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

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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 $MgSO_4$, using both commercially available $MgSO_4$ (50%) and $MgSO_4$ 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.

Conclusions: Commercially available MgSO4 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.

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

Competing Interests: None declared.

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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 $MgSO_4$, obtenu à partir de $MgSO_4$ (50%) commercialisé et de $MgSO_4$ 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 MgSO4 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.

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INTRODUCTION

Hypertensive disorders of pregnancy affect approximately 10% of all pregnant women around the world[1,2]; 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.[3]

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.[4,5] In addition, magnesium sulphate is the anticonvulsant of choice for women with eclampsia,[6] and is proven to be more effective than diazepam,[7] phenytoin,[8] or lytic cocktail.[9]

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.[10]

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)[11,12] and Zuspan (4 g IV loading dose then maintenance of 1g/h IV infusion).[13] 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."[14]

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