Access to medicines for orphan diseases: Experience in the management of a case of *Fasciola hepatica* in Mumbai, Maharashtra, India

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INTRODUCTION

Fascioliasis is an infection of herbivores caused by the parasitic trematodes *Fasciola hepatica* (F. hepatica) and *Fasciola gigantica*. There is increasing evidence of human infections worldwide, especially among the rural poor. Human disease due to *F. hepatica* is endemic in the Altiplano region of Bolivia, and the prevalence rates among humans and their sheep and cattle are high in Peru, Egypt and Iran. Only isolated case reports from India have been published till now. We present our experience in the management of fasciolosis in a 9-year-old child from Nepal, with a focus on the difficulties in accessing medicines for orphan diseases in a developing country.

THE CASE

A 9-year-old boy, who hailed from the district of Kolchibahur in Nepal and whose parents had travelled to India a few months earlier in search of a job, presented with complaints of fever, swelling of the face, a distended abdomen, abdominal pain and vomiting. Stool examination revealed the presence of ova of *F. 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 MRI of the abdomen revealed impacted debris with proximal CBD and intrahepatic biliary radicle dilatation. An endoscopic retrograde cholangiopancreatography was then carried out. The CBD was cannulated and the multiple *F. hepatica* adult flukes visualized as filling defects on the cholangiogram. A biliary sphincterotomy with partial fluke extraction and biliary stenting were carried out for symptomatic management. The drug of choice for this child was triclabendazole as 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) was available. The fourth option, nitazoxanide, has been shown to have varying rates of cure and although it is available in India (approved for *Giardia lamblia* or *Cryptosporidium parvum*), it is approved neither by the US Food and Drugs Administration (FDA) nor by the Drugs Controller General of India for the treatment of *F. hepatica* infection, nor is it recommended for use by WHO.

In an effort to obtain triclabendazole, the Special Drug Services of the Centers for Disease Control (CDC), USA was approached at drugservice@cdc.gov. The CDC replied that while it did have a small quantity for use by patients residing in the USA, it was not permitted to export the drug due to FDA regulations. It referred us to WHO (http://www.who.int/neglected_diseases/diseases/fascioliasis/en/index.html) for further information. On the basis of the information on this website, a request was sent to the WHO country office. Simultaneously, a request was sent to the Novartis office in Mumbai since the website mentioned 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 licence for importing a drug for an individual patient included: (i) obtaining a prescription for the drug from the physician in charge, (ii) handing in a one-page write-up by the physician on the urgent need to import the drug, (iii) filling form 12AA (an application form for a licence for the import of small quantities of new drugs by a government hospital or autonomous medical institution for the treatment of patients), duly forwarded by the director of the institute, (iv) filling a one-page annexure for the import of the drug, and (v) paying an amount of ₹100 (about US$ 2) 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 (www.cdso.nic.in/guidelines for port officers.pdf).

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

DISCUSSION

The management of patients with orphan diseases is associated with myriad difficulties. These include a lack of knowledge and training with respect to the disease, challenges in accessing information for the management of the disease, lack of sufficient diagnostic facilities, and finally, obstacles in accessing the drug. We were able to obtain the medicine because of the generous assistance extended by Novartis India. While all the procedures involved were fairly routine, they did take considerable time. A lot of time was also spent on scouring the internet for information on drugs and on the processes and procedures. The regulatory authorities need to make available a more expeditious, official and clearly publicized protocol on their website to improve access to medicines for rare diseases. This would be of particular use to physicians who are practising in remote areas in India and who may not have the knowhow, time or resources to procure these medicines. The time lost owing to 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 USA, it is defined as a disease that affects fewer than 200 000 individuals, while Europe defines it as a condition that affects fewer than 5 in 10 000 patients. It is estimated that approximately 5000-7000 rare diseases exist, and about 250 new ones are described every year. The high costs and risks of drug development, combined with difficulties in conducting clinical trials in small patient populations and the small size of the market,
discourage the pharmaceutical industry from developing drugs for these rare diseases. Upon doing an extensive search of the Indian regulatory website of the CDSCO, as well as other government websites, we found that there were no definitions of orphan diseases or drugs. Also, there was a dearth of sources from which one could obtain information on the diagnosis of orphan diseases and their management.

The difference between essential drugs and orphan drugs lies in the fact that the former target populations and the latter, an individual patient. Thus, finding ways of bringing drugs for rare diseases to patients is an important public health issue. This case highlights the need to have a national policy for defining orphan diseases. It also points to the need for the creation of portals that provide easy access to information on diagnosis, management and regulatory processes, both for the approval of drugs and their import, where necessary, to make it easier for the patient to access medicines. 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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REFERENCES

NATIONAL POISONS INFORMATION CENTRE
Department of Pharmacology, All India Institute of Medical Sciences, New Delhi

The National Poisons Information Centre (NPIC) is running in the Department of Pharmacology, All India Institute of Medical Sciences, New Delhi. The Centre works 24x7 and provides on the spot information on management of various poisonings to healthcare professionals, government and private hospitals, all over the country.

The NPIC provides information on:
• the likely diagnosis
• possible signs and symptoms
• management guidelines
• possible antidote and availability

What the information seeker should provide:
Information about:
• himself: name, relationship, contact number and address
• the patient: age, sex, time since exposure, substance ingested, amount, mode, signs and symptoms, treatment provided

What is not provided by NPIC:
• Active treatment of the patient
• Supply of antidotes

In case of poisoning, contact the NPIC:
Tele: 011-26589391 Fax: 011-26589691 E-mail: npicaiims2010@gmail.com

Please note that the information provided cannot be used for any legal purpose

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