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Magnesium Sulfate Versus Ipratropium Bromide in COPD Exacerbation: A Randomized Trial

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Treatment with short-acting β_2-agonists for exacerbations of chronic obstructive pulmonary disease (COPD) results in clinical improvement. It has not been established whether combining short-acting β_2-agonists to other bronchodilators is more effective than β_2-agonists alone. We conducted a study in patients presenting to the emergency department with exacerbation of COPD. They were randomized to receive nebulized ipratropium bromide (IB group; n = 62) or combined nebulized and intravenous bolus of magnesium sulfate ($MgSO_4$ group; n = 62). All nebulized drugs were administered at 30-minute intervals for 2 hours. Primary outcome included hospital admission, endotracheal intubation, and hospital death rates. Secondary outcome measures were improvement in peak expiratory flow, dyspnea score, and arterial blood gas changes within the first 3 hours. There were no significant differences in primary outcome between $MgSO_4$ and IB groups. Patients given IB average 32 L greater improvement in peak expiratory flow rate compared with magnesium sulfate (95% confidence interval, 19–43 L) at 180 minutes. Simultaneously, there was a significant reduction in $PaCO_2$ compared with baseline values in IB group but not in $MgSO_4$ group. There was a statistically nonsignificant trend toward a decrease in dyspnea score in both groups although adverse events were similar. Although the improvement in peak expiratory flow rate and arterial blood gas favored nebulized IB over magnesium sulfate, there was a nonsignificant difference between both drugs with regard to hospital admission, intubation, and hospital death rates in patients with COPD treated in the emergency department for acute exacerbation.

Keywords: acute exacerbation of chronic obstructive pulmonary disease, magnesium sulfate, emergency department

INTRODUCTION

Exacerbation is a serious concern in chronic obstructive pulmonary disease (COPD) and represents an important cause of emergency department (ED) admission, leading to high morbidity and mortality.[1,2] Despite the regular use of noninvasive ventilation (NIV) in the early treatment of the COPD exacerbation, a significant proportion of patients continue to be admitted to medical ward and/or intensive care unit (ICU).[3] Currently, short-acting inhaled β_2-adernergic (SABA) agonists are the mainstay of pharmacological therapy in patients with ACOPD.[4] However, combining SABA AU5 agents with other bronchodilators may provide greater improvement in pulmonary function and fewer hospitalization than SABA agents alone. Numerous studies have described the use of anticholinergics with SABA agents to reverse airflow limitation in AECOPD.[5–9] Overall, patients in theses studies had AU6 marginally shorter length of stay and proportionally larger increase in forced expiratory volume in the first

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second of expiration. Magnesium sulfate ($MgSO_4$) is a less common class of bronchodilators that could have a possible beneficial clinical effect when associated to SABA agents.[10] Its effectiveness in reversing bronchospasm in AECOPD was determined in one controlled clinical study.[11] However, this trial failed to show beneficial effect on hospital admission possibly because the dose of magnesium sulfate used was not sufficient. Consequently, the true effect of $MgSO_4$ on clinical outcome remains unclear. The aim of this study was to evaluate the efficacy and safety of combination of SABA and $MgSO_4$ in comparison to SABA and ipratropium bromide (IB) in patients attending the ED for AECOPD.

MATERIALS AND METHODS

Study population

This was a prospective, randomized, double-blind, controlled trial conducted in the ED of Fattouma Bourguiba University Hospital (Monastir, Tunisia) and Tahar Sfar University Hospital (Mahdia, Tunisia) between January 2005 and June 2007. The study protocol was registered and approved by the Independent Ethical Committee of Fattouma Bourguiba University Hospital. Informed consent was obtained for all patients.

Patients were included if (1) they are 40 years or older; (2) they have known or suspected COPD based on pulmonary function test, arterial blood gas, clinical history, physical examination, and chest radiograph; (3) they have criteria of acute exacerbation as following: worsening of dyspnea within 2 weeks and partial pressure of arterial carbon dioxide ($PaCO_2$) $>$45 mm Hg and at least 2 of the following criteria: respiratory rate $>$24/min, arterial pH $<$7.35, and partial pressure of arterial oxygen (Pao_2) $<$50 mm Hg under room air. Patients with the following conditions were excluded: hypersensitivity to anticholinergics and to magnesium sulfate, patients who received anticholinergics within 6 hours before ED admission, systolic arterial pressure $<$90 mm Hg, or need to vasoactive drugs, and patients who required immediate endotracheal intubation.

Study design

On admission to the ED, all patients were clinically assessed and placed on cardiac monitor and the following parameters were recorded: baseline heart rate, respiratory rate, blood pressure, oxygen saturation level, and peak expiratory flow rate (PEFR) (using a handheld Wright's mini-peak flow meter). Then, each patient received a standard treatment consisting of intravenous (IV) methylprednisolone, parenteral fluid therapy, antibiotics, and nebulized terbutaline 5 mg in 4 mL of normal saline with systematic application of NIV. NIV was performed in pressure support mode delivered through a full-face mask with a starting level of pressure support of 12 cm H_2O, a positive end-expiratory pressure of 5 cm H_2O, and a FiO_2 set to keep oxygen saturation above 95%. Subsequent changes were made according to clinical response. After baseline measurements, patients were assigned in a randomized double-blind fashion to receive IB (IB group, 0.5 mg in 3 mL of normal saline) or magnesium sulfate ($MgSO_4$ group, 150 mg in 4 mL of normal saline). Both treatments were delivered via aerosol mask at 10 L/min driven by pressurized air. Simultaneously, additional magnesium sulfate was given in $MgSO_4$ group as an IV bolus (1.5 g in 10 mL), whereas IB group received IV placebo (10 mL of normal saline). All patients received thereafter either 4 doses of nebulized IB with terbutaline at 30 minutes apart (IB group) or 4 doses of magnesium sulfate with terbutaline at 30 minutes apart ($MgSO_4$ group). Each nebulization required short-term cessation of NIV during which oxygen was administered by nasal cannula as needed. Protocol treatment preparation and allocation were performed by the hospital pharmacy in random sequence using a random table and were kept identical in their appearance. The following information was recorded for each patient: age, sex, smoking history, comorbidity, COPD duration, number of episodes of AECOPD within the last year, current treatment, and clinical characteristics of the current exacerbation including dyspnea score assessed by a visual analog scale (from 0 = no dyspnea to 10 = maximal respiratory distress). Patients were monitored every 30 minutes in the 2 first hours and at the end of the third hour. The parameters monitored were respiratory rate, heart rate, blood pressure, PEFR, and dyspnea score. Blood gas measurements were checked at 60 minutes and at the end of the protocol (180 minutes). Patients were also monitored for side effects: hypotension, arrhythmias, palpitation, headache, respiratory depression, and any symptom that developed or worsened during the course of the study. A major side effect was defined by any event that was fatal or life threatening. At the end of the 3-hour assessment, patients were allowed to be discharged home if they improved; those patients who showed marginal improvement were assessed with a second physician to determine the need for hospital admission. Patients intubated during the study protocol or still having a need for NIV at the end of the protocol based

on current practice and guidelines were transferred to the ICU. Patients who did not require ICU were admitted to the pneumology department. Endotracheal intubation was decided in the presence of respiratory arrest, respiratory pauses, a decrease of baseline arterial pH to less than 7.25, loss of consciousness, severe agitation requiring sedation, and/or hemodynamic instability defined by peripheral signs of circulatory shock or hypotension (systolic arterial pressure <70 mm Hg).

Primary outcome included combined hospital admission, need for endotracheal intubation, and hospital death rates. Secondary outcome measures were improvement in PEFR, dyspnea score, $Paco_2$, hospital length of stay, and incidence of side effects.

Statistical analysis

Results are given as mean ± SD except when otherwise indicated. Proportions and rates were compared using the χ^2 test or the Fisher exact test when appropriate. Ordinal qualitative variables or nonnormal quantitative variables were compared with the Wilcoxon rank sum test. Quantitative normal variables were compared with the Student *t* test. Changes in physiologic parameters for $MgSO_4$ and IB groups were evaluated using repeated measures analysis of variance. Based on the available studies, the rate of combined events including hospital admission, endotracheal intubation, and hospital death rates in AECOPD is around 50%. To show a reduction in this primary outcome from 50% to 25% with a power of 0.80 and 0.05, 2-sided significance

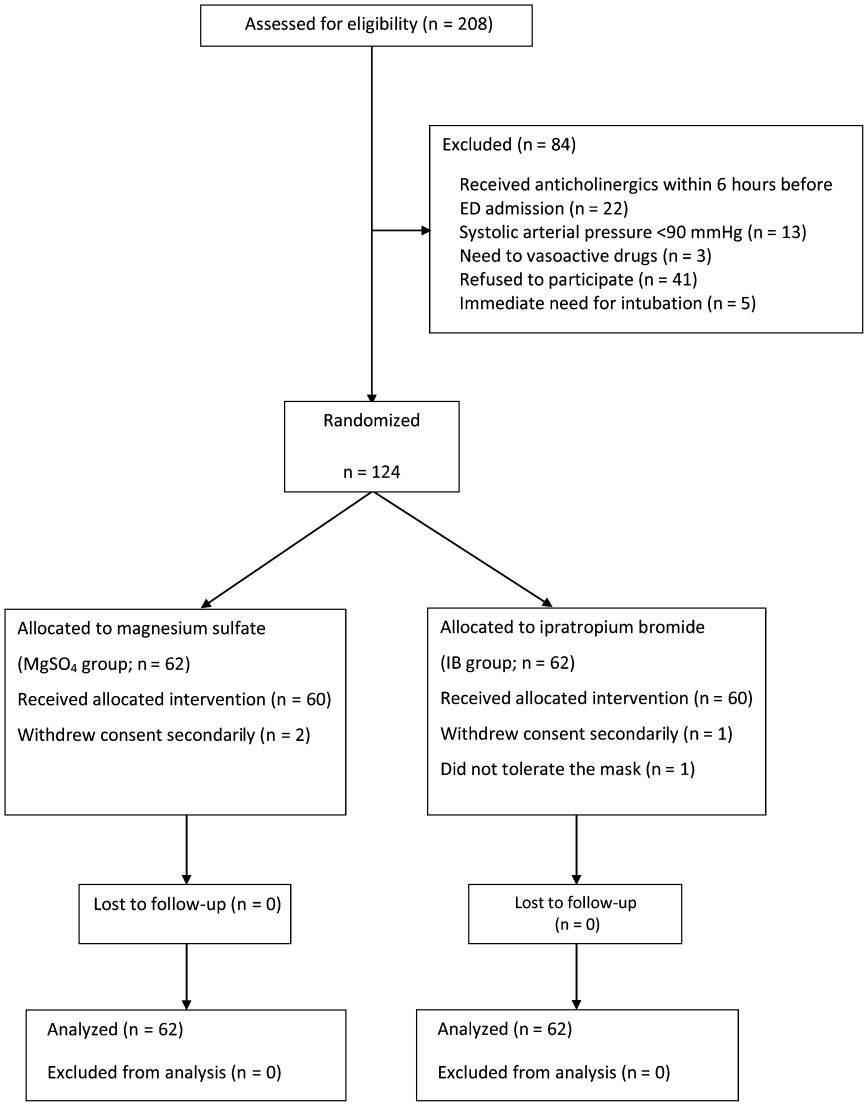

FIGURE 1. Trial profile.

Table 1. Baseline characteristics of the study patients.

	$MgSO_4$ Group (n = 62)	IB Group (n = 62)	*P*
Age, mean (SD), y	69.2 (8.6)	68.9 (7.8)	0.81
Sex: male/female, n	48/14	47/15	0.83
Duration of COPD, mean (SD), y	10.3 (4.7)	13.3 (5.6)	0.29
Current smoker, n (%)	58 (93)	52 (84)	0.09
Hospitalization for COPD within the last year, n (%)	3.6 (2.4)	3.1 (1.7)	0.48
Chronic comorbidities, n (%)			
Arterial hypertension	11 (17.7)	15 (24.1)	0.51
Left heart failure	7 (11.3)	7 (11.3)	1.0
Diabetes	7 (11.3)	3 (4.8)	0.32
Admission symptoms, mean (SD)			
Systolic arterial pressure, mm Hg	150 (23)	149 (26)	0.83
Heart rate, beats/min	101 (18)	100 (21)	0.98
Respiratory rate, breaths/min	30 (04)	30 (05)	0.85
Temperature, °C	37.3 (0.5)	37.4 (0.6)	0.27
Dyspnea score	5.7 (1.4)	5.5 (1.4)	0.40
$PaCO_2$, mm Hg	57.6 (9.8)	55.2 (9.1)	0.14
White blood cell count, $\times 10^3/mm^3$	13.7 (6.8)	11.4 (5.8)	0.44
Concomitant treatment, n (%)			
Aminophylline	9 (14.5)	15 (24.2)	0.12
Nebulized β_2-agonists	13 (21)	18 (29)	0.61
Systemic steroids	8 (12.9)	7 (10.9)	0.87
Home oxygen	9 (14.5)	10 (16.1)	0.87

level, 60 patients were needed in each arm. Analysis was performed in the 2 groups as intention to treat. No interim analyses were planned. All analyses were performed applying a bilateral hypothesis; $P \leq 0.05$ was considered significant. Analyses were performed using the SPSS software, version 11.0.

RESULTS

Patients

During the protocol period, 208 patients were referred to the ED for an exacerbation of COPD. A total of 124 patients were eligible, of whom 62 were randomized to receive IB and 62 to receive $MgSO_4$. Three patients withdrew consent 2 hours after the beginning of the protocol: 2 patients in the IB group and 1 patient in $MgSO_4$ group. Another patient from the $MgSO_4$ group was excluded from the per-protocol analysis because of the presence of exclusion criteria. The protocol was completed in 60 patients in the IB group and 60 patients in the $MgSO_4$ group (Fig. 1). Patient characteristics at baseline are shown in Table 1. Patients were similar between both groups with regard to demographic and baseline clinical characteristics including comorbidities.

Primary outcomes

Main results are shown in Table 2. Twenty-seven (43.5%) patients were admitted in the hospital in the $MgSO_4$ group and 20 (32.2%) patients in the IB group; the difference is not statistically significant ($P = 0.26$).

Table 2. Main outcomes.

	$MgSO_4$ Group (n = 62)	IB Group (n = 62)	*P*
Hospital admission, n (%)	27 (43.5)	20 (32.2)	0.26
Intubated patients, n (%)	11 (17.7)	7 (11.3)	0.44
Hospital mortality, n (%)	1 (1.6)	2 (3.2)	0.56
Combined events, n (%)*	27 (43.5)	20 (32.2)	0.26
Length of hospital stay, d	7.7 (3.5)	6.6 (4.0)	0.28

*Combined events and hospital admission rates were the same as for the same patient only the worst outcome was considered.

Eleven patients (17.7%) required endotracheal intubation in $MgSO_4$ group and 7 patients (11.3%) in IB group. One patient died (1.6%) in $MgSO_4$ group and 2 patients in IB group ($P = 0.56$). Combined event rate was similar in both groups.

Secondary outcomes

At 180 minutes, the mean PEFR improved significantly more in the IB group than in the $MgSO_4$ group compared to baseline (Fig. 2) (58 ± 19 L/mn vs. 26 ± 13 L/mn, respectively, absolute difference (32 L/mn, 95% confidence interval, 19–43 L/mn]. As compared with admission values, $PaCO_2$ and dyspnea score decreased significantly ($P < 0.01$) in both groups at 180 minutes (Fig. 2). Intergroup comparison showed that only $PaCO_2$ at 180 minutes was significantly different between groups. Hospital length of stay was similar with both treatments (Table 2). Adverse events are summarized in Table 3. Nineteen (11.6%) adverse events were reported during the 3 hours of the protocol, but no significant difference was found between study groups. All adverse events were mild and self-limiting; in no patient was the medication discontinued because of adverse effect.

DISCUSSION

The aim of the present study was to investigate the clinical effects of $MgSO_4$ given as an IV bolus combined to multiple nebulizations compared with repeated doses of nebulized IB in patients with AECOPD. Although the results for main clinical outcomes (hospital admission and death and intubation rates) did not demonstrate any difference between both study drugs, we found a statistically significant difference in the improvement of PEFR and hypercapnia in favor of IB.

The beneficial effects of $MgSO_4$ in the treatment of bronchospasm has been shown since many decades.[12] They are the results of the inhibition of contractile tension of bronchial smooth muscle.[13,14] In addition, it has been shown that hypomagnesemia is associated with increased airway hyperreactivity.[15–17] Several studies have addressed the potential of $MgSO_4$ to reduce bronchospasm and improve dyspnea in patients with acute asthma.[12,18] A recent systematic review was undertaken to estimate its effect on both hospital admission and pulmonary function in adults and children with acute asthma.[10] It was demonstrated that only IV $MgSO_4$ is effective in children but not in adults. Nevertheless, regarding the low risk of serious side effects from magnesium sulfate, it was concluded that IV $MgSO_4$ could be helpful in adults

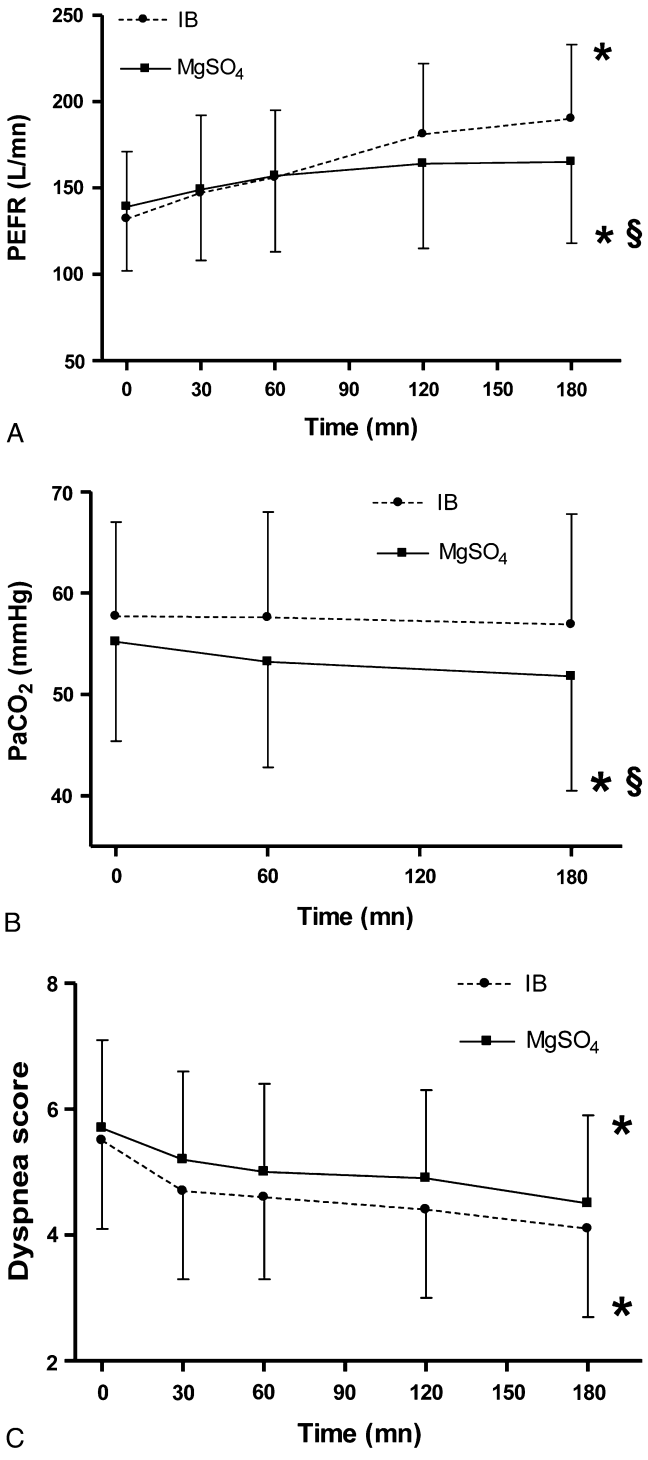

FIGURE 2. Changes in physiologic parameters over time for patients receiving magnesium sulfate ($MgSO_4$) or IB. A, Peak expiratory flow, (B) $PaCO_2$, (C) dyspnea score. §$P < 0.05$ for difference between groups; *$P < 0.05$ for difference from baseline values in each group.

Table 3. Adverse events.

	$MgSO_4$ Group (n = 62)	IB Group (n = 62)	*P*
Adverse events, n (%)*	11 (17.7)	8 (12.9)	0.22
Skin, n	3	0	
Headache, n	3	3	
Cardiovascular, n	3	1	
Tremor, n	2	4	

*Some patients had more than one adverse event.

with life-threatening features. In patients with AECOPD, this issue is less clear because only a few studies have been performed to assess $MgSO_4$ in this setting. In one controlled, randomized, and double-blind study including 72 patients who came to ED with AECOPD, Skorodin et al[11] have demonstrated that IV $MgSO_4$ is associated to a modest bronchodilator effect when given after β_2-agonists. However, there was a statistically nonsignificant trend toward reduced need for hospitalization between $MgSO_4$ and placebo. Given the low dose used in that study, it was suggested that higher doses would yield more significant bronchodilation. However, although $MgSO_4$ is remarkably safe, serious cardiovascular toxic reactions and respiratory depression may occur when high doses are given.[19,20] Consequently, to avoid toxic blood levels, we choose to use $MgSO_4$ as a combination of IV bolus and repeated nebulizations. In our study, no major adverse reactions were observed that support the safety of this administration method. A more recent Spanish,[21] randomized, controlled trial study conducted in patients with AECOPD demonstrated that IV administration of $MgSO_4$ (1.5 g) has no significant bronchodilator effect. Nevertheless, this study demonstrated that the effect of inhaled β_2-agonists was significantly enhanced after $MgSO_4$ administration, suggesting a synergistic action.[22] In the present study, we were unable to show any superiority of $MgSO_4$ compared with IB; however, we found that both drugs provide a significant bronchodilator effect when added to SABA agents. In addition, dyspnea score significantly improved from baseline in both groups. This is an important finding because most of previous randomized studies comparing SABA alone with SABA plus anticholinergics during AECOPD did not demonstrate a difference in lung function changes between treatment groups.[5–8] Our results could be regarded as one of the few evidence supporting combination therapy in AECOPD. Our method of drug administration could explain this beneficial effect as, in contrast to the above-mentioned studies, we used serial repetitive nebulizations that may provide a significant additive effect compared with conventional administration.[23]

Limitations

First, an underpowered study with a sample size not large enough (type 2 error) may explain the absence of difference between groups in main outcome. In fact, the rate of primary outcome was lower than that hypothesized for the sample size calculation, possibly because patients were less sick than that was expected. Second, because patients who required an immediate intubation were not included in our study, we cannot comment on the effect of both protocol treatments in patients who present with this degree of severity. Whether a significant difference between both protocol treatments would exist in more severe patients is an issue that warrants further investigations. Third, we acknowledge that the use of PEFR as a measure of bronchospasm severity is not perfect. Nevertheless, PEFR was combined to other outcome measures such as $PaCO_2$, and both parameters demonstrated consistent changes, which suggest that clinical changes in our patients may be reliably reflected in PEFR measurements.

In conclusion, when added to nebulized SABA, $MgSO_4$ and IB seem equivalent in terms of hospital admission and intubation and death rates but IB seemed more effective in terms of bronchodilator effect and arterial blood gas improvement in AECOPD.

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S. Nouira was responsible for study design and writing of the article. G. M. Habib, B. Kaouther, T. M. Naceur, and B. Hamdi were responsible for data collection. B. Wahid and B. Riadh prepared the protocol treatment. M. Soudani and L. Mondhor supervised data collection and took part in data management and analysis. The corresponding author declares that he had access to and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors thank Miss Hela Souied and Miss Imen Sassi for their help in drafting the article.

REFERENCES

1. Murray GJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. *Lancet*. 1997;349:1498–1504.
2. Niederman MS, McCombs JS, Unger AN, et al. Treatment cost of acute exacerbations of chronic bronchitis. *Clin Ther*. 1999;21:576–591.
3. Yuze PJ, Steven MU, Hans PG, et al. Oral or IV prednisolone in the treatment of COPD exacerbations. A randomized, controlled, double-blind study. *Chest*. 2007;132:1741–1747.
4. Kunisaki KM, Rice KL, Niewoehner DE. Management of acute exacerbations of chronic obstructive pulmonary disease in the elderly: an appraisal of published evidence. *Drugs Aging*. 2007;24:303–324.
5. Rebuck AS, Chapman KR, et al. Nebulized anticholinergic and sympathomimetic treatment of asthma and chronic obstructive pulmonary disease in the emergency room. AU8 *Am J Med*. 1978;82:59–64.
6. O'Driscoll BR, Taylor RJ, Horsley MG, et al. Nebulized salbutamol with and without ipratropium bromide in acute airflow obstruction. *Lancet*. 1989;1:1418–1420.
7. Patrick DM, Dales RE, Stark RM, et al. Severe exacerbations of COPD and asthma: incremental benefit of adding ipratropium to usual therapy. *Chest*. 1990;98:295–297.
8. Shrestha M, O'Brien T, Haddox R, et al. Decreased duration of emergency department treatment of chronic obstructive pulmonary disease exacerbations with the addition of ipratropium bromide to beta-agonist therapy. *Ann Emerg Med*. 1991;20:1206–1209.
9. Moayyedi P, Congleton J, Page RL, et al. Comparison of nebulized salbutamol and ipratropium bromide with salbutamol alone in the treatment of chronic obstructive pulmonary disease. *Thorax*. 1995;50:834–837.
10. Mohammed S, Goodacre S. Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis. *Emerg Med J*. 2007;24:823–830.
11. Skorodin MS, Tenholder MF, Yetter B, et al. Magnesium sulfate in exacerbations of chronic obstructive pulmonary disease. *Arch Intern Med*. 1995;155:496–500.
12. Skobeloff EM, Spivey WH, McNamara RM, et al. Intravenous magnesium sulphate for the treatment of acute asthma in the emergency department. *JAMA*. 1989;262: 1210–1213.
13. Dominguez LJ, Barbgallo M, Di Lorenzo G, et al. Bronchial reactivity and intracellular magnesium: a possible mechanism for the bronchodilating effects of magnesium in asthma. *Clin Sci*. 1998;95:137–142.
14. Spivy WH, Skobelof EM, Levin RM. Effect of Mg chloride on rabbit bronchial smooth muscle. *Ann Emerg Med*. 1990; 19:1107–1112.
15. Dhingra S, Solven F, Wilson A, et al. Hypomagnesemia and respiratory muscle power. *Am Rev Respir Dis*. 1984; 129:497–498.
16. Alamoudi OS. Hypomagnesaemia in chronic, stable asthmatics: prevalence, correlation with severity and hospitalization. *Eur Respir J*. 2000;16:427–431.
17. Aziz HS, Blamoun AI, Shubair MK, et al. Serum magnesium levels and acute exacerbation of chronic obstructive pulmonary disease: a retrospective study. *Ann Clin Lab Sci*. 2005;35:423–427.
18. Silverman RA, Osborn H, Runge J, et al; Acute Asthma/Magnesium Study Group. IV magnesium sulphate in the treatment of acute severe asthma: a multicenter randomized controlled trial. *Chest*. 2002;122: 489–497.
19. Viskin S, Belhassen B, Laniado S. Deterioration of ventricular tachycardia to ventricular fibrillation after rapid intravenous administration of magnesium sulfate. *Chest*. 1992;101:1445–1447.
20. Clark BA, Brown RS. Unsuspected morbid hypermagnesemia in elderly patients. *Am J Nephrol*. 1992;12: 336–343.
21. Gonzalez JA, Garcia CH, Gonzalez PA, et al. Effect of intravenous magnesium sulfate on chronic obstructive pulmonary disease exacerbations requiring hospitalization: a randomized placebo-controlled trial. *Arch Bronconeumol*. 2006;42:384–387.
22. Skorodin MS, Freebeck PC, Yetter B, et al. Magnesium sulfate potentiates several cardiovascular and metabolic actions of terbutaline. *Chest*. 1994;105:701–705.
23. Rodrigo GJ, Rodrigo C. First-line therapy for adult patients with acute asthma receiving a multiple dose protocol of ipratropium bromide plus albuterol in the emergency department. *Am J Respir Crit Care Med*. 2000; 161:1862–1868.