Medicine and Society

Title: Access to medicines for orphan diseases- experiences in the management of a case of *Fasciola Hepatica* in Mumbai, India

Introduction

Fascioliasis is primarily an infection of herbivores caused by the parasitic trematodes *Fasciola hepatica* and *Fasciola gigantica* and there is increasing evidence of human infections worldwide, especially in the rural poor. Human disease due to *F. hepatica* is endemic in the Altiplano region of Bolivia with high prevalence rates in humans and their sheep and cattle [1, 2] in Peru, Egypt [3] and Iran [4]. At the point of writing this paper, only isolated case reports from India have been published [5, 6.] We present here, our experience in the management of fasciolosis in a 9 year old child hailing from Nepal with emphasis on challenges of access to medicines for orphan diseases in a developing country.

Case description

KV, a 9 year old male child hailing from the Kolchibahur district of Nepal, and whose parents had traveled to India a few months prior in search of a job presented with complaints of fever, swelling of the face, distended abdomen, abdominal pain and vomiting. A stool examination showed the presence of ova of *Fasciola Hepatica.* An ultrasound of the abdomen showed mild hepatomegaly, dilatation of the common bile duct (CBD) and ill-defined anechoic lesions in both lobes of the liver. A plain magnetic resonance imaging of the abdomen revealed impacted debris with proximal CBD and intra hepatic biliary radicle dilatation. An endoscopic retrograde cholangiopancreatography was then done; the CBD canulated and the multiple *Fasciola hepatica* adult flukes visualized as filling defects on the cholangiogram. A biliary spinchterotomy with partial fluke extraction and biliary stenting was then done for symptomatic management. The drug of choice for this child was triclabendazole[7] as both albenbazole and praziquantel do not act on all forms of the trematode. Triclabendazole is not registered for human use in India although a veterinary product (which is not recommended for use in humans) is available. The fourth option Nitazoxanide has been shown to have varying cure rates and is available in India, but is not approved by the US FDA for treatment of *Fasciola Hepatica* infection, nor recommended for use by the World Health Organization.[8, 9]

In an effort to obtain triclabendazole, the Special Drug Services of the Centre for Disease Control (CDC), USA was approached at drugservice@cdc.gov. The CDC replied that while they do have a small quantity for use for patients residing in the United States, they are not permitted to export the drug outside their country due to FDA regulations and referred us to the WHO (available at http://www.who.int/neglected_diseases/diseases/fascioliasis/en/index.html) for further information.

Per the information on this website, a request was sent to the WHO country office. A request was also sent simultaneously to the Novartis office in Mumbai since the website alluded to the fact that WHO was partnering with Novartis to make triclabendazole available. The company readily agreed to assist in importing the drug.

The subsequent procedures as per the Central Drugs Standard Control Organization (CDSCO, Ministry of Health and Family Welfare, Government of India) for obtaining a license for an individual patient use included 1) writing a prescription for the drug by the physician in charge, 2) a one page write up by the physician on the urgent need to import the drug, 3) filling of form 12AA (application form for license to import small quantities of for new drugs by a Government hospital or autonomous medical institution for treatment of patients) duly forwarded by the Director of the institute 4) Filling of a one page Annexure for drug import and 5) Payment of an amount of Rs 100/- (2USD) through a disbursement slip. The authorization to import the drug was then issued by the Mumbai office of the Assistant Drugs Controller (India) who also authorized customs clearance. (available at www.cdsco.nic.in/guidelines for port officers.pdf)

Three weeks after the original diagnosis, the patient received triclabendazole (EGATEN ^{TM}) in the dose of 10mg/kg (total dose 250 mg) in the intensive care unit. Two weeks post treatment, the patient improved symptomatically, the stool was negative for ova of *Fasciola hepatica*, and 4 weeks post treatment, a follow up ultrasound abdomen showed no adult flukes.

Discussion

The management of patients with orphan diseases is associated with myriad difficulties. These include - lack of knowledge and training in the disease area, challenges in accessing information to manage the disease, lack of sufficient diagnostic facilities, and finally obstacles in accessing the drug. [10] We were able to obtain the medicine because of generous assistance from Novartis India. While all procedures were fairly routine, they did take considerable time. Significant time was also spent on scouring the internet drug information and for these processes and procedures. A more expeditious, official, clearly publicized protocol by the regulatory authorities on their website needs to be in place to improve access to medicines for rare diseases. This will particularly help physicians practicing in remote areas in the country who may not have the knowhow, the time or resources to procure these medicines. The time lost in the procedure to obtain the medicine (3 weeks in our case) can well mean the difference between life and death.

Different countries have differing definitions of orphan disease. In the United States, it is a disease that affects fewer than 200,000 individuals in the country while Europe defines it as a condition that affects fewer than 5 in 10,000 patients. [11] It is estimated that approximately 5,000 to 7,000 rare diseases exist, and every year about 250 new ones are described. [6] The high costs and risks of drug development, combined with difficulties in conducting clinical trials in small patient populations and the small market size, discourage the pharmaceutical industry from developing drugs for these rare diseases. [12] An extensive search of the Indian regulatory website of the CDSCO as well as other government websites revealed no definitions of orphan diseases or drugs as also lack of sources to find information on diagnosis and management.

The fundamental difference between essential drugs and orphan drugs lies in the fact that the former targets populations and the latter, an individual patient. Thus, finding ways to bring drugs for rare diseases to patients is an important public health issue. [6] This case highlights the need to have a specific national policy for defining an orphan disease as also creation of portals for easy retrievable information on diagnosis, management and regulatory processes, both for drug approval or import where necessary so that patient access to medicines is made that much easier. Simpler and expeditious processes for importing drugs that are not registered in the country also need to be put in place. These are crucial particularly for diseases where the drug may be life-saving.

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