Potential consequences of essential drug shortages in Canada: Brain abscess due to Nocardia farcinica associated with dapsone prophylaxis for Pneumocystis jirovecii pneumonia

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In 2012, Canadian pharmacies experienced a shortage of trimethoprim-sulfamethoxazole (TMP-SMX) tablets. Drug shortages may result in unintended clinical consequences such as infection with pathogens against which the alternative medication is ineffective. This is highlighted in the present article, which describes a case of brain abscess due to Nocardia species that developed while receiving dapsone as an alternative for prophylaxis against Pneumocystis jirovecii pneumonia in a highly immune-suppressed patient. Clinicians should be cognizant of these issues when prescribing alternative agents.

Key Words: Drug shortage; Nocardia; PCP prophylaxis; Pneumocystis jirovecii; Trimethoprim-sulfamethoxazole

Case Report

A 54-year-old man with chronic lymphocytic leukemia experienced an incomplete response to several courses of combination chemotherapy. His disease was determined to be high risk on the basis of his poor treatment response and his relatively young age. A 10/10 human leukocyte antigen-matched, related, allogeneic peripheral stem cell transplant (SCT) was performed following a myeloablative conditioning regimen. After weaning of his immunosuppressive regimen, he developed chronic graft-versus-host disease (GVHD) involving the skin, mouth and lungs in the 12 to 18 months following SCT. He was placed back on immunosuppression with mycophenolate mofetil, sirolimus, 1 mg/kg daily prednisione and topical tacrolimus cream. He had also been initiated on extracorporeal photopheresis. Prophylactic antimicrobials consisted of dapsone 100 mg three times per week and penicillin V 500 mg/day.

He presented 20 months after transplantation with a new fever of 38.8°C, and was noted to have a headache of mild to moderate intensity as well as photophobia. He appeared otherwise well, with normal vital signs, mental status and neurological examinations, and no evidence of meningismus. His peripheral white blood cell count was 13.3×10⁹/L with a left shift and toxic granulation. A lumbar puncture performed to investigate the headache syndrome revealed abnormal cerebrospinal fluid (CSF) with a leukocytosis and neutrophilic pleocytosis (white blood cell count 6.75×10⁶/L with 84% neutrophils, 5% lymphocytes and 11% monocytes), hypoglycorrhachia (CSF glucose 1.5 µmol/L and serum glucose 5.6 µmol/L), and elevated protein of 3.52 g/L. A CSF Gram stain revealed no organisms, and a cryptococcal antigen test performed on the CSF was negative. Empirical therapy for a bacterial meningitis syndrome with vancomycin, ceftriaxone and ampicillin was associated with clinical improvement within 36 h.

Magnetic resonance imaging of the brain, six days after initiation of the antimicrobial agents, revealed a 5 mm ring-enhancing lesion in the right frontal lobe in the corpus callosum, immediately adjacent to the lateral ventricle (Figure 1). A thin, branching Gram-positive rod was isolated from the CSF culture, and ultimately identified by polymerase chain reaction 16s DNA sequencing as Nocardia farcinica/Nocardia otitidiscaviarum, which demonstrated in vitro susceptibility to TMP-SMX. It was presumed that his clinical presentation was...
related to cerebral Nocardia abscess with intraventricular rupture and subsequent meningeal reaction. The antimicrobial regimen was substituted with high-dose TMP-SMX oral suspension due to a national shortage ofTMP-SMX tablets. Follow-up magnetic resonance imaging of the brain at an interval of six weeks demonstrated improvement in the size of the ring-enhancing lesion. A treatment duration of 12 months was planned.

DISCUSSION

In May 2012, the supply chain of oral TMP-SMX tablets was threatened by back-ordering of its two major manufacturers in Canada, Apotex and Teva. We contacted both companies, but the cause of the back-order was not made available to us. Drug shortages are not uncommon in developed countries such as Canada; they may be due to unanticipated demand, shortage of a single-source pharmaceutical ingredient, manufacturing errors or product discontinuation (2). Drug shortages in the United States have tripled in recent years for a variety of reasons (2) and are likely to become more common in the future.

The effects of drug shortages on clinical care should be anticipated, planned for and, when possible, avoided. There are many stakeholders responsible for an effective national drug supply, including individual clinicians, pharmacies, pharmaceutical companies and governmental organizations. Canada has been criticized for not doing enough to anticipate and mitigate the impact of drug shortages (3). As an initial strategy, steps toward the creation of a national mandatory reporting system for anticipated drug shortages should be undertaken. In the meantime, clinicians must develop contingency plans for interruptions in medication supply. Furthermore, it is important to consider the clinical consequences of specific drug shortages, such as TMP-SMX, on specific clinical scenarios such as PCP prophylaxis.

Nocardia species are Gram-positive aerobic branching bacilli, ubiquitous in soil and decaying plant matter. It is transmitted by inhalation or direct skin inoculation, and can cause localized or disseminated disease (including brain abscess) in humans. Immunosuppression, especially impairment of cell-mediated immunity, is the main risk factor for disease (4,5). The epidemiology of Nocardia infection in specific populations is not well studied. A large single-centre registry analysis determined an overall infection rate of 0.6% in solid organ transplant recipients (5); infection rates in SCT recipients are likely to be similar.

A recent microbiological survey from Quebec (6) showed an increase in the total number of new clinical Nocardia isolates from 1997 to 2008. The increasing frequency of Nocardia infection is likely due, at least in part, to increasing immnosuppression, including solid and hematopoietic transplantation.

Prophylaxis against PCP is recommended by the Canadian Blood and Marrow Transplant Group, the Infectious Disease Society of America and other international societies (7) for patients receiving an allogeneic SCT for six months post-transplant and until patients have completed all immunosuppressive medications. Similar recommendations have been made for PCP prophylaxis in solid organ transplantation (8). Ongoing indications for immunosuppression, such as GVHD, often necessitate a longer duration of PCP prophylaxis. TMP-SMX is the preferred agent, due to superior efficacy, compared with the alternatives dapsone, atovaquone and aerosolized pentamidine (1,7,8).

In addition to its established efficacy in prophylaxis of PCP, TMP-SMX has antimicrobial activity against other pathogens for which transplant recipients are at risk. Nocardia species are highly susceptible to TMP-SMX. Infection with Nocardia species is uncommon, and the effect of prophylaxis on their incidence has never been formally studied in any patient population. Other pathogens that are susceptible to TMP-SMX include Streptococcus pneumoniae, Staphylococcus aureus, Listeria monocytogenes, Haemophilus influenzae, Legionella pneumophila, Toxoplasma gondii, Plasmodium species, Fungi and Pneumocystis jirovecii.

The safety and utility of TMP-SMX for the prevention of infectious diseases other than PCP in immunocompromised patients is established. In a randomized controlled trial, TMP-SMX has been shown to prevent urinary tract and bloodstream infection in the early postrenal transplant setting (9). TMP-SMX is more effective in preventing central nervous system reactivation of Toxoplasma gondii, compared with aerosolized pentamidine, in persons with HIV (10); its use is also recommended in the post-transplant population for this purpose (7,8). Prophylaxis using agents other than TMP-SMX, therefore, is likely to increase the risk of infection due to a number of important pathogens, in addition to PCP. Infectious diseases proven or likely to be reduced by TMP-SMX are presented in Box 1.

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With a few exceptions, alternative agents for the prophylaxis of PCP have little or no activity against many of the pathogens listed in Box 1 and could be expected to have little effect on their prevention. Aerosolized pentamidine does not penetrate the central nervous system, and its use in prophylaxis would not be expected to affect the frequency of pathogens other than PCP (7). Atovaquone is highly active against protozoal infections including Plasmodium species (ie, marketed
in combination with proguanil as Malarone [GlaxoSmithKline, USA] as well as against T gondii. However, it has not been adequately studied for the purposes of T gondii prophylaxis (7). Dapsone, a sulphone antibiotic, has some activity against T gondii (7). Plasmodium and Nocardia species (3). Generally, dapsone must be combined with a dihydrofolate reductase inhibitor, such as pyrimethamine, to obtain clinical potency against these pathogens. This combination may result in significant bone marrow toxicity including irreversible agranulocytosis. Its use alone in prophylaxis against T gondii is also not well studied (7).

In summary, with the unavailability of TMP-SMX tablets, PCP prophylaxis with dapsone was associated with a breakthrough Nocardia infection of the central nervous system in this immunosuppressed SCT recipient. In this instance, TMP-SMX oral suspension, a viable alternative, remained available throughout the tablet shortage but was not considered. Prophylaxis using an alternative to TMP-SMX results in unreliable activity and unproven clinical utility against a wide spectrum of clinically relevant infectious pathogens. Strategies to mitigate these risks are also unknown. In patients at high risk for reactivation for toxoplasmosis, including SCT patients within the first six months after transplant or with steroid-refractory GVHD, additional use of clarithromycin or, alternatively, pyrimethamine plus leucovorin is appropriate (6). The incremental value of adding agents for primary prophylaxis of other bacterial infections, including Nocardia and Listeria, is unknown, and is not recommended at the present time (7,8).

As drug shortages become more common, the Canadian shortage of TMP-SMX raises important considerations for clinicians, who may be forced to choose an alternative drug. Drug shortages may cause unintended consequences for the patient, thereby adding to the complexity of care and increasing costs to the health care system. As illustrated in the present report, Nocardia and other infections are more likely to occur in transplant recipients who use PCP prophylactic agents other than TMP-SMX. Clinicians should be aware of the potential gaps in antimicrobial activity afforded by the use of these other agents.

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