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Drug quality analysis through high performance liquid chromatography of isometamidium chloride hydrochloride and diminazene diaceturate purchased from official and unofficial sources in Northern Togo

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ABSTRACT

Trypanocidal drugs remain the most accessible and thus commonly used means of controlling tsetse transmitted animal African trypanosomosis. In Togo, trypanocides are sold on official as well as unofficial markets, but the quality of these trypanocides is undocumented so a drug quality assessment study was conducted from May 2013 to June 2014. Trypanocides supplied by European, Indian and Chinese pharmaceutical companies and sold on official and unofficial markets in Togo were purchased. In total fifty-two trypanocides were obtained, 24 of these samples from official markets and 28 from unofficial markets made up of a total of 36 diminazene diaceturate and 16 isometamidium chloride hydrochloride samples. The samples were analysed in the reference laboratory of the OIE (World Organisation for Animal Health), Laboratory for the Control of Veterinary Medicines (LACOMEV) in Dakar which uses galenic testing and high performance liquid chromatography (HPLC) testing as standard reference analysis methods. The results revealed a high proportion of trypanocides of sub-standard quality on the Togolese market: 40% were non-compliant to these quality reference standards. All of the HPLC non-compliant samples contained lower amounts of active ingredient compared to the concentration specified on the packaging. Non-compliance was higher in samples from the unofficial (53.57%) than from the official markets (25%; $p = 0.04$).The main drug manufacturers, mostly of French origin in the study area, supply quality drugs through the official legal distribution circuit. Products of other origins mostly found on illegal markets present a significantly lower quality.

1. Introduction

Animal African trypanosomosis control is targeting either the vector or the parasite or both, respectively. Despite the existence of ambitious programs in sub-Saharan Africa such as the Pan African Tsetse and Trypanosomosis Eradication Campaign

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(PATTEC) and numerous governmental initiatives in different countries to achieve elimination of the vector, tsetse flies are still omnipresent. *Glossina* spp. are resilient vectors whose populations can restore quickly after control operations cease. Even though many efficient techniques are available for tsetse control, such as traps and targets (Esterhuizen et al., 2011), insecticide treated cattle (Bauer et al., 1995; Vale et al., 1999; Shaw et al., 2015), ground/aerial spraying, and sterile insect technique (Bouyer et al., 2014), elimination or even eradication of tsetse is unlikely to succeed in the near future because such interventions must be tediously planned at a continental scale in order to prevent tsetse re-infestation (Schofield and Kabayo, 2008). This is not possible for small-scale livestock owners in tsetse-infested areas who rely on access to trypanocidal drugs and self-organised or community-based vector control activities to decrease the negative impacts of the disease on livestock production (Affognon et al., 2010; Clausen et al., 2010; Muhanguzi et al., 2015). Ideally, trypanocidal drugs should be limited to use in treating clinical cases but in areas with high cattle densities under tsetse pressure, the restricted use of insecticides applied to the cattle's legs, lower belly, udder and the perianal region offers a much higher cost/benefit ratio (Shaw et al., 2013, 2014, 2015). Despite this and increasing drug resistance, animal trypanosomosis are still largely controlled by using trypanocides (Clausen et al., 2010; Mungube et al., 2012; Shaw et al., 2015).

Three compounds are in use, either diminazene diaceturate (DA) as a curative treatment, or as prophylaxis both isometamidium chloride hydrochloride (ISM) and homidium salts (homidium bromide and homidium chloride ethanoate). However, the use of homidium salts is no longer advisable due to their mutagenic effects (Sutcliffe et al., 2014). Because of their extensive and wide-spread use, resistance to DA and ISM has been increasingly reported in African countries such as Togo (Delespaux et al., 2008; Tchamdja, 2013), and this threatens the sustainability of trypanosomosis prevention and control. The poor quality of these drugs is often cited as contributing to both the development and spread of trypanocidal drug resistance (Geerts et al., 2001; Grace, 2003; Clausen et al., 2010).

Studies conducted in 2003 in Togo and Benin (Teko-Agbo et al., 2003) and in 2007 in Senegal (Walbadet, 2007) showed that a high proportion of trypanocidal drugs circulating in the region were of poor quality. In 2013, the trypanocides DA and ISM accounted for the largest proportion of sales of veterinary medicines in Togo, at 38% of the 1.13 million euros declared in the official market (Kombiagou, 2013). This relatively high value trypanocide market encourages the maintenance of a large unofficial trade network, often operated by untrained people in weekly livestock or food markets, which in turn can lead to poor treatment outcomes if drugs are of sub-standard quality.

Experts agree that the use of sub-standard or counterfeit trypanocides has severe implications for animal health, public health and the local economy (Van Gool and Mattioli, 2009; Sutcliffe et al., 2014). Even though the true proportion of such medicines is difficult to ascertain at a global scale, some research indicates that substandard drugs are being sold in significant numbers, generating a multi-billion dollar industry. The International Federation for Animal Health reports for example that the trade in unregistered and substandard veterinary drugs is worth $400 million annually (Kingsley, 2015). At the same time, a sociological survey conducted in Nigeria states that farmers themselves identified poor quality trypanocides as a negative impact on their livestock (Kingsley, 2015). Industry representatives on the other hand emphasized that the large market for substandard or fake products acted as a major disincentive for the development of new products, whereby the direct damage of sub-standard drugs was held responsible for treatment failure (Kingsley, 2015).

The objectives of this study were thus to assess the quality of trypanocidal drugs sold in official and unofficial markets by different suppliers from different countries and to discuss the results within the framework of the rules and regulations for veterinary pharmaceuticals in Togo.

This study is part of a joint initiative for trypanocidal drug quality control in Africa whose partners include the Global Alliance for Livestock Veterinary Medicines (GALVmed), the Food and Agriculture Organization of United Nations (FAO), the International Federation of Animal Health (IFAH), the International Atomic Energy Agency (IAEA) and the EC-funded Trypanosomosis Rational Chemotherapy program (TRYRAC).

2. Materials and methods

2.1. Study site and period

The study was conducted in Northern Togo in Kara and Savannah regions (Fig. 1), where 71% of the country's livestock production is concentrated (Ministère de l'Agriculture Elevage et Pêche, 2013). Drugs were purchased from two wholesalers and from four veterinary pharmacies, owned and run by veterinarians (official market) as well as from six weekly markets (unofficial). The trypanocidal drugs were collected in May 2013 and analysed at the Laboratory for the Control of Veterinary Medicines (LACOMEV) in Dakar, Senegal from July 2013 until July 2014.

2.2. Purchase of medicines

The protocol for purchasing DA and ISM was developed by LACOMEV, one of the reference laboratories of the World Animal Health Organisation (OIE). The products were purchased from the sellers (official and unofficial) and then sealed in plastic bags identified by a unique ID number. Information about (i) the trade name, (ii) the supplier, (iii) the place and date of manufacture, (iv) the expiry date and finally (v) the place of purchase were recorded on a standardised form.

To ensure sufficient sample quantity for analysis, 5 sachets of 10.5 g and 10 sachets of 1.05 g as well as 5 sachets of 1 g and 10 sachets of 125 mg were purchased for each DA and ISM sample, respectively.

In total, 52 samples (36 of DA and 16 of ISM) representing 25 different trade names were purchased (24 and 28 from the official and unofficial market respectively), and analysed at LACOMEV prior to the expiry date. The distribution of the samples according to active ingredient and marketing channel (official versus unofficial) is provided in Table 1.

2.3. Identification and storage of samples

The samples received at LACOMEV were entered into a Microsoft Access database. Identification codes were assigned to each sample and samples were stored in the sample laboratory where temperature is maintained at 22° +/− 2 °C.

2.4. Quality assessment

Quality was assessed by (i) galenic tests, (ii) identification and (iii) measure of the concentration of the active ingredient. The galenic test included pH measurement, the solubility of ready-made solutions as well as solutions prepared from DA granules or ISM powder according to the manufacturer's recommendations. The pH was measured using a Mettler-Toledo MP 230 pH meter with a pH between 4 and 7 considered as compliant. The solubility of solutions (ready-made or reconstituted) was assessed