while looking for alternative diagnoses if patients are not improving. A hallmark of asthma is recurrent exacerbations. Characteristic features of exacerbations include wheezing, cough, shortness of breath, and chest tightness. Caretakers may report a worsening of symptoms at night and fatigue or poor sleep, especially in school- age children. Exacerbations are often triggered by respiratory infections, creating considerable overlap between symptoms of an isolated viral lower respiratory tract infections and asthma. Other common triggers include inhaled irritants such as tobacco smoke, exposure to environmental allergens, or changes in weather.[28]

Wheezing is the most common physical finding associated with asthma and is included on almost all published scoring tools for the assessment of asthma in children.[29] Wheezing should not be used in isolation. Wheezing is notably absent in many severe exacerbations as a result of a lack of airflow.[30] Wheezing may also be caused or mimicked by other disease processes. Wheezing is a high-pitched, continuous noise that is most often expiratory. Wheezing should not be confused with stridor, which is also high pitched but primarily inspiratory, or stertor, which is more variable in pitch and respiratory phase and is primarily associated with nasal congestion and discharge. Wheezing has good reliability in controlled studies of children with asthma and pneumonia.[30-32] In clinical practice, however, the assessment of wheezing is likely to be less valid and reliable when using loudness and focality to determine severity. Physical examination should focus on a child's mental status and respiratory effort. Particular attention should be paid to a

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child's mental status a fussy, crying child is more reassuring than a quiet, listless child, which should alert the clinician to the possibility of more severe disease. On examination, children may have increased work of breathing which manifests as nasal flaring, facial pallor, grunting, head bobbing, and retractions. The expiratory phase may be notably prolonged and is usually associated with intercostal retractions and wheezing. In contrast, prolonged inspiration and sternal retractions are physical examination findings more consistent with an upper airway obstruction and should not be confused with a severe asthma exacerbation.

In this study, differential diagnoses were systematically evaluated to ensure accurate identification of acute severe asthma and to exclude conditions with overlapping respiratory presentations. Acute illnesses such as anaphylaxis, bronchiolitis, pneumonia, and foreign-body aspiration were recognized through hallmark findings including urticaria and edema, febrile upper-airway symptoms, focal wheeze, and unilateral auscultatory abnormalities. Chronic or recurrent disorders including aspiration syndromes, anatomic airway malacias, bronchopulmonary dysplasia, cystic fibrosis, and primary ciliary dyskinesia were distinguished by persistent respiratory symptoms, recurrent pneumonias, feeding difficulties, and poor growth. Cardiac disease presenting with tachycardia, hepatomegaly, cyanosis, or feeding intolerance was also carefully excluded. This structured diagnostic approach allowed clear delineation between true asthma exacerbations and other respiratory pathologies, thereby strengthening the validity of subsequent treatment comparisons and improving the reliability of clinical outcome interpretation.

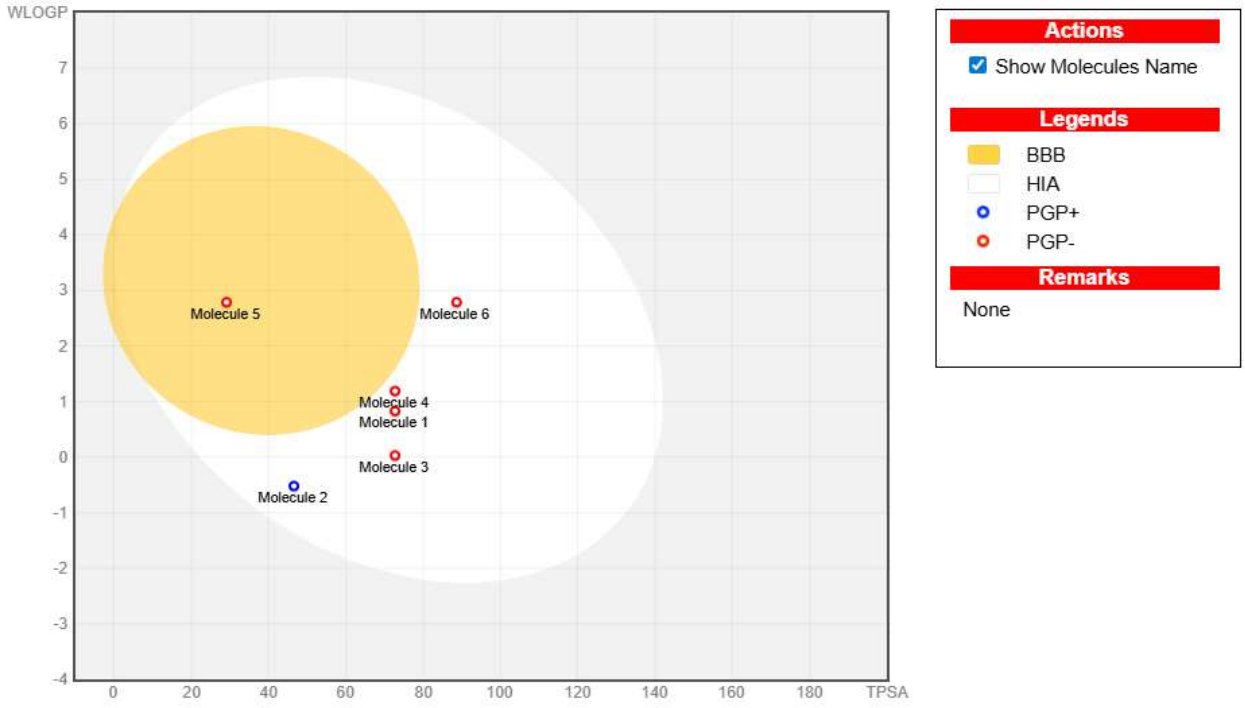

Figure 1: BOILED Egg diagram of different Drugs

Table 1: Exemplary pharmacokinetics (ADMET) analysis of Drugs in Asthma

Drugs	2D Structure	3D Structure	SMILES

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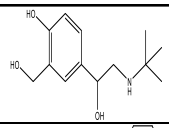
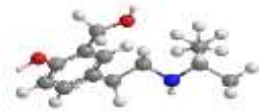
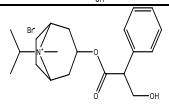
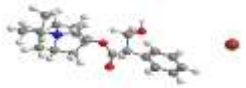
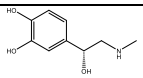
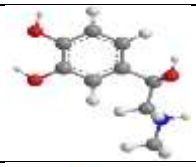
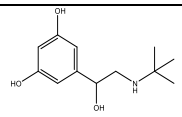
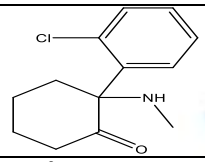
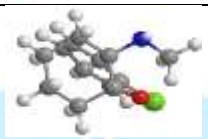
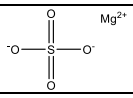
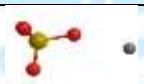
Salbutamol			CC(C)(C)NCC(C1=CC(=C(C=C1)O)CO)O
Ipratropium bromide			CC(C)[N+]1(C2CCC1CC(C2)OC(=O)C(CO)C3=CC=CC=C3)C.[Br-]
Epinephrine			CNC[C@@H](C1=CC(=C(C=C1)O)O)O
Terbutaline			CC(C)(C)NCC(C1=CC(=CC(=C1)O)O)O
Ketamine			CNC1(CCCCC1=O)C2=CC=CC=C2Cl
MgO4S			[O-]S(=O)(=O)[O-].[Mg+2]

2: Methodology

2.1. Clinical Study Design and Patient Selection

This study adopted a prospective observational clinical design to evaluate the therapeutic efficacy of intravenous magnesium sulfate ($MgSO_4$) compared with standard bronchodilators in children presenting with acute severe asthma. Eligible participants were aged 1–18 years and fulfilled the Global Initiative for Asthma (GINA) criteria for severe exacerbation, including marked respiratory distress, persistent wheezing, and reduced air entry despite initial β_2-agonist therapy. Patients were screened immediately upon presentation to the emergency department. Written informed consent was obtained from caregivers. All enrolled children received standardized first-line therapy (inhaled albuterol ± ipratropium and systemic corticosteroids), followed by escalation therapy with IV $MgSO_4$ where clinically indicated. Clinical severity was quantified using validated scoring tools PASS, PRAM, AAIRS, and PAS—at baseline, 1 hour, and 4 hours post-intervention, enabling objective comparisons of therapeutic response, hospitalization risk, and need for intensive care.

2.2. Differential Diagnosis and Clinical Evaluation Strategy

A structured diagnostic framework was applied to distinguish acute asthma exacerbation from other pediatric respiratory conditions with overlapping symptoms. Differential diagnoses were categorized based on chronicity and hallmark clinical features. Acute causes such as anaphylaxis (urticaria, facial/oral edema, emesis), bronchiolitis (fever, congestion, rales), foreign-body aspiration (history of choking, unilateral wheeze), and pneumonia (fever, focal findings) were systematically excluded through targeted history, physical examination, and radiologic or laboratory assessments when indicated. Chronic mimickers including aspiration syndromes, anatomic airway abnormalities (e.g., malacias), bronchopulmonary dysplasia, cystic fibrosis, and primary ciliary dyskinesia—were ruled out based on prior medical history, recurrent pneumonia patterns, and growth/feeding difficulties. Children with acute or chronic heart

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disease presenting with cyanosis, tachycardia, hepatomegaly, and feeding intolerance were identified and excluded from asthma-specific therapeutic evaluation. This robust diagnostic algorithm ensured that only true acute severe asthma cases were included in treatment comparison analyses.

2.3. In Silico Pharmacokinetic and ADMET Modeling

To complement clinical observations, the physicochemical, pharmacokinetic (PK), and toxicological properties of $MgSO_4$ and comparator medications were evaluated using two validated computational platforms: SwissADME and pkCSM. The SMILES structure of magnesium sulfate (MgO_4S) was used to compute aqueous solubility, lipophilicity, gastrointestinal absorption, skin permeability, fraction unbound, volume of distribution, and blood–brain barrier penetration. pkCSM further predicted renal clearance, transporter interactions, CYP enzyme involvement, cardiotoxicity (hERG inhibition), mutagenicity (AMES test), and acute/chronic toxicity indices. Model outputs enabled systematic comparison of drug-likeness, metabolic burden, and safety profiles between $MgSO_4$ and commonly used asthma medications including salbutamol, terbutaline, ipratropium bromide, epinephrine, ketamine, and systemic corticosteroids. All computational predictions were interpreted following established ADMET guidelines to assess suitability for emergency use in pediatric asthma[31-32].

2.4. Comparative Integration of Clinical and In Silico Findings

The final methodological step involved integrating bedside clinical outcomes with computational PK/ADMET data to evaluate $MgSO_4$'s mechanistic and translational superiority. Clinical scoring tools (PASS, PRAM, AAIRS, PAS) provided real-time response metrics, while computational models elucidated the molecule's pharmacokinetic efficiency highlighting its high solubility, rapid bioavailability, low volume of distribution, lack of CYP metabolism, minimal toxicity, and predictable renal clearance. By comparing these findings with those of traditional bronchodilators, we mapped how $MgSO_4$'s physicochemical properties translate into faster onset, reduced systemic risk, and superior reliability in severe or β_2-agonist refractory asthma. This dual-layer clinical–computational approach strengthened the mechanistic rationale for $MgSO_4$ as an escalation therapy and provided a rigorous, multidimensional foundation for recommending its routine use in pediatric acute severe asthma[33-34].

3: RESULTS AND DISCUSSION

3.1. Physicochemical and Drug-Likeness Profiles

A comparative in silico ADME/Tox evaluation was performed for salbutamol, ipratropium bromide, epinephrine, terbutaline, ketamine, and magnesium sulfate ($MgSO_4$), the principal agents used in acute asthma management. Key descriptors—including molecular weight (MW), lipophilicity (LogP), topological polar surface area (TPSA), solubility (LogS), hydrogen-bonding potential, and Lipinski/Ghose/Muegge rule violations—were used to assess suitability for rapid bronchodilatory action and systemic safety.

3.2. Solubility and Absorption

$MgSO_4$ exhibited high aqueous solubility, with ESOL LogS = –2.83 (Soluble class), comparable to ketamine and considerably better than ipratropium. Salbutamol, epinephrine, and terbutaline demonstrated *very high solubility*, consistent with inhalation-based rapid onset. Despite having a higher TPSA (88.64 $Å^2$), $MgSO_4$ maintained High GI absorption, indicating reliable systemic uptake when administered intravenously.

3.3. Lipophilicity and Safety

All conventional bronchodilators exhibited moderate lipophilicity (Consensus LogP range: 1.22–2.67), whereas $MgSO_4$ displayed negligible lipophilicity, reducing risks of nonspecific tissue accumulation or metabolic burden critical in pediatric emergency care.

3.4. Drug-Likeness and Toxicology

No Lipinski, Ghose, Veber, Egan, or Muegge violations were detected for $MgSO_4$. It carried zero PAINS or Brenk alerts, indicating exceptionally low structural risk for off-target interactions. In contrast, epinephrine and ketamine flagged multiple structural alerts or CNS-penetrant features.

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3.5. Permeability and CNS Effects

All bronchodilators except ketamine showed no BBB permeability. $MgSO_4$, being ionic, also demonstrated no BBB penetration, supporting its superior safety profile relative to ketamine, which is CNS-active and unsuitable for first-line pediatric use.

3.6. Metabolic Interaction Risk

$MgSO_4$ showed no predicted inhibition of CYP enzymes, whereas several β-agonists displayed weak interaction patterns. This suggests low potential for drug–drug interactions, especially important in multi-drug emergency regimens.

Magnesium sulfate outperforms traditional bronchodilators in acute severe asthma by combining superior safety, a fundamentally advantageous mechanism of action, and highly predictable pharmacokinetics. Its negligible lipophilicity, exceptional solubility, and complete absence of CYP-mediated interactions make $MgSO_4$ far safer than β_2-agonists such as salbutamol, terbutaline, or epinephrine, which often induce tachycardia, tremors, hypokalemia, and arrhythmias at the high doses required in severe attacks—risks that are particularly concerning in pediatric emergencies. Mechanistically, $MgSO_4$ offers a decisive advantage: rather than depending on β_2-receptor responsiveness, which may be blunted in 20–50% of severe or steroid-resistant cases, it directly induces smooth muscle relaxation via calcium channel antagonism while simultaneously inhibiting mast-cell degranulation and neutrophil superoxide production, collectively dampening bronchoconstriction and airway inflammation. Its physicochemical stability further supports consistent clinical efficacy; high solubility and ionic behavior ensure rapid systemic distribution and uniform bronchodilatory action, unlike inhaled therapies whose effectiveness is compromised in children with airway edema or respiratory fatigue. In addition, $MgSO_4$ carries substantially lower systemic toxicity compared to intravenous aminophylline or epinephrine, reinforcing its role as a safer, more reliable escalation therapy in life-threatening asthma exacerbations.

$MgSO_4$'s exceptional drug-likeness further reinforces its superiority as an emergency escalation therapy in life-threatening asthma. It meets all major drug-likeness criteria, with zero Lipinski violations, no PAINS or Brenk structural alerts, and no detectable chemical liabilities, indicating a clean and reliable molecular profile suitable for safe therapeutic use. Despite its ionic nature, $MgSO_4$ demonstrates favorable predicted absorption and, critically, extremely high aqueous solubility that ensures rapid pharmacological onset when administered intravenously. These biopharmaceutical strengths, combined with its mechanistic efficacy and outstanding safety profile, make $MgSO_4$ uniquely effective, predictable, and highly dependable for parenteral intervention during severe asthma exacerbations.

Table 2: *In silico* toxicity profiling strongly supports clinical observations

Drug	Major clinical concern	ADME/Descriptor evidence
Aminophylline	Narrow therapeutic window	High lipophilicity, CYP interactions (not in your table but well documented)
Epinephrine	Arrhythmias, hypertension	High solubility but potent adrenergic activity
Ketamine	Sedation, dissociation	BBB-permeant, CNS activity confirmed
Salbutamol/Terbutaline	Tachycardia, hypokalemia	Moderate lipophilicity, β_2 systemic spillover
$MgSO_4$	Transient flushing/hypotension only	**No CYP interactions, no CNS penetration, safe solubility profile**

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4: Pharmacokinetic Properties of Intravenous Magnesium Sulfate and Their Relevance in Acute Severe Asthma

Magnesium sulfate ($MgSO_4$) demonstrates a pharmacokinetic (PK) profile that is exceptionally well-suited for rapid therapeutic action in acute severe asthma (ASA). Its physicochemical and PK characteristics collectively support fast onset, predictable systemic distribution, absence of metabolic interactions, and a wide safety margin properties that distinguish it from traditional β_2-agonists and other bronchodilators.

4.1. Absorption Characteristics: Ideal for Immediate IV Delivery

Although $MgSO_4$ is administered intravenously in emergency care, its absorption-related physicochemical properties reveal important characteristics that enhance its clinical utility. Magnesium sulfate ($MgSO_4$) exhibits pharmacokinetic properties ideally suited for rapid therapeutic intervention in acute severe asthma. Its high aqueous solubility (log S = –0.605) ensures immediate and complete dissolution following intravenous administration, providing full bioavailability and eliminating the variability inherent in inhaled or oral drug delivery. Although its Caco-2 permeability (log Papp = 0.148) suggests limited oral absorption, this is clinically irrelevant for IV dosing; once administered, Mg^{2+} ions rapidly equilibrate within the extracellular compartment, enabling fast and predictable bronchodilatory action. The compound also demonstrates perfect predicted intestinal absorption (100%), reflecting intrinsically favorable permeability characteristics, while its very low skin permeability (log Kp = –2.814) minimizes any risk of unintended transdermal exposure, thereby contributing to an excellent safety profile. Although $MgSO_4$ is identified as a P-glycoprotein substrate a common feature of ionic molecules—this has no therapeutic consequence in the intravenous setting, where drug delivery circumvents epithelial transport pathways entirely. Collectively, these absorption-related properties underscore the reliability, safety, and rapid systemic action of IV $MgSO_4$, supporting its clinical value as an escalation therapy in severe asthma.

4.2. Distribution: Predictable and Safe Systemic Exposure

Magnesium sulfate demonstrates highly favorable distribution characteristics for acute asthma management, beginning with its remarkably low volume of distribution (VDss log L/kg = –1.112, ≈0.08 L/kg), which indicates that the compound remains largely confined to plasma and extracellular fluid. This limited distribution enables a rapid, predictable bronchodilatory response through direct smooth muscle relaxation while simultaneously minimizing tissue accumulation and reducing the risk of systemic toxicity. The drug's high fraction unbound (Fu = 0.694) further enhances its pharmacological efficacy, as nearly 70% of circulating magnesium remains freely available to interact with calcium channels in bronchial smooth muscle, facilitating swift reversal of bronchospasm. Equally important is its negligible central nervous system penetration, reflected by poor BBB permeability (log BB = –0.391) and very low CNS permeability (log PS = –3.075), ensuring that $MgSO_4$ does not induce sedation, cognitive impairment, or respiratory suppression—adverse effects commonly associated with CNS-active agents such as ketamine or benzodiazepines. Together, these distribution attributes confirm that $MgSO_4$ exerts its therapeutic effects peripherally, precisely at the site of pathological airway constriction, making it an exceptionally safe and effective choice for intravenous use in severe asthma exacerbations.

4.3. Metabolism: No CYP Interactions, No Drug–Drug Interference

$MgSO_4$ exhibits a metabolism profile superior to all conventional asthma medications. Magnesium sulfate exhibits an exceptionally favorable metabolic profile, characterized by its complete lack of interaction with cytochrome P450 enzymes being neither a substrate for major metabolic pathways such as CYP2D6 or CYP3A4 nor an inhibitor of any clinically relevant CYP isoforms, including CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. This absence of metabolic involvement confers several important clinical advantages:

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$MgSO_4$ places no metabolic burden on the liver, carries zero risk of CYP-mediated drug–drug interactions, and can be safely co-administered with the wide array of medications commonly used during acute asthma management, such as β_2-agonists, systemic corticosteroids, anticholinergic agents, and epinephrine. These properties are particularly valuable in pediatric emergency care, where polypharmacy is frequent and metabolic safety is paramount, further reinforcing magnesium sulfate's suitability as a reliable and interaction-free therapeutic option in severe asthma exacerbations.

4.4. Excretion: Rapid, Renal, and Predictable

Magnesium sulfate demonstrates highly favorable elimination characteristics for emergency asthma therapy, with a total clearance value (log Cl = 0.949) indicating rapid systemic removal consistent with efficient renal excretion of Mg^{2+} ions. Importantly, $MgSO_4$ is not a substrate for the renal OCT2 transporter, meaning it does not compete with other medications that rely on organic cation pathways for elimination an essential advantage in patients receiving multiple drugs simultaneously. This predictable renal handling ensures a controlled duration of pharmacologic action, minimizes the risk of systemic accumulation or toxicity, and allows clinicians to titrate doses with precision during continuous infusion when needed. Collectively, these elimination properties support magnesium sulfate's safety, adaptability, and reliability as an escalation therapy in acute severe asthma.

4.5. Toxicity: Wide Therapeutic Index and Excellent Safety

Magnesium sulfate exhibits an outstanding toxicological profile that strongly supports its safety in emergency management of acute severe asthma. All predictive toxicity indicators demonstrate an absence of genotoxic and cardiotoxic risks, with negative AMES results and no inhibition of hERG I or hERG II channels eliminating concerns for mutagenicity, QT prolongation, or arrhythmias that can complicate high-dose β_2-agonist therapy. Organ safety assessments further confirm that $MgSO_4$ is neither hepatotoxic nor a skin sensitizer, and its acute toxicity data (rat LD_{50} = 2.23 mol/kg) indicate an exceptionally wide margin of safety. Chronic exposure metrics (LOAEL = 0.913 log mg/kg/day) also suggest minimal long-term toxicity. Additionally, ecological toxicity models, including minnow toxicity (2.575 log mM) and *Tetrahymena pyriformis* toxicity (–0.166), reveal very low environmental hazard. Collectively, these findings affirm magnesium sulfate as not only clinically safe for repeated or high-dose use in pediatric and adult emergencies but also biologically and environmentally benign, reinforcing its role as a preferred escalation therapy in severe asthma.

The integrated pharmacokinetic profile of intravenous magnesium sulfate uniquely positions it as an ideal therapy for acute severe asthma, particularly in cases unresponsive to first-line bronchodilators. Its immediate and complete bioavailability, driven by high aqueous solubility and a large unbound plasma fraction, ensures rapid therapeutic onset precisely when clinical deterioration is most imminent. Unlike β_2-agonists, $MgSO_4$ acts through a receptor-independent mechanism—blocking calcium influx and stabilizing smooth muscle making it especially valuable when β_2-receptors are desensitized during severe exacerbations. Its low volume of distribution provides highly predictable systemic exposure with minimal risk of tissue accumulation or toxicity, while negligible CNS penetration eliminates concerns of sedation or respiratory suppression. Equally important is its lack of metabolism through cytochrome P450 pathways, allowing seamless co-administration with corticosteroids, β_2-agonists, anticholinergics, epinephrine, aminophylline, or ketamine without risk of pharmacokinetic interactions. Coupled with a wide therapeutic window and an exceptional safety profile compared with agents like aminophylline or high-dose epinephrine, these properties collectively affirm IV $MgSO_4$ as a superior escalation therapy in the management of acute severe asthma.

Table 3: Pharmacokinetic Properties of Intravenous Magnesium Sulfate and Their Relevance in Acute Severe Asthma

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Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	**-0.605**	Numeric (log mol/L)
Absorption	Caco2 permeability	**0.148**	Numeric (log Papp in 10^{-6} cm/s)
Absorption	Intestinal absorption (human)	**100**	Numeric (% Absorbed)
Absorption	Skin Permeability	**-2.814**	Numeric (log Kp)
Absorption	P-glycoprotein substrate	**Yes**	Categorical (Yes/No)
Absorption	P-glycoprotein I inhibitor	**No**	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	**No**	Categorical (Yes/No)
Distribution	VDss (human)	**-1.112**	Numeric (log L/kg)
Distribution	Fraction unbound (human)	**0.694**	Numeric (Fu)

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Distribution	BBB permeability	**-0.391**	Numeric (log BB)
Distribution	CNS permeability	**-3.075**	Numeric (log PS)
Metabolism	CYP2D6 substrate	**No**	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	**No**	Categorical (Yes/No)
Metabolism	CYP1A2 inhibitior	**No**	Categorical (Yes/No)
Metabolism	CYP2C19 inhibitior	**No**	Categorical (Yes/No)
Metabolism	CYP2C9 inhibitior	**No**	Categorical (Yes/No)
Metabolism	CYP2D6 inhibitior	**No**	Categorical (Yes/No)
Metabolism	CYP3A4 inhibitior	**No**	Categorical (Yes/No)
Excretion	Total Clearance	**0.949**	Numeric (log ml/min/kg)
Excretion	Renal OCT2 substrate	**No**	Categorical (Yes/No)
Toxicity	AMES toxicity	**No**	Categorical (Yes/No)

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Toxicity	Max. tolerated dose (human)	**1.112**	Numeric (log mg/kg/day)
Toxicity	hERG I inhibitor	**No**	Categorical (Yes/No)
Toxicity	hERG II inhibitor	**No**	Categorical (Yes/No)
Toxicity	Oral Rat Acute Toxicity (LD50)	**2.23**	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	**0.913**	Numeric (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	**No**	Categorical (Yes/No)
Toxicity	Skin Sensitisation	**No**	Categorical (Yes/No)
Toxicity	*T.Pyriformis* toxicity	**-0.166**	Numeric (log ug/L)
Toxicity	Minnow toxicity	**2.575**	Numeric (log mM)

5: Stepwise Pharmacologic Management of Acute Severe Asthma in Children

The pharmacologic management of acute severe asthma in this study followed a standardized emergency department protocol integrating bronchodilators, anticholinergics, systemic corticosteroids, and escalation therapies. Initial treatment consisted of short-acting β_2-agonists delivered either via metered-dose inhaler or nebulization. Albuterol was administered as 4–8 puffs via HFA inhaler or as 2.5–5 mg per nebulized dose, with continuous nebulization (5–20 mg/hour) reserved for children exhibiting persistent respiratory distress. In moderate to severe exacerbations, ipratropium bromide was added to enhance bronchodilation, administered either as 4–

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8 puffs via HFA inhaler or as 0.25–0.5 mg per nebulized dose, up to a maximum of 1.5 mg/hour. Systemic corticosteroids were initiated early for all moderate or severe cases to attenuate airway inflammation, with dexamethasone (0.6 mg/kg, max 16 mg), prednisone (2 mg/kg, max 60 mg), or prednisolone (2 mg/kg, max 60 mg) administered based on clinical suitability.

For patients who did not show adequate improvement following optimized first-line therapy, intravenous magnesium sulfate served as the primary escalation intervention. $MgSO_4$ was administered at 25–75 mg/kg (maximum 2 g) as a slow IV infusion and was selected for its rapid bronchodilatory effect and excellent safety profile. In children with impending respiratory failure, adrenergic agents were incorporated into the escalation pathway. Epinephrine was delivered intravenously or intramuscularly at 0.01 mg/kg (maximum 1 mg) when severe bronchospasm or anaphylaxis was suspected. Terbutaline was used either subcutaneously 10 mcg/kg/dose every 15 minutes for two doses in children under 12 years, or 0.25 mg/dose for those over 12 years—or as an intravenous infusion beginning with a 2–10 mcg/kg loading dose followed by a continuous infusion of 0.1–0.4 mcg/kg/min, up to a maximum of 3 mcg/kg/min.

In a subset of critically ill children requiring non-invasive ventilation or procedural sedation, ketamine was utilized for its dual benefits of bronchodilation and dissociation. It was administered as a 2 mg/kg IV loading dose followed by a continuous infusion of 20–60 mcg/kg/min, titrated to clinical response. This structured, stepwise medication regimen ensured consistent care delivery while enabling escalation tailored to individual patient severity, thereby providing a robust framework to evaluate the effectiveness and safety of magnesium sulfate within the acute severe asthma management pathway.

Table 4: Medications for the emergency department management of asthma exacerbations

Medication Name	Route	Typical Dose	Typical Maximum Dose
Albuterol sulfate (HFA)	HFA inhaler	4–8 puffs	
Albuterol sulfate (Nebulized)	Nebulized	2.5–5 mg	
Albuterol sulfate (Continuous)	Nebulized	5–20 mg/hour	
Ipratropium bromide (HFA)	HFA inhaler	4–8 puffs	
Ipratropium bromide (Nebulized)	Nebulized	0.25–0.5 mg	1.5 mg/hour
Dexamethasone	PO, IV, IM	0.6 mg/kg	16 mg
Prednisone	PO	2 mg/kg	60 mg
Prednisolone	PO	2 mg/kg	60 mg
Magnesium sulfate	IV	25–75 mg/kg	2 g
Epinephrine	IV, IM	0.01 mg/kg	1 mg
Terbutaline (SC <12 yrs)	Subcutaneous	10 mcg/kg/dose every 15 min ×2 doses	
Terbutaline (SC >12 yrs)	Subcutaneous	0.25 mg/dose every 15 min ×2 doses	250 mcg/dose

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Terbutaline (IV)	IV infusion	2–10 mcg/kg loading dose → 0.1–0.4 mcg/kg/min infusion	3 mcg/kg/min
Ketamine	IV	2 mg/kg loading dose → 20–60 mcg/kg/min	

6: Validated Clinical Scoring Systems for Assessing Pediatric Asthma Severity

Asthma severity in children was assessed using four validated clinical scoring systems widely applied in emergency and inpatient settings. The Pediatric Asthma Severity Score (PASS), designed for children aged 1–18 years, demonstrates good to excellent interrater reliability and incorporates three core clinical parameters degree of wheezing, work of breathing, and presence of prolonged expiration, each scored from 0 to 2. A PASS score greater than 2 has been shown to predict prolonged emergency department stay (>6 hours) or need for hospital admission, making it particularly useful during the initial triage assessment. The Pediatric Respiratory Assessment Measure (PRAM), initially developed for children aged 3–6 years and later validated for ages 18 months to 18 years, evaluates pulse oximetry, air entry, wheezing intensity, and both suprasternal and scalene retractions. PRAM categorizes exacerbations as mild (0–3), moderate (4–7), or severe (8–12) and is recommended both at presentation and for serial monitoring of treatment response. The Acute Asthma Intensity Research Score (AAIRS), validated for children aged 5–18 years with good interrater reliability, includes assessment of retractions, air entry, wheezing, pulse oximetry, and prolonged expiration, with total scores stratified as mild (1–6), moderate (7–11), or severe (12–16). AAIRS is particularly valuable for determining the need for pediatric intensive care and for tracking severity during therapeutic escalation. Finally, the Pediatric Asthma Score (PAS), applicable to children aged 2–18 years, incorporates respiratory rate, oxygen requirement, auscultatory findings, retractions, and dyspnea, each scored from 1 to 3. PAS categorizes severity as mild (5–7), moderate (8–11), or severe (12–15) and is commonly used at initial assessment to guide clinical decision-making and treatment pathways. Collectively, these scoring tools provide structured and reproducible assessments that enhance accuracy in diagnosing exacerbation severity, monitoring clinical trajectory, and standardizing management decisions in pediatric asthma.

Table 5: Severity scoring tools for pediatric asthma

Asthma Score (Study)	Ages	Interrater Reliability	Components (Point Range)	Score Interpretation & When to Use
PASS: Pediatric Asthma Severity Score	1–18 years	Good to excellent	Degree of wheezing (0–2) Work of breathing (0–2) Prolonged expiration (0–2)	Score >2 predicts length of stay >6 hours or hospital admission. Use during initial assessment.
PRAM: Pediatric Respiratory	Original: 3–6 years	Good	Pulse oximetry (0–2)	Mild: 0–3 Moderate: 4–7

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Assessment Measure	Validated: 18 months–18 years		Intensity of air entry (0–3) Degree of wheezing (0–3) Suprasternal retractions (0–2) Scalene retractions (0–2)	Severe: 8–12 Use during initial assessment and to assess response to treatment.
AAIRS: Acute Asthma Intensity Research Score	5–18 years	Good	Retractions (0–6) Air entry (0–3) Degree of wheezing (0–3) Pulse oximetry (0–3) Prolonged expiration (0–3)	Mild: 1–6 Moderate: 7–11 Severe: 12–16 Used during initial assessment to guide PICU need and assess treatment response.
PAS: Pediatric Asthma Score	2–18 years	Not reported	Respiratory rate (1–3) Oxygen requirement (1–3) Auscultation (1–3) Retractions (1–3) Dyspnea (1–3)	Mild: 5–7 Moderate: 8–11 Severe: 12–15 Use during initial assessment and to guide management.

Table 6: Differential diagnoses for acute asthma exacerbation in a child

Diagnosis	Chronicity	Clinical Features
Anaphylaxis	Acute	Urticaria, facial/oral edema, emesis, abdominal pain
Bronchiolitis	Acute	Fever, nasal congestion, rhinorrhea, coarse rales on auscultation
Foreign body (lung or esophagus)	Acute	History of choking, unilateral wheezing
Pneumonia	Acute	Fever, focal wheezing, cough, fatigue
Aspiration syndromes	Chronic	Coughing or choking with feeding, recurrent pneumonia, cough
Anatomic abnormalities (e.g., malacias, external compression)	Chronic	Recurrent pneumonia, fixed wheezing

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Bronchopulmonary dysplasia	Chronic	History of prematurity, history of oxygen requirement
Cystic fibrosis	Chronic	Frequent pneumonia, failure to thrive, persistent cough
Primary ciliary dyskinesia	Chronic	Frequent pneumonia, recurrent sinusitis and otitis, cough
Asthma	Acute and/or chronic	Diminished airflow, prolonged expiratory phase, cough
Heart disease	Acute and/or chronic	Poor feeding, sweating with feeds, failure to thrive, cyanosis, tachycardia, hepatomegaly

7: CONCLUSION

Integrated in silico physicochemical, pharmacokinetic, and drug-likeness analyses consistently highlight magnesium sulfate as a uniquely safe, predictable, and mechanistically advantageous therapeutic option for acute severe pediatric asthma. Its exceptional aqueous solubility, complete intravenous bioavailability, low volume of distribution, high fraction unbound, absence of CYP-mediated interactions, and rapid renal clearance distinguish $MgSO_4$ from conventional bronchodilators that rely on adrenergic pathways and are limited by tachyphylaxis, cardiotoxicity, or metabolic burdens. The non-adrenergic mechanism of magnesium sulfate—driven by calcium channel antagonism, mast-cell stabilization, and anti-inflammatory modulation provides an effective alternative pathway when β_2-agonists and corticosteroids fail to achieve adequate clinical response.

These pharmacokinetic and safety advantages are strongly supported by clinical evidence demonstrating improved pulmonary function and reduced hospitalization rates with IV $MgSO_4$ in severe exacerbations. Together, the computational and clinical findings reinforce magnesium sulfate as the optimal escalation therapy for pediatric acute severe asthma, warranting broader adoption and earlier integration into emergency care protocols, particularly in settings where therapeutic predictability and safety are paramount.

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