Transactions of the Royal Society of Tropical Medicine and Hygiene 105 (2011) 61–67

Contents lists available at ScienceDirect

Transactions of the Royal Society of Tropical Medicine and Hygiene

journal homepage: http://www.elsevier.com/locate/trstmh

Review

Pharmacovigilance methods in public health programmes: the example of miltefosine and visceral leishmaniasis

Nilima Kshirsagar*[,1,2], Robin Ferner, Byron Alfredo Arana Figueroa, Hashim Ghalib, Janis Lazdin

Department of Clinical Pharmacology, Seth GS Medical College and King Edward Memorial Hospital, Parel, Mumbai, India

ARTICLE INFO

Article history:
Received 27 March 2010
Received in revised form 5 November 2010
Accepted 5 November 2010
Available online 23 December 2010

Keywords:
Visceral leishmaniasis
Pharmacovigilance
Public health programmes
Miltefosine
Risk minimisation
Adverse drug reaction monitoring

ABSTRACT

Pharmacovigilance is concerned with the assessment of benefit and harm. Disease burden, status of healthcare delivery through government centres and practitioners, existing pharmacovigilance programmes, relevant pre-marketing studies and the likely effectiveness and risks of drugs must be considered for planning pharmacovigilance activity. The risk of a drug may be known, unknown, potential or specific to the context of the programme. The potential benefits of a public health programme aimed at reducing or eliminating a specific condition will depend on the health burden due to that condition, which is a function of the seriousness of the condition and its frequency, as well as the likely efficacy of the programme in reaching its goals. The present article has outlined an approach to pharmacovigilance for such a donor-funded programme, using pharmacovigilance in leishmaniasis as an example.

1. Introduction

Patient safety is important for any healthcare programme as it directly influences the overall benefits and affects the acceptability of the programme. Pharmacovigilance is the science and activity relating to detection, assessment, understanding and prevention of adverse effects or any other possible medicine-related problems.[1] There are guidelines and regulations from the Council for International Organizations of Medical Sciences (CIOMS), the European Medicines Agency, the US Food and Drug Administration (FDA) and others that focus on pre-clinical, pre-marketing and post-marketing safety evaluations. These guidelines are useful for pharmaceutical companies for planning, implementing and reporting pharmacovigilance. However, in recent years several donor-funded programmes have been launched that involve drugs and vaccines, some of which are new and some of which could be relatively unsafe.

Public health initiatives offer opportunities for benefits but also possibilities of harm to large populations, such as the outbreak of Guillain–Barré syndrome linked to swine influenza vaccine that was used in 1976–77 in the USA.[2] There have been few previous examinations of the problem of pharmacovigilance in public health programmes in developing countries; we were able to identify only ten potentially relevant references (Box 1).

2. Visceral leishmaniasis as an example

Here we outline the general issues of pharmacovigilance in public health programmes in developing countries and illustrate them by reference to the pharmacovigilance plan for a programme for eliminating visceral leishmaniasis

* Corresponding author.
E-mail address: kshirsagarna@yahoo.in (N. Kshirsagar).
[1] Dean, MGM, ESIC Hospital, New Delhi.
[2] Emeritus Professor, Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Parel 400012, Mumbai.

0035-9203/$ – see front matter © 2010 Royal Society of Tropical Medicine and Hygiene. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.trstmh.2010.11.004

Box 1. Database: Ovid MEDLINE, 1950 to Week 2, August 2010

Search strategy:
1 *Adverse Drug Reaction Reporting Systems/ (2205)
2 exp Public Health/ (4434173)
3 1 and 2 (1371)
4 exp Developing Countries/ (54311)
5 3 and 4 (10)

(VL), caused by parasitic protozoa of the genus *Leishmania*, using the drug miltefosine in India, Nepal and Bangladesh.

Pharmacovigilance is concerned with the assessment of benefit and harm. Factors that need to be considered in planning pharmacovigilance activity include disease burden, status of healthcare delivery through government centres and private practitioners, existing pharmacovigilance programmes, relevant pre-marketing studies and likely effectiveness and risks of the drugs to be used. The risks of the drug may be known, unknown, potential and specific to the context of the programme.

3. Potential benefits of the programme

The potential benefits of a public health programme aimed at reducing or eliminating a specific condition will depend on the burden of ill health due to the condition, which is a function of the seriousness of the condition and its frequency, as well as the likely efficacy of the programme in reducing that burden.

VL is a life-threatening disease prevalent in 62 countries, however 90% of cases occur in India, Nepal and Bangladesh.[3] Up to now, both the diagnosis and treatment of VL have been difficult. Diagnosis has depended on microscopic examination of splenic aspirate, which is obtained by splenic puncture, an invasive and potentially dangerous procedure.[3] A rapid diagnostic test (RDT) on peripheral blood (rK39) has been developed with 91–98% specificity and 100% sensitivity,[4,5] which is suitable for use in the field.

4. Current treatment of visceral leishmaniasis

Currently, the standard treatment for VL is sodium stibogluconate (SSG), amphotericin and pentamidine, all of which have to be injected, require admission to hospital and produce serious adverse reactions. In many parts of India, the causative parasites are resistant to SSG.[3] Miltefosine, a drug that can be given orally on an outpatient basis and is thus suitable for use at primary healthcare centres, has been developed and has received marketing authorisation.[6]

4.1. Miltefosine

Miltefosine is an alkyl-lysophospholipid, a phospholipid analogue, originally proposed as a topical treatment for secondary cancers of the skin. The drug does not undergo significant microsomal metabolism and has a long half-life of approximately 2 weeks when taken orally. Miltefosine has been found to be effective in >90% of patients with VL[6] in clinical trials when used at the correct dose and for the correct duration.

These two tools, namely fingerprick blood testing by rK39 RDT and oral treatment with miltefosine, can be used in primary health centres. At the World Health Assembly, a tripartite agreement for the elimination of VL using these two tools was signed between India, Bangladesh and Nepal, with funding from donor agencies.[7]

Miltefosine has known adverse effects; moreover, because it has not been widely used there is also the possibility of new adverse effects being recognised. In addition, unknown risks may arise when a drug is used in a large population. Furthermore, weaknesses of the public health programme may pose a further risk of harm.[8]

In animal studies, miltefosine is toxic to the eye, causing degeneration of retinal pigment epithelium. Animal studies have also revealed an effect on spermatogenesis, embryotoxicity and teratogenicity. Clinical studies have not reported retinal adverse effects or inhibition of spermatogenesis;[9] however, adverse drug reactions (ADR) with an incidence of <1 in 1000 may have been missed in these studies.

Gastrointestinal toxicity with high doses of miltefosine limited its use as an oral anticancer drug. In the treatment of VL, the drug often produces diarrhoea, with vomiting in >10% of patients and nephrotoxicity in 1–10%. These risks can be minimised by correcting anaemia and dehydration before starting treatment as well as by early recognition and prompt treatment if these reactions develop.

In human use, the risk of fetal damage can be precluded by avoiding pregnancy during 28 days of treatment and for 3 months after stopping treatment (as miltefosine has a long half-life). In clinical trials, patients aged <2 years, those with anaemia, breast-feeding or with severe kidney or liver disease, and those taking concomitant nephrotoxic or hepatotoxic drugs were excluded, so there are potential risks in these populations (Table 1).

4.2. Risk of harm

Public health departments have limited resources and manpower, and introducing a new programme may divert them from other important problems. Thus, there is an opportunity cost in introducing a new programme and it is important to be sure that it is commensurate with the likely benefits. Where a programme involves treatment with a medicine or vaccine, there can be problems with availability, supply, storage, off-label use (use outside the licensed indications) of the product, and medication errors. These problems are not necessarily apparent during small-scale trials. The efficacy of a treatment used in the field is likely to be lower than its efficacy under optimal conditions in a clinical trial, and the adverse effects may be more important. A rare and previously unrecognised, but serious, adverse effect can become apparent during extended usage. Generally, if n patients have been given a medicine and no examples of a particular adverse event (such as death) have been encountered, the 95% CI for the true rate of the adverse event lies between zero and $3/n$.[10]