Heliyon 7 (2021) e07099

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Emergency medicine: magnesium sulphate injections and their pharmaceutical quality concerns

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ARTICLE INFO

Keywords:
Magnesium sulphate
Women's health
Pre-eclampsia
Eclampsia
Quality drugs

ABSTRACT

Objectives: World Health Organization has recognized magnesium sulphate as the drug of choice for prevention and treatment of fits associated with preeclampsia and eclampsia which are amongst the leading causes of maternal morbidity and mortality. In this study, the pharmaceutical quality of magnesium sulphate injections marketed in Anambra state was assessed.

Methods: Ninety samples of magnesium sulphate obtained from the 3 senatorial zones in Anambra state were subjected to identification tests, microbiological analysis consisting of Growth promotion test, sterility and endotoxin test. Content analysis using titrimetric method and pH analysis were also carried out on the samples.

Results: Twenty percent (20%) of samples obtained from Onitsha failed identification test as they had no Registration number in Nigeria. All samples subjected to the microbiology tests (sterility and endotoxin test) passed. Twenty percent (20%) and thirty-three percent (33.3%) of samples sourced from Onitsha and Nnewi respectively failed the pH analysis test. All the samples passed microbiological tests and had their Active Pharmaceutical Ingredients (API) within the acceptable limit.

Conclusions: This study reveals that there are still some substandard magnesium sulphate injections in circulation in the locality. The supply chain of these drugs should be monitored to ensure a reduction in the incidences of substandard magnesium sulphate and positive therapeutic outcome which translates to reduced maternal mortality associated with pre-eclampsia and eclampsia in Nigeria.

1. Introduction

Poor-quality drugs have been and are still global crises posing a threat to global health. Substandard medicinal products as described by WHO are drugs that contain inadequate amount of active ingredients, contain the wrong active ingredients, are contaminated with harmful substances and/or are falsely labeled [1, 2, 3]. The consequences of such drugs have always been emphasized but all efforts to control the illicit availability and use of these drugs seem to be lagging [1, 4, 5]. Addressing the issue of poor-quality medicines is complex and requires collaboration and concerted efforts among drug manufacturers, distributors and government agencies across the global medicine supply chains [1, 4]. These drugs enter the supply chain through avenues that include, the manufacturers, distributors or retailers [6, 7].

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https://doi.org/10.1016/j.heliyon.2021.e07099
Received 29 March 2021; Received in revised form 3 May 2021; Accepted 14 May 2021

Substandard or counterfeit drugs constitute serious threat to the health care system, especially in emergency medical situations, such as in maternal health. The circulation of substandard medicines remains a serious problem in developing countries like Nigeria (may be due to weak boarders between the countries in the region) where a large number of drugs available for sale are imported [8].Nigeria's population of over 200 million people makes it an attractive market for sale and use of pharmaceuticals and allied products. Over 60% of medicines are imported into the country and largely reflects the inadequate capacity to produce and monitor essential medicines in the country leading to a high failure rates of drugs in circulation such as magnesium sulfate injections [9]. This highlights the importance of close monitoring of the quality of the drugs since any change in quality can drastically affect patients' health management and outcome.

There is a high prevalence of maternal mortality in developing nations such as Nigeria, of which the use of substandard drugs, among other factors, may play some contributory role [9, 10]. The quality of magnesium sulphate remains suspect in Nigeria where majority of drugs in use are imported, with persistent issues in the supply chain and distribution systems. Therefore, this study was performed to evaluate the quality of magnesium sulphate injections marketed in Anambra State of Nigeria.

2. Materials and methods

2.1. Materials

Ninety (90) samples of magnesium sulphate injections consisting of 5 different brands purchased from different locations across the three senatorial districts of Anambra State of Nigeria were used for the study.

2.2. Culture media

Soybean casein digest media (TM Media, India), Fluid thioglycolate media (TM Media, India), Soybean Case in Digest Agar, Nutrient Agar (Oxoid limited, UK) Sabouraud Dextrose Agar (Oxoid limited, UK), Clostridia Agar (Oxoid limited, UK), and Peptone water (TM Media, India).

2.3. Reagents

Reagent used in the study include EDTA, Ammonium chloride, Mordant black, Isopropyl alcohol, LAL (Limulus Amebocyte Lysate) reagent water, Savlon Antiseptic Liquid (Johnson & Johnson (Pty), South Africa), Distilled water, Ammonium Chloride, Sodium Hydroxide, Hydrochloric acid.

2.4. Equipment and instrument

The equipment used include Incubator (Genlab UK), Autoclave (EQUITRON Medica, Instrument India), Hot Air Oven (Genlab, UK), Water-bath sonicator (PCI Analytics, India), Laminar Flow chamber (Krishna Scientific suppliers, India), LAL kit (pyrotell: Control Standard Endotoxin, Limulus Amebocyte Lysate, LAL Reagent Water).

3. Method

3.1. Sampling strategy and sample size

Simple random sampling of drug outlets in Anambra State was done after stratifying them into senatorial districts of the State. Samples of Magnesium sulphate injections were then purchased from the drug outlets located in the three major cities representing each of the 3 senatorial districts that make up the State. During the period of the samples collection (May to July 2019), five (5) different brands were available from Onitsha, 3 brands from Nnewi and 1 brand from Awka. Ten ampoules of each brand (giving a total of 90 samples) were analyzed.

3.2. Identification tests

The samples were inspected for correct labeling and packaging conditions. The samples were also inspected according to the requirements of the regulatory authorities on injectables including name of product, list of active ingredients, batch number, expiration and manufacturing dates, indications for use, name and address of manufacturer, storage conditions and physical inspection of products for any particulate matter (visual screening).

3.3. Microbiological analysis

A total of 3 isolates (*Clostridium sporogenes*, *Bacillus subtilis* and *Aspergillus brasiliensis*) previously stored from clinical samples in the postgraduate laboratory of the Department of Pharmaceutical Microbiology and Biotechnology of School of Pharmaceutical Sciences, Awka were used for the Growth Promotion Test [11]. Before the analyses, the isolates were revalidated and confirmed using the standard protocols as previously reported [12, 13].The sterility test was carried out aseptically using the direct inoculation method [14]. The samples were incubated and monitored daily for 14 day at a temperature of 22.5 °C±2 °C for Soybean-Casein Digest media and 30–35 °C±2 °C for the Fluid thioglycolate media. The results were read at the completion of the incubation time.

3.4. Endotoxin test

The endotoxin test was performed using compendial method [15] using Pyrotell® Gel-Clot Endotoxin kit (Cytiva, USA).

3.5. Hydrogen ion index (pH) analysis

A pH electrode connected to a pH meter (PHS-3C) was rinsed with distilled water, cleaned with tissue and inserted into the sample. The pH meter was turned on and the reading was taken in triplicate.

3.6. Content analysis

The content analysis was carried out using titrimetric method [9]. Titrimetry is the compendial method for the analysis of $MgSO_4$ Injection. Five (5) ml of the sample was titrated against 0.05M EDTA using mordant black as an indicator and ammonium (10.9 = pH) as a buffer. A colour change to blue by the reaction mixture indicates the end of the titration while taking note of the initial volume of the volumetric solution and its final volume (volume at the point of colour change). The estimated amount of the sample (Equation 1) and percentage assay (Equation 2) were calculated using the formulae below [15].

$$\text{Estimated amount, \% w / v} = \frac{\text{Titre value (F)} \times 100 \times \text{conc. of 0.05 EDTA} \times 0.01232 \times 40}{\text{Vol. of sample taken} \times 0.05} \quad (1)$$

where,

Titer value, F = Initial volume of sample – final volume of sample.

Concentration of 0.05M EDTA = concentration of the volumetric solution after standardization.

0.01232 = 12.32g of $MgSO_47H_2O$ divided by 1000.

Table 1. Physical evaluation of the sampled products.

Brand name	Colour in ampoules	Packaging condition	NAFDAC number	Batch number	Mfg. date	Exp date	Sampling location
Brand A	Clear liquid	10ml rubber ampoules and carton not so good.	A11-0088	77HE03	May 2018	April 2021	Onitsha (All samples were stored on the shelves)
Brand B	Clear liquid	10ml amber colour ampoules, cartons good.	B4-0358	171201	Dec 2017	Dec 2020	
Brand C	Clear liquid	10ml white ampoules. Packaged individually. Carton best condition	Nil	0077073	Nov 2017	Nov 2020	
Brand D	Clear liquid	10ml white coloured ampoules. Carton very good condition	A4-9648	N-9897	Aug 2017	July 2020	
Brand E	Clear liquid	10ml white coloured ampoules. Carton very good	B4-3492	171101	Nov 2017	Nov 2020	
Brand A	Clear liquid	10ml amber colour ampoules, cartons good.	B4-0358	171201	Dec 2017	Dec 2020	Awka (Stored on the shelves)
Brand B	Clear liquid	10ml white coloured ampoules. Carton very good condition	A4-9648	N-9897	Aug 2017	July 2020	
Brand C	Clear liquid	10ml white coloured ampoules Carton very good.	B4-3492	171101	Nov 2017	Nov 2020	
Brand A	Clear liquid	10ml rubber ampoules and carton not so good.	A11-0088	77HE02	May 2018	April 2021	Nnewi (On the shelves)

40 is the diluting factor (i.e. 200ml which is the diluent divided by 5ml which is the amount of EDTA sample taken for standardization).

Volume of sample taken = volume of the test sample used, 0.05 is a theoretical concentration constant.

$$\textbf{Assay},\ \% = \frac{(\text{Estimated amount in \%w/v}) \times 100}{\text{Label claim in \%w/v}} \quad (2)$$

where,

estimated amount, %w/v = result obtained from Eq. (1).

Label claim, %w/v = 50% (as indicated on the sample packages) [15].

3.7. Data presentation

The results were expressed as Mean ± Standard Deviation (SD) of triplicate readings.

4. Results

4.1. Identification test

A total of 90 samples of magnesium sulphate injection were collected and subjected to their registration verification. It was observed that all samples, except ten (one brand from Onitsha) were registered with NAFDAC; the drug regulatory agency in Nigeria. Labeling information regarding brand name, active ingredient and batch number were all provided on the labels. Seventy (70) samples, comprising of 40 from Onitsha and 30 from Nnewi had their expiry date set to be 1 year from the time of sampling while the remaining 20 samples, comprising of 10 each from Onitsha and Awka, were set at 2 years (Table 1).

The labels on the products were examined to verify the completeness of their identities. The samples from Nnewi and Awka had full identity while 20% of the samples from Onitsha had incomplete identity.

4.2. Microbiological analysis

The Growth promotion test performed on the media is shown in Table 2. The media supported the growth of the organism as expected thereby confirming that the media were fit for use for the sterility test.

The samples were subjected to the sterility test and endotoxin test. The results of the tests are as shown in Table 3. The Sterility test showed that all the samples were negative for bacterial growth after 3, 6, and 14 days of culturing in fluid thioglycolate medium and Soybean casein digest broth. Also, all the samples were negative for LAL qualitative Test. All the samples were, therefore, deemed to have passed the microbiological tests.

4.3. Content analysis

The USP [15] limits for the content analysis of Magnesium Sulphate Injection is 93.0–107.0%. The samples had a content analysis range of 94–102 % (Table 4). They were, therefore, considered to have their content analyses within the USP limits and so passed the test.

4.4. Hydrogen ion index (pH) study

Table 5 shows the pH analysis of the samples. Two brands (one brand from Onitsha and one brand from Nnewi) have pH below the acceptable limit of 5.5–7.0.

5. Discussion

Most developing countries have a fragile health care system, a condition that is further exacerbated by the circulation and use of substandard drugs. Magnesium sulphate used in maternal health for the treatment of preeclampsia and eclampsia reduces the burden of maternal mortality. In addition to the use of Magnesium sulfate injections for the management of preeclampsia and eclampsia they are also indicated for use in other critical health challenges, including nephritis in children, replacement therapy in acute hypomagnesaemia, in preventing or control of magnesium deficiency associated with total parental nutrition, etc.

Our findings documented the availability of magnesium sulphate in open market where it is freely available for purchase without prescription. Majority of the populace in our study reside in Onitsha and Nnewi areas where most of the failures occurred (20% identification and 33% pH test). Considering the vast scope of medical recommended uses of magnesium sulfate injections, the findings of this study further bring to focus that the continued circulation and use of substandard magnesium sulfate injections adversely impacts the health outcome of more people. Five different brands of magnesium sulphate were used for this study with two brands being more readily available in all the different locations. The study showed that 20 % of samples obtained from Onitsha failed the identification test as they had no NAFDAC registration number. This product was made by a foreign company and imported into Nigeria. This finding implies that such product was not registered for use in Nigeria and was probably smuggled into the country and thereby did not undergo certification by NAFDAC, the regulatory body in charge of

Table 2. Growth promotion test.

Test Organisms (Inoculum Size = 70CFU)	Sampling Time post-inoculation (Days)					
	Fluid thioglycolate medium			Soybean casein digest broth		
	3	6	14	3	6	14
Clostridium sporogenes	+ve	+ve	+ve	+ve	+ve	+ve
Bacillus subtilis	+ve	+ve	+ve	+ve	+ve	+ve
Aspergillus brasiliensis	+ve	+ve	+ve	+ve	+ve	+ve

Table 3. Microbiological quality of the magnesium sulphate Injections.

Sterility test							Pyrogen test			
Product Code	Sampling Time post-inoculation (Days)						Product Code	Number tested	LAL Qualitative Result	Number passed (%)
	Fluid thioglycolate medium			Soybean casein digest broth						
	3	6	14	3	6	14				
Opa	-ve	-ve	-ve	-ve	-ve	-ve	Opa	10	-ve	10
Omk	-ve	-ve	-ve	-ve	-ve	-ve	Omk	10	-ve	10
Oma	-ve	-ve	-ve	-ve	-ve	-ve	Oma	10	-ve	10
Ofe	-ve	-ve	-ve	-ve	-ve	-ve	Ofe	10	-ve	10
Oju	-ve	-ve	-ve	-ve	-ve	-ve	Oju	10	-ve	10
Npa	-ve	-ve	-ve	-ve	-ve	-ve	Npa	10	-ve	10
Nfe	-ve	-ve	-ve	-ve	-ve	-ve	Nfe	10	-ve	10
NMk	-ve	-ve	-ve	-ve	-ve	-ve	NMk	10	-ve	10
Aju	-ve	-ve	-ve	-ve	-ve	-ve	Aju	10	-ve	10

Key: +ve = positive while –ve = negative.
OPa, OMk, OMa, OJu, OFe = codes for brands of magnesium sulphate injection gotten from Onitsha.
NPa, NMa, NFe = codes for brands of magnesium sulphate injection gotten from Nnewi.
AJu = code for brand of magnesium sulphate injection gotten from Awka.

Table 4. Quantitation of magnesium sulphate molecules in the samples.

Product code	(Samples'Readings (Titre value in mL)				Est. Amt., (% *w/v*)	% Label Claim	% W/V calculated	Assay Calculation (%)	Inference (*Pass/Fail*)
	1	2	3	Mean ± SD					
Opa	9.45	9.60	9.60	9.55 ± 0.09	0.0502	50%	47.251	95	Pass
Ofe	9.75	9.80	9.85	9.80 ± 0.05	0.0502	50%	48.888	97	Pass
Oma	9.40	9.55	9.70	9.55 ± 0.15	0.0502	50%	47.251	95	Pass
Omk	9.95	9.80	9.95	9.90 ± 0.09	0.0502	50%	48.982	98	Pass
Oju	10.25	10.40	10.25	10.30 ± 0.09	0.0502	50%	50.961	102	Pass
Npa	19.25	19.60	19.55	19.47 ± 0.19	0.0499	50%	48.198	96	Pass
Nfe	20.05	20.10	20.00	20.05 ± 0.05	0.0499	50%	49.304	99	Pass
NMk	19.70	19.75	19.65	19.70 ± 0.05	0.0499	50%	48.444	99	Pass
Aju	9.60	9.60	9.55	9.58 ± 0.03	0.0498	50%	47.120	94	Pass

Table 5. pH Analysis for the samples.

Product code	Readings				Inference
	Sample 1	Sample 2	Sample 3	Mean ± SD	
Opa	6.02	6.01	6.02	6.017 ± 0.006	All PASS
Ofe	5.61	5.60	5.61	5.607 ± 0.006	All PASS
Oma	5.86	5.84	5.85	5.855 ± 0.007	All PASS
Omk	5.28	5.25	5.27	5.267 ± 0.015	All FAIL
Oju	6.00	6.01	6.00	6.003 ± 0.006	All PASS
Npa	5.76	5.75	5.77	5.760 ± 0.010	All PASS
Nfe	5.64	5.63	5.65	5.640 ± 0.010	All PASS
NMk	5.42	5.41	5.40	5.410 ± 0.010	All FAIL
Aju	5.89	5.90	5.88	5.890 ± 0.010	All PASS

certifying locally manufactured as well as imported medicinal products for use in Nigeria.

All the samples used in this study passed the microbiological tests similar to the results obtained on childhood immunization vaccines [16]but differs from another study on metronidazole and ciprofloxacin infusions marketed in south Eastern Nigeria [13], were it was reported that 18.75% of the infusions failed the microbiological tests. Similarly, all samples of the magnesium sulphate tested in the present study passed the content analysis test. Our findings were slightly different from that of Anyakora et al. [9] where a failure rate of 2.4 % for content analysis was reported. Our study showed that all the sampled products passed the content analysis test. The differences may be due to differences in the study sites, different batches and/or manufacturers. Our study sampled from Anambra State whereas Anyakora et al sampled from Abia state and suggested that substandard Magnesium Sulphate injections were found in circulation in each of the six geopolitical zones of Nigeria.

The pH analysis of the samples showed that four (4) brands constituting 40 samples purchased from Onitsha were within the acceptable limit (5.5–7.0) while one (1) brand constituting 10 samples failed to meet the acceptable pH limit. Similarly, 10 samples (1 brand) out of the 30 samples obtained from Nnewi failed the pH test. Overall, 20 % (10 samples out of the 50 samples) of drug samples from Onitsha and 33.3 % (10 out of the 30 samples) from Nnewi failed to meet the acceptable standard of pH for magnesium sulphate injection as required by the USP. Coincidentally, the samples from Onitsha and Nnewi that failed the pH analysis were of the same brand. The pH profile of a drug can be used to determine the pH at which the product was formulated, and this usually correlates to the pH of maximum stability of that drug as well as enhance solubility of the drug. Significant variance from the ideal pH can lead to drug decomposition or precipitation and has been reported as a significant cause of phlebitis in peripheral veins [17, 18]. Studies suggest that significant pH deviations from the blood pH of 7.4 causes tissue damage, although the mitigating effect of short duration infusions has not yet been determined [19, 20, 21].

This study reveals that substandard magnesium sulphate injections are in circulation in Anambra state and potentially other states in the country. Quality medicines, safe portable water and immunization are pivotal to the attainment of quality healthcare [13, 22].

6. Conclusions

The results of this study indicate that there are still some substandard magnesium sulphate injections in circulation in the study area. It also revealed the presence and circulation of unregistered magnesium sulphate injections and may suggest the likelihood of other pharmaceutical products not registered within the drug management and supply system in Nigeria. Therefore, strict governmental policies and commitments are urgently needed to curb these disturbing and dangerous trends.

7. Recommendation

Considering the varied uses of the drug in critically ill patients, adequate control and monitoring of the relevant market-supply sources for magnesium sulfate injections by the government, manufacturer, etc, will assist to ensuring that patients whose medical conditions necessitate the intake of the drug are receiving high quality and reliable medical care when administered with this medication. A regional-wide surveillance study on the quality of magnesium sulphate injections is therefore recommended to cover the 5 states in the region and possibly include other geographical regions of Nigeria in order to enhance comprehensive governmental decision making/policies in the overall control of substandard medications. Education of the key players in the pharmaceutical supply chain, which includes health workers and drug retailers, could help to ensure a full understanding of the challenges that substandard drugs poses to the health care system. More frequent market surveillance of these drugs by governmental agencies, such as NAFDAC and drug manufacturers could help alleviate the sale of counterfeit drugs while improving the standard of medicines available to consumers in Nigeria.

8. Limitations

- Study time/sampling time was short so could not sample more batches of the same brand.
- The determination of particulate matters was carried out by visual observation only.

Declarations

Author contribution statement

Angus Nnamdi Oli: Conceived and designed the experiments; Wrote the paper.

Chukwuebuka Emmanuel Umeyor: Conceived and designed the experiments.

Ezinne Janefrances Nwankwo: Performed the experiments; Wrote the paper.

Jude Nnaemeka Okoyeh: Analyzed and interpreted the data.

Chukwuemeka Chukwubuikem Okoro: Analyzed and interpreted the data.

Chijioke M. Ofomata: Contributed reagents, materials, analysis tools or data.

Emmanuel Chinedum Otakagu: Contributed reagents, materials, analysis tools or data.

Ruth Asikiya Afunwa: Contributed reagents, materials, analysis tools or data.

Ugochukwu Stanley Umeh: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Gordon C. Ibeanu: Conceived and designed the experiments; Wrote the paper.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Acknowledgements

Authors wish to thank the parents of EJN for funding the study. This study is part of the M. Sc thesis of EJN.

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