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How to reduce the treatment gap for people with epilepsy in resource-limited settings by innovative galenic formulations: A review of the current situation, overview of potential techniques, interests and limits

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ABSTRACT

Epilepsy is a chronic neurological disease affecting more than 69 million people worldwide, nearly 90% of them in low and middle-income countries (LMICs). In those countries, only four major antiepileptic drugs are commonly used: phenobarbital, carbamazepine, sodium valproate and phenytoin. There are also problems with the accessibility, availability and quality of drugs. The main objective was to review the literature concerning "long" sustained-release formulations of AEDs that have the potential to reduce the number of administrations and help overcome problems of compliance, accessibility and the treatment gap. The main endpoint was a releasing of the active ingredient over more than 24 h. We also assessed the feasibility and acceptability in resource-limited settings. Two drugs were found in unconventional release formulations: carbamazepine and sodium valproate; but they were not "long" sustained release because they required administration once a day. Several techniques were available, including: esterification, transdermal devices, liposomes and polymeric devices preformed or formed *in situ*. *In situ* methods for the preparation of injectable biodegradable microparticles or implants for controlled delivery seemed best suited to the objective. Furthermore, they appear to fulfil the requirements of feasibility and cost. Sodium valproate appeared as well to be a relevant candidate for a "long" sustained release formulation that would improve access to medicines for people with epilepsy in resource-limited settings. .

Contents

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Introduction

Epilepsy is a huge health problem that accounts for more than 0.5% of the global burden of disease (Ngugi et al., 2010). It affects more than 69 million people worldwide, of whom about 90% live in resource-limited settings which belong to low- and middle-income countries (LMICs) according to the World Bank income classification (Newton and Garcia, 2012; Ngugi et al., 2010). These data concern lifetime epilepsy (LTE). People with active epilepsy (AE), those who may require a treatment, were estimated to 32.7 million with 83% in developing countries. Rural areas in those regions are deeply impacted with 73% of LTE and 63% of AE. Furthermore, the populations of these countries face some issues which are either absent or less important in high-income countries. These include difficulties related to accessibility, affordability, availability and poor quality of antiepileptic drugs (Cameron et al., 2012; Laroche et al., 2005; Mac et al., 2008), the first three being clearly the most important barriers to the efficient care of epilepsy. In this study, we raised the question of how to reduce the problem of accessibility and thereby improve medication adherence. Broadly, urban areas are usually supplied with sufficient quantities of AEDs and with a choice of suitable molecules recommended by the WHO model list of essential medicines to treat epilepsy (valproic acid, carbamazepine, phenytoin and phenobarbital). Most often, those medications are only available in LMICs mainly due to their affordable cost (Cameron et al., 2012).

However, semi-urban and rural areas are less well supplied and with proportionately fewer health facilities and specialists. The proportion of people with epilepsy (PWE) who require a treatment but do not receive it (called treatment gap) is very high. A recent meta-analysis have shown a treatment gap of over 75% in low income countries (LICs) and over 50% in most lower middle- and upper middle-income countries, with higher figures in rural areas (rate ratio, RR: 2.01; 95% confidence interval, CI: 1.40–2.89) (Meyer et al., 2010). Consequently, treating epilepsy remains more complicated in rural than in urban areas. This represents a high burden in resource-limited settings and some of the factors involved are a poor drug supply and long travel times to reach healthcare facilities (Mbuba et al., 2008). Furthermore, although phenobarbital is a first-line AED and registered on the WHO essential medicines list, it remains a controlled substance. This feature complicates its use (importation, manufacturing, distribution, etc.) and strengthens the treatment gap in countries where it is broadly used (Bhalla et al., 2015).

The treatment gap improvement assumption in developing countries

For almost 70% of PWE, seizures are sufficiently controlled by AEDs. However, this disease is a chronic affection and those drugs cannot definitely cure it. PWE will need to continue taking medications for several years. Adherence to a treatment is even more important for a chronic disease that requires a long-term therapy and a specific drug concentration to be efficient. A report published by the WHO in 2003 has shown that several barriers could compromise adherence: social and economic factors, healthcare system, characteristics of the disease, disease therapies and patient-related factors. Reducing the frequency of doses (French, 1994) and providing a regular, uninterrupted supply of medicines in developing countries (Desai et al., 1998) have been pointed to be relevant interventions to improve adherence to AEDs.

Improving access to care of people with epilepsy in LMICs can be done at several levels. The hypothesis of this paper is directly based on an optimization of existing therapeutics targeted on barriers mentioned above: decreasing the number of administrations of a drug by using long sustained release forms may improve adherence and contribute to reduce the accessibility issue. This new formulation could also contribute to minimize the impact of an irregular drug intake with often long therapeutic windows that can dramatically disturb the steady-state condition, leading to a potential therapeutic failure. The purpose of this innovative therapeutic is mainly focused on barriers for the treatment of non-communicable diseases found in resource-poor settings. A sustained release form could have a direct and/or indirect positive influence on several factors that affect adherence: socio-economic related factors (e.g., long distance from treatment settings (Elechi, 1991)); health system-related factors (e.g., irregular or poor drug supply (Elechi, 1991)); condition-related factors (e.g., forgetfulness (Garnett, 2000); memory deficits (Hargrave and Remler, 1996)). In addition, a “long” sustained release form could be relevant to minimize the oversight of taking the drug. .

This assumption not only concern the improvement for PWE in LMICs but also all patients with a chronic disease and although our researches are focused on developing countries, the usefulness of such forms could not be limited to these parts of the world. Moreover, this improvement is conceivable for new molecules such as third or fourth generation AEDs but the cost of new formulated drugs would be even more expensive considering the cost of active ingredients except for those that have generics. To complete, a study carried out in 2009 in 40 developing countries has shown that generic medicines for chronic conditions were significantly