

# Magnocaine: Physical Compatibility and Chemical Stability of Magnesium Sulphate and Lidocaine Hydrochloride in Prefilled Syringes

Sara Houlihan, BSc, BSP, MD,<sup>1</sup> Diane Decarie, BSc,<sup>2</sup> Cindy Benes, RT,<sup>3</sup> Richard Cleve, MD, FRCPC,<sup>3</sup> Marianne Vidler, BA, MPH,<sup>1</sup> Laura A. Magee, MSc, MD, FRCPC,<sup>4,5</sup> Mary H. H. Ensom, PharmD, FASHP, FCCP, FCAHS,<sup>2,6</sup> Peter von Dadelszen, MB ChB, DPhil, FRCOG<sup>4,5</sup>

<sup>1</sup>Department of Obstetrics and Gynaecology, University of British Columbia, Vancouver BC

<sup>2</sup>Department of Pharmacy, Children's and Women's Health Centre of BC, Vancouver BC

<sup>3</sup>Department of Laboratory Medicine, Surrey Memorial Hospital, Surrey BC

<sup>4</sup>Institute of Cardiovascular and Cell Sciences, St George's University Hospitals, University of London, London, UK

<sup>5</sup>Department of Obstetrics and Gynaecology, St George's University Hospitals, NHS Foundation Trust, London, UK

<sup>6</sup>Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver BC

## Abstract

**Objective:** To evaluate the physical compatibility and chemical stability of mixtures of magnesium sulphate and lidocaine in order to determine the feasibility of manufacturing a prefilled syringe combining these two drugs for use as an intramuscular (IM) loading dose for eclampsia prevention and/or treatment. This ready-to-use mixture will provide a more tolerable and accessible route of administration appropriate for widespread use.

**Methods:** Physical compatibility (pH, colour, and formation of precipitate) and chemical stability (maintaining > 90% of initial concentrations) of mixtures of MgSO<sub>4</sub>, using both commercially available MgSO<sub>4</sub> (50%) and MgSO<sub>4</sub> reconstituted from salt (61%), with lidocaine hydrochloride (2%) were evaluated every 14 days over six months. The concentration of lidocaine was determined by a stability indicating high performance liquid chromatographic method, while the concentration of magnesium was determined by an automated chemistry analyzer.

**Results:** No changes in pH, color or precipitates were observed for up to 6 months. The 95% confidence interval of the slope of the curve relating concentration to time, determined by linear regression, indicated that only the admixtures of commercially-available magnesium sulfate and lidocaine as well as the 61% magnesium sulfate solution (reconstituted from salt) maintained at least 90% of the initial concentration of both drugs at 25°C and 40°C at 6 months.

**Key Words:** Preeclampsia, eclampsia, magnesium sulphate, chemical stability

Competing Interests: None declared.

Accepted on April 13, 2016

Revised on March 7, 2016

<http://dx.doi.org/10.1016/j.jogc.2016.04.097>

**Conclusions:** Commercially available MgSO<sub>4</sub> and lidocaine hydrochloride, when combined, are stable in a pre-filled syringe for at least six months in high heat and humidity conditions. This finding represents the first step in improving the administration of magnesium sulphate in the treatment and prevention of eclampsia in under-resourced settings.

## Résumé

**Objectif :** Évaluer la compatibilité physique et la stabilité chimique des mélanges du sulfate de magnésium et de lidocaïne, afin de déterminer la possibilité de fabriquer une seringue préremplie de ces deux médicaments, aux fins d'utilisation comme dose de charge, par voie intramusculaire (IM). Ce mélange prêt à l'utilisation permettra d'avoir une voie d'administration plus tolérable et plus accessible, dont l'usage pourrait être généralisé.

**Méthodes :** La compatibilité physique (pH, couleur, et formation de précipité), ainsi que la stabilité chimique (taux des concentrations initiales maintien à plus de 90 %) d'une combinaison de MgSO<sub>4</sub>, obtenu à partir de MgSO<sub>4</sub> (50%) commercialisé et de MgSO<sub>4</sub> reconstitué à partir du sel (61 %), et de chlorhydrate de lidocaïne (2 %) ont été évaluées tous les 14 jours, pendant six mois. La concentration de lidocaïne a été déterminée à l'aide de la chromatographie liquide à haute performance, tandis que la concentration de magnésium a été déterminée à l'aide d'un analyseur chimique automatisé.

**Résultats :** Aucun changement du pH, de la couleur ou des précipités n'a été observé pendant une période allant jusqu'à 6 mois. L'intervalle de confiance à 95 % de la pente de la courbe reliant la concentration et le temps, déterminée par la régression linéaire, a indiqué que seuls les mélanges de sulfate de magnésium et de lidocaïne commercialisés, ainsi que la solution de sulfate de magnésium à 61 % (reconstitué à partir du sel) ont gardé au moins 90 % de la concentration initiale des deux médicaments, à 25°C et 40°C, après 6 mois.

**Conclusion :** Lorsqu'ils sont combinés dans une seringue préremplie, le MgSO<sub>4</sub> commercialisé et le chlorhydrate de lidocaïne restent stables, pendant six mois au moins, dans un milieu très chaud et très humide. Ce résultat constitue un premier pas vers l'amélioration de l'administration du sulfate de magnésium pour le traitement et la prévention de l'éclampsie dans des milieux défavorisés.

Copyright © 2016 The Society of Obstetricians and Gynaecologists of Canada/La Société des obstétriciens et gynécologues du Canada. Published by Elsevier Inc. All rights reserved.

J Obstet Gynaecol Can 2016;38(10):936–944

## INTRODUCTION

Hypertensive disorders of pregnancy affect approximately 10% of all pregnant women around the world<sup>1,2</sup>; 2% to 8% of pregnant women with hypertension will develop preeclampsia and risk progressing to eclampsia. This multisystem disorder leads not only to placental insufficiency and resultant neonatal morbidity but also to maternal organ dysfunction, making it a major cause of maternal morbidity and mortality worldwide.<sup>3</sup>

The treatment of choice for both the prevention and the treatment of eclampsia is magnesium sulphate. The use of magnesium sulphate, compared with placebo or no anticonvulsant, is associated with halving the risk of women with preeclampsia progressing to eclampsia.<sup>4,5</sup> In addition, magnesium sulphate is the anticonvulsant of choice for women with eclampsia,<sup>6</sup> and is proven to be more effective than diazepam,<sup>7</sup> phenytoin,<sup>8</sup> or lytic cocktail.<sup>9</sup>

A recent Cochrane review showed that there is little reliable evidence from randomized trials assessing the minimum effective dose, the comparative effects of alternative routes of administration, or the ideal duration of therapy.<sup>10</sup>

## ABBREVIATIONS

CL2	commercially available lidocaine HCl 2%
CM50	commercially available magnesium sulphate 50%
CM50CL2	commercially available magnesium sulphate 50% combined with lidocaine
HPLC	high performance liquid chromatography
IM	intramuscular
IS	internal standard
IV	intravenous
MS	magnesium sulphate heptahydrate USP dissolved in SWI
MSCL2	magnesium sulphate heptahydrate USP dissolved in SWI combined with lidocaine HCl 2%
SWI	sterile water for injection
USP	United States Pharmacopeia

Currently, the most widely used and studied regimens for administration of magnesium sulphate are those of Pritchard (10 g, injecting 5 g intramuscularly into each buttock, combined with a 4 g intravenous loading dose and a 5 g IM maintenance dose every 4 hours)<sup>11,12</sup> and Zuspan (4 g IV loading dose then maintenance of 1g/h IV infusion).<sup>13</sup> Regardless of the regimen used, the WHO advises using any dose of magnesium sulphate in women with preeclampsia, stating that “the patient (is) likely to be better off with only the loading dose than without it.”<sup>14</sup>

This recommendation is important; despite being widely used, IV regimens present difficulties in less developed countries in which resources and support for IV administration are not routinely available. The IM route is logistically an easier route of administration and does not require continuous monitoring. IM administration is also more appropriate in health centres that are staffed by lay health workers with limited training. However, IM injection also has potential disadvantages, especially pain and infection at the injection site. The pain experienced is in large part due to the 10 mL volume of solution that must be injected into each buttock to administer the loading dose. Using either a smaller volume for injection (a more concentrated solution) or combining magnesium sulphate with a local anaesthetic agent, such as lidocaine, prior to injection would presumably ease this pain. However, to our knowledge, the stability of neither a more concentrated solution of magnesium sulphate nor the combination of magnesium sulphate with lidocaine hydrochloride has been investigated.

The purpose of this study was to evaluate the physical compatibility and chemical stability of the combination of magnesium sulphate and lidocaine hydrochloride, compounded from United States Pharmacopeia solution and salt and stored in polypropylene syringes at room temperature (25°C) and at high heat (40°C) for up to 168 days. Establishing these characteristics is critical for determining the feasibility of manufacturing a prefilled syringe combining these two drugs as an IM loading dose for eclampsia prevention and/or treatment in under-resourced settings.

## METHODS

### Preparation of Magnesium Sulphate and Lidocaine and Set Up

Stock solutions of magnesium sulphate, lidocaine, and magnesium sulphate-lidocaine mix were prepared, filtered, placed in sterile VIAFLEX bags (Baxter Corp., Mississauga ON), and aliquoted into 5 mL sterile BD Luer-Lok plastic syringes (VWR International LLC, Mississauga ON). The syringes (Kendall Pharmaceuticals, Charlotte, NC) were

**Table 1. Products and controls prepared**

Product/Control	Components	Conc MgSO <sub>4</sub>	Total Volume
<b>Experimental Products</b>			
CM50CL2	10 mL commercially-available MgSO <sub>4</sub> (50%) AND 1 mL Lidocaine HCl (2%)	45.5%	10 mL
MSCL2	5 g MgSO <sub>4</sub> salt dissolved in 5.3 mL sterile water for injection AND 1 mL Lidocaine HCl (2%)	54%	9.2 mL
<b>Controls</b>			
MS	5 g MgSO <sub>4</sub> salt dissolved in 5.3 mL sterile water for injection	61%	8.2 mL
CM50	10 mL commercially-available MgSO <sub>4</sub> (50%)	50%	10 mL
CL2	1 mL Lidocaine HCl (2%)	N/A	1 mL

capped. As outlined in [Appendix 1](#), one half of the syringes (225 syringes) were stored in a lightless container at 25°C and the remainder were stored in a lightless humidified incubator set at 40°C.

The concentrations and volumes of each mixture are summarized in [Table 1](#). A mixture of 540 mL of commercially available magnesium sulphate 50% USP (Pharmaceutical Partners of Canada Inc., Richmond Hill ON) and 54 mL of lidocaine HCl 2% (Alveda Pharmaceuticals Inc., Toronto ON) was prepared and labelled as CM50CL2. Magnesium sulphate heptahydrate USP (610 g) (Medisca Pharmaceuticals Inc., Richmond BC) was dissolved in sterile water for injection (Baxter Corp., Mississauga ON) to a volume of 1 L and labelled as MS. Magnesium sulphate heptahydrate USP (543.5 g) was dissolved in SWI. Lidocaine HCl 2% (108.7 mL) was added to the solution. The volume of the solution was adjusted to 1 L with SWI; the sample was labelled as MSCL2. Commercially available magnesium sulphate 50% USP, labelled as CM50, and commercially available lidocaine HCl 2%, labelled as CL2, were used as controls.

### Physical Compatibility

Physical characteristics of the solutions were evaluated at the time of preparation and at 14-day intervals up to 168 days. At each time point, three syringes of each group were examined visually for obvious changes in colour and precipitation. The contents of the 5 mL syringes were transferred to conical tubes to determine pH. The model 800 pH meter (VWR International LLC, Mississauga ON) was calibrated at the beginning of each session using

commercially available standards (pH 7.0 and 4.00, Fisher Scientific Co., Whitby ON). Immediately following the physical observations, a 1.8 mL aliquot from each sample was transferred to a polypropylene CryoVial (VWR International LLC Mississauga ON) and stored at -85°C until analysis.

## CHEMICAL STABILITY

### Chemistry analyzer

Magnesium assay part no. 445360 and UniCel Dx C 600i Synchron Access clinical system (Beckman Coulter Inc., Brea, CA) was used to determine the concentration of magnesium. A detailed description of the assay has been previously published<sup>15</sup> and is outlined in [Appendix 2](#). The analysis was performed in triplicate with results reported as means.

### High performance liquid chromatography instrumentation

Full details of HPLC methodology are provided in [Appendix 2](#).<sup>16,17</sup>

### Statistical Analysis

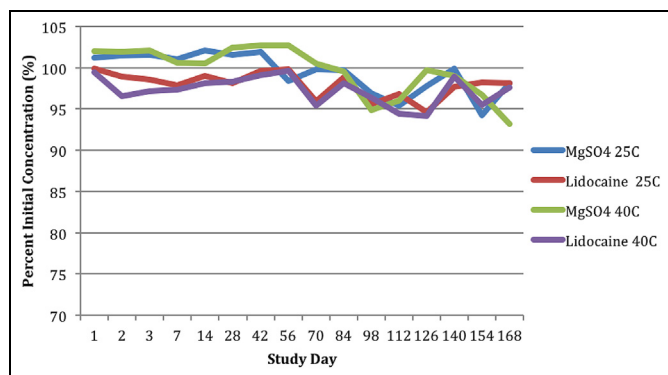
Mean, standard deviation, coefficient of variation, and accuracy were calculated for all of the samples analyzed. For each study day, the percentage of the remaining concentration of magnesium sulphate and lidocaine was calculated. The percentage remaining at the end of the study period was calculated from the concentration on the last day (day 168) as determined by linear regression and the concentration observed on day 0, according to the following formula: (concentration on day 168/concentration on day 0) × 100%. The 95% confidence interval of the amount remaining on day 168 was calculated from the lower limit of the 95% CI of the slope of the curve relating concentration to time according to the following formula: lower limit of the 95% CI of the concentration on day 168/concentration on day 0 × 100%. Stability was defined as maintenance of at least 90% of the initial concentrations.

## RESULTS

### Physical Stability

After 168 days, there were no visible signs of particulate matter in any of the syringes. Each solution remained colourless over the course of the study. There were no major changes in pH for all of the clear solutions. The mean (± standard deviation) pH values were 5.69 ± 0.118 and 5.52 ± 0.127 for CL2 stored at 25°C and 40°C, respectively; 5.58 ± 0.368 and 5.22 ± 0.483 for MSCL2 stored at 25°C and 40°C, respectively; 5.60 ± 0.396 and 5.22 ± 0.380 for CM50CL2 stored at 25°C and 40°C,

Figure 1. Chemical stability of CM50CL2



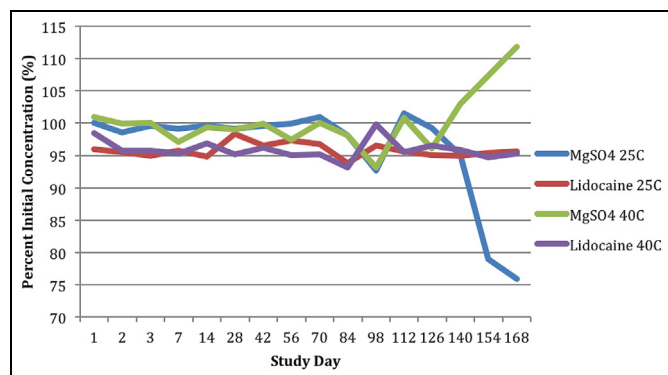
respectively;  $7.52 \pm 0.397$  and  $7.48 \pm 0.25$  for MS stored at 25°C and 40°C, respectively; and  $6.60 \pm 0.217$  and  $6.75 \pm 0.216$  for CM50 stored at 25°C and 40°C, respectively.

### Chemical Stability

The analysis of the peak ratio of lidocaine to dexamethasone (the internal standard) versus the concentration of each lidocaine standard demonstrated linearity over the range of concentrations with coefficient of determination ( $r^2$ )  $\geq 0.999$  ( $n = 4$ ). The intra-day and inter-day coefficients of variation were within acceptable limits of 0.94% and 1.64% at 0.1 mg/mL, 0.33% and 0.95% at 0.25 mg/mL, 0.55% and 0.58% at 0.4 mg/mL, and 0.54% and 0.54% at 0.6 mg/mL, respectively. The intra-day and inter-day accuracy were also within acceptable limits at  $98.7\% \pm 1.13\%$  and  $99.2\% \pm 0.79\%$  at 0.1 mg/mL,  $98.8\% \pm 1.03\%$  and  $98.8\% \pm 1.22\%$  at 0.25 mg/mL,  $99.2\% \pm 0.32\%$  and  $99.2\% \pm 0.80\%$  at 0.4 mg/mL, and  $99.6\% \pm 0.40\%$  and  $99.6\% \pm 0.39\%$  at 0.8 mg/mL, respectively.

The retention times were 3.8 minutes for lidocaine and 5.8 minutes for the IS dexamethasone. None of the peaks generated by forced degradation interfered with the peaks of interest (lidocaine or the IS dexamethasone). When CL2 was force degraded, the lidocaine peaks were decreased by 28.6% and 46.3% when exposed to NaOH at 25°C and 100°C, respectively; by 18.3% and 14.9% when exposed to HCl at 25°C and 100°C, respectively; and by 85.0% and 97.6% when exposed to 30% H<sub>2</sub>O<sub>2</sub> at 25°C and 100°C, respectively. The forced degradation decreased the MSCL2 lidocaine peaks by 55.7% and 74.9% when exposed to NaOH at 25°C and 100°C, respectively; by 60.4% and 70.7% when exposed to HCl at 25°C and 100°C, respectively; and by 84.2% and 97.1% when exposed to H<sub>2</sub>O<sub>2</sub> at 25°C and 100°C, respectively. Finally, the CM50CL2 lidocaine peaks were decreased by 22.8% and 60.2% when exposed to NaOH at 25°C and 100°C, respectively; by 14.7% and 19.7% when exposed to HCl at 25°C and

Figure 2. Chemical stability of MSCL2

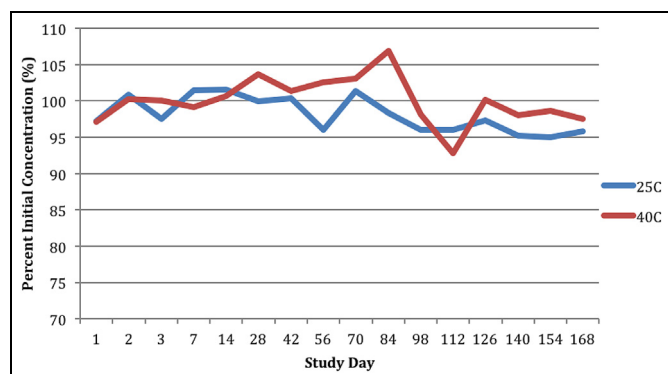


100°C, respectively; and by 97.5% and 94.7% when exposed to H<sub>2</sub>O<sub>2</sub> at 25°C and 100°C, respectively. Thus, the HPLC method was deemed capable of indicating stability.

The HPLC analysis showed that all preparations stored at 25°C or 40°C maintained at least 90% of their original lidocaine concentration for 168 days (Figures 1, 2, and 3). The lower limit of the 95% confidence interval relating concentration to time determined by linear regression indicated that the lidocaine and lidocaine-magnesium sulphate solutions stored at 25°C maintained 97.5% (CL2), 96.4% (MSCL2), and 95.7% (CM50CL2), respectively, of their initial concentration throughout the study period (168 days). The solutions stored at 40°C maintained 95.0% (CL2), 98.6% (MSCL2), and 95.2% (CM50CL2), respectively, of their initial concentrations throughout the study period (Tables 2, 3, and 4).

The UniCel DxC 600i Synchron Access clinical system was tested for interference by analyzing the control CL2 samples stored for up to 168 days at both 25°C and 40°C. No magnesium was detected in any of the lidocaine samples (in which the lower analytical range was 0.4 mmol/L). Similarly, when normal saline stored in polypropylene syringes was run through the chemical analyzer, no magnesium was

Figure 3. Chemical stability of MS





**Table 2. Percentage of initial concentration of commercially available magnesium sulphate and commercially available lidocaine hydrochloride remaining after 168 days of storage at 25°C and 40°C (CM50CL2)**

Variable	25°C		40°C	
	Magnesium sulphate (mmol/L)	Lidocaine hydrochloride (mg/mL)	Magnesium sulphate (mmol/L)	Lidocaine hydrochloride (mg/mL)
Initial concentration	1861	1635	1861	1635
Study Day				
1	101.2	99.9	102.0	99.4
2	101.5	98.9	101.9	96.5
3	101.6	98.6	102.1	97.1
7	101.0	97.9	100.6	97.3
14	102.1	99.0	100.5	98.1
28	101.6	98.1	102.4	98.3
42	101.9	99.6	102.7	99.1
56	98.4	99.8	102.7	99.6
70	99.8	95.9	100.5	95.4
84	99.7	98.8	99.5	98.1
98	96.9	95.6	94.9	96.3
112	95.4	96.8	96.0	94.4
126	97.8	94.6	99.7	94.1
140	99.9	97.7	99.0	98.9
154	94.3	98.2	96.7	95.5
168	98.1	98.1	93.2	97.6
Estimated % remaining on day 168	95.0	97.7	93.9	97.7
Lower 95% CI for % remaining	93.4	95.7	92.0	95.2

detected, thereby ruling out leaching of magnesium from the syringes. Finally, when a known concentration of magnesium sulphate was added to the samples of lidocaine and measured for magnesium (method of standard addition), no deviations from the expected concentrations were found, thus ruling out negative interference.

The magnesium assay showed that only the CM50CL2 maintained more than 90% of the initial concentration of magnesium sulphate in both storage conditions for 168 days (Table 2 and Figure 1). The reconstituted magnesium sulphate salt alone also retained more than 90% of its initial concentration at both temperatures (Table 5 and Figure 3) but when combined with commercially available lidocaine, was only chemically stable at 40°C (Table 3 and Figure 2).

The lower limit of the 95% confidence interval relating concentration to time (determined by linear regression) indicated that magnesium and magnesium-lidocaine solutions stored at 25°C maintained 93.4% (CM50CL2), 80.0% (MSCL2), 93.1% (CM50), and 93.3% (MS), respectively, of their initial concentration throughout the study period. The solutions stored at 40°C maintained 92.0% (CM50CL2), 99.6% (MSCL2), 89% (CM50), and 94.3% (MS), respectively, of their initial concentrations throughout the study (Tables 2, 3, 5, and 6).

**DISCUSSION**

This study has shown that commercially available magnesium sulphate and lidocaine hydrochloride, when combined, are stable in a prefilled syringe for at least 168 days at 25°C and in conditions of high heat and humidity. This finding represents the first step in improving the administration of magnesium sulphate in the treatment and prevention of eclampsia.

Although it is well established that magnesium sulphate reduces morbidity and mortality associated with pre-eclampsia and eclampsia, it is not used regularly in some resource-limited settings. In a multi-country survey of maternal and newborn health conducted by the WHO, only 85.7% of women with eclampsia received the life-saving drug magnesium sulphate.<sup>18</sup> Identifying and eliminating barriers remains an important priority for clinicians and policy makers.

IV regimens for drug administration are difficult to establish and maintain in less developed countries where the necessary resources and technical support may not be available. In addition, the majority of care in areas remote from health centres is provided by community health care providers who have little formal training. IM injection is a

**Table 3. Percentage of initial concentration of reconstituted magnesium sulphate salt and commercially available lidocaine hydrochloride remaining after 168 days of storage at 25°C and 40°C (MSCL2)**

Variable	25°C		40°C	
	Magnesium sulphate (mmol/L)	Lidocaine hydrochloride (mg/mL)	Magnesium sulphate (mmol/L)	Lidocaine hydrochloride (mg/mL)
Initial concentration	2227	1863	2227	1863
Study Day				
1	100.0	95.9	100.9	98.4
2	98.6	95.5	99.9	95.7
3	99.6	94.9	100.0	95.7
7	99.1	95.7	97.1	95.3
14	99.6	94.8	99.3	96.9
28	99.1	98.3	99.0	95.1
42	99.6	96.5	99.9	96.2
56	99.9	97.3	97.4	95.0
70	100.9	96.7	100.0	95.1
84	98.1	93.8	98.1	93.1
98	92.7	96.5	93.1	99.8
112	101.5	95.6	100.8	95.5
126	99.2	95.0	96.1	96.5
140	95.0	94.9	103.0	95.8
154	79.0	95.4	<sup>a</sup>	94.7
168	75.9	95.6	111.8	95.3
Estimated % remaining on day 168	85.9	98.5	104.2	99.6
Lower 95% CI for % remaining	80.0	96.4	99.6	98.6

<sup>a</sup>Insufficient sample to measure concentration.

validated mode of administration of magnesium sulphate used in both the Magpie<sup>5</sup> and the Collaborative Eclampsia<sup>6</sup> Trials and is an easier route of administration than IV administration. The injection not only requires less training

**Table 4. Percentage of initial concentration of lidocaine hydrochloride remaining after 168 days of storage at 25°C and 40°C (CL2)**

Variable	25°C	40°C
	Lidocaine hydrochloride (mg/mL)	Lidocaine hydrochloride (mg/mL)
Initial concentration	21 841	21 841
Study Day		
14	97.9	95.4
28	97.5	100.0
56	95.7	98.4
84	98.7	99.9
112	98.8	99.0
140	100.4	96.2
168	99.0	99.6
Estimated % remaining on day 168	101.3	100.0
Lower 95% CI for % remaining	97.5	95.2

to enable safe administration but also does not require the same level of monitoring or cumbersome supplies required by IV administration (which requires continuous monitoring). These factors are critical when the IM injection is given in a remote setting or when it is given in units in which the number of patients exceeds the number of available health care professionals, and they permit wider use of the medication. Furthermore, providing an injection of the IM loading dose prior to transfer of a patient prevents any delay in patients receiving this lifesaving treatment.

The disadvantage of IM administration is the pain associated with injection. In several studies evaluating pain with IM injection of benzathine penicillin and ceftriaxone, reported pain was greatly reduced by combining the antibiotic with a local anaesthetic agent such as lidocaine.<sup>19–22</sup> Very few studies of the use of magnesium sulphate in preeclampsia and eclampsia have described lidocaine being added to relieve the pain of the IM injection. In those that have described doing so, 1 mL of either a 1% or 2% lidocaine hydrochloride solution was drawn up in the same syringe as magnesium sulphate immediately before administering the IM injection.<sup>11,23–25</sup> This extra step complicates the dosing of magnesium sulphate, particularly

**Table 5. Percentage of initial concentration of reconstituted magnesium sulphate salt remaining after 168 days of storage at 25°C and 40°C (MS)**

Variable	25°C	40°C
	Magnesium sulphate (mmol/L)	Magnesium sulphate (mmol/L)
Initial concentration	2461	2461
Study Day		
1	97.3	97.1
2	100.9	100.3
3	97.6	100.1
7	101.5	99.1
14	101.6	100.7
28	100.0	103.7
42	100.4	101.4
56	96.1	102.6
70	101.4	103.1
84	98.4	106.9
98	96.1	98.1
112	96.1	92.8
126	97.4	100.2
140	95.3	98.0
154	95.0	98.6
168	95.9	97.5
Estimated % remaining on day 168	95.2	97.6
Lower 95% CI for % remaining	93.3	94.3

in the case of a minimally trained health care provider; withdrawing two solutions from two different vials may lead to dosing errors, an increased risk of contamination, and inadvertent needle stick injuries.

Concern about the side effects caused by magnesium sulphate is another reason cited for practitioners' reluctance to use the drug. Although administration of magnesium sulphate is commonly associated with a feeling of warmth, flushing, and nausea and vomiting, toxic side effects leading to central nervous system and/or respiratory depression are uncommon. In a review of 24 studies of a total of 9556 women treated with magnesium sulphate for eclampsia prevention or treatment in low to middle income countries, side effects of concern were rare; they included absent patellar reflexes (1.6%), respiratory depression (1.3%), and the need to use calcium gluconate to counteract the effects of magnesium sulphate (0.2%).<sup>26</sup> These were comparable to the 1% incidence of adverse side effects in the Magpie study, which had the largest study population of over 5000 women.<sup>5</sup> In fact, McDonald et al. conducted a systematic review of "real-world" use of magnesium sulphate and found that the maternal benefits far outweighed the small risk of magnesium toxicity.<sup>27</sup>

**Table 6. Percentage of initial concentration of commercially available magnesium sulphate remaining after 168 days of storage at 25°C and 40°C (CM50)**

Variable	25°C	40°C
	Magnesium sulphate (mmol/L)	Magnesium sulphate (mmol/L)
Initial concentration	2003	2003
Study Day		
14	103.0	106.6
28	102.4	102.0
56	103.7	103.2
84	103.7	105.2
112	97.1	95.3
140	99.8	102.6
168	99.3	96.1
Estimated % remaining on day 168	96.7	94.5
Lower 95% CI for % remaining	93.1	89.0

Lidocaine is also a very safe drug. Also known as lignocaine, this agent has also been used systemically as an antiarrhythmic and for treatment of neuropathic pain. Both of these indications involve 1.0–1.5 mg/kg doses administered as an IV bolus or infusion.<sup>28</sup> Toxicity results from single doses greater than 300 mg (4.5 mg/kg without epinephrine), and this far exceeds the 20 mg proposed for combination with magnesium sulphate in the prefilled syringe.<sup>29</sup> Accidental intravascular injection of lidocaine can lead to central nervous system and cardiovascular intoxication, but the overall rate of adverse drug reactions with lidocaine is low (0.01%).<sup>30</sup> Nevertheless, care should be taken to avoid inadvertent intravascular injection, by aspiration prior to injection, by incremental injection, and by dose limitation.<sup>31</sup> The safety of lidocaine in pregnancy has also been declared by the United States Food and Drug Administration, which classifies it as a category B drug. This indicates that although there are no well controlled studies in pregnant women, reproductive studies performed revealed no evidence of harm to fetus,<sup>28</sup> and it is not contraindicated during labour and delivery. In fact, it is listed as an option in the American Congress of Obstetricians and Gynecologists Practice Bulletin on appropriate obstetric analgesia and anaesthesia.<sup>32</sup>

We believe that the ideal solution to encourage wider use of magnesium sulphate would be to provide the active drug in combination with lidocaine in a prefilled, ready-to-use syringe for IM injection, easing both administration and pain. Our study has shown that the combination of these drugs can remain stable for up to six months.

Unfortunately, although the commercially available magnesium sulphate remained stable in combination with lidocaine, the reconstituted magnesium sulphate salt in combination with commercially available lidocaine did not retain 90% of its initial concentration in both storage conditions at 168 days. The benefit of reconstituting the magnesium sulphate from salt was to enable a higher concentration (61% vs. 50%), thereby reducing the volume of injection from 10 mL to 8 mL. Even in the processing phase, we had difficulty maintaining the higher concentration in solution. Despite a solubility in water at 20°C of 71 g/100 mL,<sup>33</sup> mixtures containing more than 69 g/100 mL became cloudy. Interestingly, both the magnesium sulphate reconstituted from salt alone and in combination with commercial lidocaine was more stable at 168 days at 40°C, which could be attributed to greater solubility at the higher temperature. However, because of variable production, conditions of transport, and storage temperature, particularly in less-developed countries in which these prefilled syringes would be most useful, the higher concentration would not likely remain in solution and would thereby result in suboptimal doses.

Future research in a clinical trial with human subjects will be required to determine the extent of the pain relief provided by including lidocaine in the IM injection of magnesium sulphate. Research is also ongoing to determine how to best use magnesium sulphate, including the minimum effective dose and whether the initial dose can safely be given before transfer to hospital.<sup>10</sup> We hope these findings will contribute to increased use of magnesium sulphate and decreased maternal mortality and morbidity related to preeclampsia and eclampsia.

## **CONCLUSION**

The combination of commercially available magnesium sulphate and lidocaine hydrochloride is physically and chemically stable in a prefilled syringe for at least 168 days at high heat and humidity. These findings make feasible the concept of a prefilled “Magnocaine” syringe for IM injection for the prevention and/or treatment of eclampsia.

## **ACKNOWLEDGEMENTS**

This project was funded by the Pre-eclampsia—Eclampsia Monitoring, Prevention & Treatment Initiative, University of British Columbia, a grant recipient of the Bill & Melinda Gates Foundation.

Sara Houlihan wishes to acknowledge the inspiration of her father, Richard Houlihan, who passed away in December 2015. As a scientist, he understood the struggles

involved in conducting research; his sage advice and encouragement will not be forgotten.

## **SUPPLEMENTARY DATA**

Supplementary Data related to this article can be found at <http://dx.doi.org/10.1016/j.jogc.2016.04.097>.

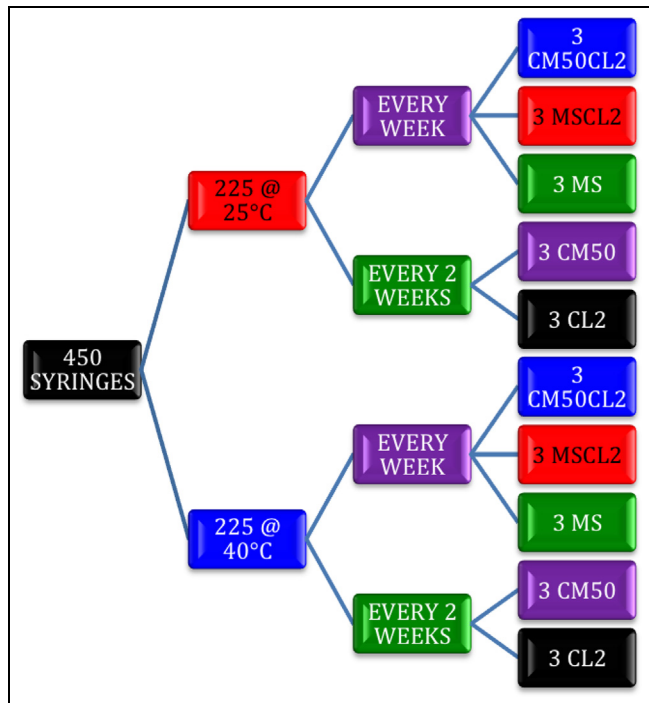
## **REFERENCES**

1. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol* 2009;33:130–7.
2. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet* 2010;376:631–44.
3. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet* 2006;367:1066–74.
4. Duley L, Gulmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. *Cochrane Database Syst Rev* 2010;(11):CD000025.
5. Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet* 2002;359:1877–90.
6. The Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet* 1995;345:1455–63.
7. Duley L, Henderson-Smart DJ, Walker GJ, Chou D. Magnesium sulphate versus diazepam for eclampsia. *Cochrane Database Syst Rev* 2010;(12):CD000127.
8. Duley L, Henderson-Smart DJ, Chou D. Magnesium sulphate versus phenytoin for eclampsia. *Cochrane Database Syst Rev* 2010;(10):CD000128.
9. Duley L, Gulmezoglu AM, Chou D. Magnesium sulphate versus lytic cocktail for eclampsia. *Cochrane Database Syst Rev* 2010;(9):CD002960.
10. Duley L, Matar HE, Almerie MQ, Hall DR. Alternative magnesium sulphate regimens for women with pre-eclampsia and eclampsia. *Cochrane Database Syst Rev* 2010;(8):CD007388.
11. Pritchard JA. The use of the magnesium ion in the management of eclampogenic toxemias. *Surg Gynecol Obstet* 1955;100:131–40.
12. Pritchard JA, Cunningham FG, Pritchard SA. The Parkland Memorial Hospital protocol for treatment of eclampsia: evaluation of 245 cases. *Am J Obstet Gynecol* 1984;148:951–63.
13. Zuspan FP. Problems encountered in the treatment of pregnancy-induced hypertension. A point of view. *Am J Obstet Gynecol* 1978;131:591–7.
14. Liu S, Joseph KS, Liston RM, Bartholomew S, Walker M, Leon JA, et al. Incidence, risk factors, and associated complications of eclampsia. *Obstet Gynecol* 2011;118:987–94.
15. Newby B. Stability of magnesium sulfate 20% in viaflex bags. *Can J Hosp Pharm* 2008;61:356–65.
16. Hagan RL, Carr-Lopez SM, Strickland JS. Stability of nafcillin sodium in the presence of lidocaine hydrochloride. *Am J Health Sys Pharmacy* 1995;52:521–3.
17. Shaalan RA, Belal TS. HPLC-DAD stability indicating determination of nitrofurazone and lidocaine hydrochloride in their combined topical dosage form. *J Chromatogr Sci* 2010;48:647–53.
18. Souza JP, Gulmezoglu AM, Vogel J, Carroli G, Lumbiganon P, Qureshi Z, et al. Moving beyond essential interventions for reduction of maternal



- mortality (the WHO Multicountry Survey on Maternal and Newborn Health): a cross-sectional study. *Lancet* 2013;381:1747–55.
19. Amir J, Ginat S, Cohen YH, Marcus TE, Keller N, Varsano I. Lidocaine as a diluent for administration of benzathine penicillin G. *Pediatr Infect Dis J* 1998;17:890–3.
  20. Patel IH, Weinfeld RE, Konikoff J, Parsonnet M. Pharmacokinetics and tolerance of ceftriaxone in humans after single-dose intramuscular administration in water and lidocaine diluents. *Antimicrob Agents Chemother* 1982;21:957–62.
  21. Hayward CJ, Nafziger AN, Kohlhepp SJ, Bertino JS Jr. Investigation of bioequivalence and tolerability of intramuscular ceftriaxone injections by using 1% lidocaine, buffered lidocaine, and sterile water diluents. *Antimicrob Agents Chemother* 1996;40:485–7.
  22. Schichor A, Bernstein B, Weinerman H, Fitzgerald J, Yordan E, Schechter N. Lidocaine as a diluent for ceftriaxone in the treatment of gonorrhoea. Does it reduce the pain of the injection? *Arch Pediatr Adolesc Med* 1994;148:72–5.
  23. WHO Department of reproductive health and research Managing complications in pregnancy and childbirth: a guide for midwives and doctors. 2 ed. Geneva: WHO Press; 2007:S-45.
  24. Tukur J. The use of magnesium sulphate for the treatment of severe pre-eclampsia and eclampsia. *Ann African Med* 2009;8:76–80.
  25. Sharma P, Mir S, Rizvi M, Akthar S. Efficacy of magnesium sulphate versus phenytoin in seizure control and prophylaxis in patients of eclampsia and severe pre-eclampsia. *JK Science* 2008;10:181–5.
  26. Smith JM, Lowe RF, Fullerton J, Currie SM, Harris L, Felker-Kantor E. An integrative review of the side effects related to the use of magnesium sulfate for pre-eclampsia and eclampsia management. *BMC Pregnancy Childbirth* 2013;13:34.
  27. McDonald SD, Lutsiv O, Dzaja N, Duley L. A systematic review of maternal and infant outcomes following magnesium sulfate for pre-eclampsia/eclampsia in real-world use. *Int J Gynaecol Obstet* 2012;118:90–6.
  28. Lexicomp Online, Lexi-Drugs, Hudson, Ohio: Lexi-Comp, Inc.; July 7, 2013.
  29. Sweetman SC. *Martindale: the complete drug reference*. 36 ed. London-Chicago: Pharmaceutical Press; 2009.
  30. Liu W, Yang X, Li C, Mo A. Adverse drug reactions to local anesthetics: a systematic review. *Oral Surg Oral Med Oral Path Oral Radiol* 2013;115:319–27.
  31. Mulroy MF. Systemic toxicity and cardiotoxicity from local anesthetics: incidence and preventive measures. *Regional anesthesia and pain medicine* 2002;27:556–61.
  32. Goetzl LM. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists, Number 36, July 2002. Obstetric analgesia and anesthesia. *Obstet Gynecol* 2002;100:177–91.
  33. MJ ON. *Merck Index*. 14 ed. New Jersey: Merck & Co. Inc; 2006.

APPENDIX 1. Flow of Experimental and Control Products



## APPENDIX 2. DETAILED METHODOLOGY

### Chemistry Analyzer

MG reagent<sup>TM</sup>, used in conjunction with the SYNCHRON UniCel Dx600i system, determined the magnesium concentration of each sample. In the reaction, MG reagent<sup>TM</sup> combines with calmagite to form stable chromogen. The product is formed rapidly giving reproducible results with a minimum of interferences (known interferents include chelating agents such as EDTA/citrate/oxalate, gadolinium and hemolysis given that erythrocytes contain magnesium). The system then monitors change in absorbance at 520 nanometers. This change in absorbance is directly proportional to the concentration of magnesium in the sample. Two levels of assayed quality control were used to verify method performance. The method performance was based on monthly coefficients of variation (CVs). This method has a CV of 2.4% at a target concentration of 2.05 mmol/L and 1.2% at 4.92 mmol/L.

### Preparation of magnesium reagent

The assay used to determine magnesium concentration with the UniCel Dx600i Synchron Access clinical system has been previously published.<sup>16</sup> No preparation of the reagent was required as it was supplied by the manufacturer. The reagent used was calibrated with the manufacturer's calibrators prior to analysis. The magnesium in the calibrator is traceable to NIST SRM 929. (The traceability process is based on prEN ISO 17511.) Commercially available magnesium sulphate 50% USP (PPC Pharmaceutical Partners of Canada; Richmond Hill, Ontario; lot 6101127; expiry date June 2013) was used to as the internal control.

### Preparation of the magnesium sulphate samples

Each magnesium sample (CM50CL2, CM50, MS, MSCL2) was thawed, vortex-mixed then diluted with sterile normal saline 1:1000 to meet the analytical range of the assay used. Final theoretical concentrations of magnesium sulphate were: 1844 mmol/L (CM50CL2), 2029 mmol/L (CM50), 2475 mmol/L (MS), and 2205 mmol/L (MSCL2).

### Degradation of Magnesium

Given that magnesium is a stable element, degradation is unlikely. However, to prove that there is no interference or cross-reactivity between magnesium and lidocaine degradation products, magnesium-free solutions of commercially available lidocaine and normal saline were analyzed by the Synchron. The samples of lidocaine were those stored up to 168 days as well as a commercially available stock solution to assess for the interference of lidocaine degradation products. The second control with normal saline assessed for leaching of magnesium from the polypropylene syringes. Finally, a standard addition of magnesium was also performed to observe for a negative interference.

### HPLC instrumentation<sup>15,16</sup>

The HPLC instrument (Waters Alliance System, model 2690; Waters Corporation; Mississauga ON) consists of a delivery pump, an automatic injector equipped with a 200  $\mu$ L injector a Symmetry C8 4.6  $\times$  250 mm column (Waters Corporation; Mississauga ON; lot 01843724213648), a Symmetry C8 3.9  $\times$  20 mm guard column (Waters Corporation; Mississauga ON; lot 0184372211) and an ultraviolet (UV) detector set at 234 nm. The mobile phase consisted of a mixture of 30% acetonitrile (Fisher Scientific; Whitby ON; lot 126537) 70% ammonium formate buffer (Sigma-Aldrich; lot BCBG3990V) pH 3.0. The assay was performed at room temperature. All solvents were HPLC-grade and filtered before use. The flow rate was set at 1.2 mL/min.

### Preparation of lidocaine stock standard solutions

Lidocaine standards were prepared as follows. Lidocaine 20 mg/mL was diluted to 4 mg/mL in HPLC-grade water (Fisher Scientific; Whitby ON; lot 127395). Dexamethasone powder 1 mg/mL (Sigma-Aldrich; Oakville ON; lot 120M1331V) diluted in HPLC-grade water was selected as IS. Lidocaine standard solutions containing 0.25 mg/mL of the IS were prepared in HPLC-grade water to final concentrations of 0.100, 0.200, 0.300, 0.500, 0.700, and 0.800 mg/mL. In order to prevent injection of impurities onto the column, all standards were filtered through a GHP (Gelman hydrophobic polyethylene) 13 mm diameter, 0.45  $\mu$ m microfilter Acrodisc<sup>TM</sup> (Waters Corporation; Mississauga ON; lot 21770796) prior to injection.

**APPENDIX 2. Continued**

A 6-point calibration curve was prepared with a blank (water) at the beginning of each run to ensure that there is no carry-over between runs. The range of the standard curve (0.100–0.800 mg/mL) encompassed the diluted test concentrations of all the study solutions. The calibration curve was generated by the least square regression of the peak area ratio of lidocaine to dexamethasone and the concentration of each lidocaine standard.

The precision of the assay was evaluated by intra-day and inter-day validation methods. Intra-day validation was determined by running the standard's lower limit of quantitation, low, medium, and high concentrations (0.100, 0.250, 0.400, 0.600 mg/mL) in quadruplicate throughout a single day. The inter-day validation was determined by running the same standard concentrations in quadruplicate daily for 4 days. Accuracy of the assay was calculated as the mean deviation between nominal and observed concentrations. Mean, standard deviation, and coefficient of variation were also calculated. Acceptable limits of coefficients of variation for precision were defined *a priori* as less than 10% and acceptable limits for accuracy were defined as greater than 90%.

**Preparation of lidocaine samples**

Each lidocaine study sample (CL2, MSCL2, and CM50CL2) was thawed and then vortex-mixed for 10 seconds. The CL2 sample was diluted 10-fold with HPLC-grade water. A 0.250 mL of either the diluted CL2 sample or the MSCL2 and CM50CL2 sample was added to 0.250 mL of IS and 0.500 mL of HPLC-water for final theoretical concentrations of 0.50 mg/mL CL2, 0.454 mg/mL MSCL2, 0.544 mg/mL CM50CL2, and 0.250 mg/mL IS. Each sample was filtered through a 0.45 mm Acrodisc<sup>TM</sup> microfilter before a 25  $\mu$ L was injected onto the column.

**Degradation of lidocaine**

Sets of 1 mL CL2 (1:10), CM50CL2, and MSCL2 samples were treated with 500  $\mu$ L of either 1N NaOH, 1N HCl, or 30% H<sub>2</sub>O<sub>2</sub> and water as control and then vortex-mixed. A set of solutions was kept at room temperature and the remaining samples were placed in a water bath at 100°C for 2 hours. The controls were kept at room temperature. Both sets of samples and the controls were stored protected from UV light. After the specific period, the samples were placed at 4°C overnight. They were then allowed to warm up to room temperature and were neutralized and the final volume was adjusted to 2 mL. The aliquots were then diluted 1:2 in water without internal standard. The samples were filtered and injected onto the column. The chromatograms obtained were compared to a chromatogram obtained from the calibration curve to determine any changes in concentration, retention time, and peak shape.