Original Article

Trends and patterns of national antimicrobial consumption in Japan from 2004 to 2016

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ABSTRACT

Frequent use of broad-spectrum antimicrobial classes has been reported in Japan; however, little is known about the long-term trend of national antimicrobial consumption, and that of individual agents. This study analyzed the national sales data of systemic antimicrobials from 2004 to 2016, derived from the IMS Japan Pharmaceutical Market database, to assess the consumption patterns of antimicrobial classes and agents in Japan. The number of defined daily doses per 1000 inhabitants per day (DID) was calculated for each antimicrobial agent. During the last 13 years, total antimicrobial consumption fluctuated by only 5% around the average of 14.41 DID. In 2016, the most used class was macrolides (32%), followed by cephalosporins (28%) and fluoroquinolones (19%). Oral agents comprised a large proportion (93%) of antimicrobial consumption. The most used agent, clarithromycin, accounted for 25% of all oral compounds used in 2016. The consumption of oral agents with high bioavailability, such as fluoroquinolones, amoxicillin, and sulfamethoxazole/trimethoprim increased, whereas that of cephalosporins decreased. In 2016, ceftriaxone was the most consumed parenteral agent, followed by cefazolin. The consumption of parenteral agents increased after 2009 when high-dose regimens of piperacillin/tazobactam, meropenem, and ampicillin/sulbactam were approved by the health insurance system. National antimicrobial consumption has been stable over the last 13 years. Moreover, shifts in the use of agents with high bioavailability and those approved for high-dose regimens were observed. However, the increased use of broad-spectrum agents is worrisome. A multifaceted approach is required to reduce overall antimicrobial consumption.

1. Introduction

Inappropriate and unnecessary use of antimicrobials accelerates the emergence and transmission of resistant bacteria [1]. Nevertheless, up to 50% of antimicrobial agents used in acute-care hospitals and more than 50% in outpatient settings are considered instances of misuse or overuse [2,3]. Considering that antimicrobial resistance (AMR) is a public health threat, antimicrobial stewardship programs (ASP) are being promoted to support the prudent use of antimicrobials and improve their associated susceptibilities [2–6]. Monitoring the antimicrobial use is one of the main components of ASPs [4,5].

The measurement of national antimicrobial consumption provides a basis to formulate policies and analyze the effect of interventions. National sales and reimbursement data are used as data sources, and the defined daily dose (DDD) per 1000 inhabitants per day (DID) is usually calculated [7]. Recently, the first report of national antimicrobial sales data elucidated the trends and patterns of antimicrobial consumption in Japan; the three major classes of antimicrobials used were macrolides, cephalosporins, and fluoroquinolones [8].

However, the previous study only showed the trend of national antimicrobial consumption in 2009, 2011, and 2013; as such, the more long-term trend remains to be elucidated. Furthermore, the national antimicrobial consumption of individual agents in Japan has not been reported to date. Given the wide variety of agents in each class, especially in terms of antimicrobial spectrum and

pharmacodynamics, antimicrobial consumption at the individual level varies. National reports produced by Public Health England and the National Institute for Public Health and the Environment of the Netherlands show trends in consumption for a certain number of antimicrobial agents over five and 10 years, respectively [9,10]. For example, the national report in England revealed that the progress of surveillance and action related to antimicrobial prescribing resulted in the reduction of total antimicrobial consumption and the use of broad-spectrum agents such as piperacillin/ tazobactam and meropenem in 2016. Therefore, understanding the antimicrobial consumption of individual agents is essential to provide more targeted information to improve the quality of antimicrobial use.

In the present study, we analyzed the long-term trend of national antimicrobial consumption from 2004 to 2016 and revealed the top 10 ranking antimicrobial agents for both oral and parenteral preparations in 2016 for the first time in Japan. This was primarily aimed at adequately assessing the consumption patterns of not only antimicrobial classes, but also commonly used agents in Japan.

2. Materials and methods

2.1. Data source

Antimicrobial sales data are commonly used as a measure of consumption [8,11]. National antimicrobial sales data from 2004 to 2016 were obtained from IMS Japan K.K. (Tokyo, Japan), which covers 99% of the total sales in Japan. The IMS data for our analysis consisted of systemic antimicrobials mostly administered via the oral and parenteral routes. Topical agents were excluded. Antimycobacterial, antifungal, antiviral, and antiparasitic agents were outside the scope of our analysis; however, aminoglycosides used as antimycobacterial agents were included. Metronidazole was excluded because it was categorized as an antiparasitic agent in the IMS Japan Pharmaceutical Market (JPM) database. Sulfonamides were also excluded because of the lack of quantitative data during extraction from the IMS JPM database.

2.2. Data analysis

Antimicrobial quantities from IMS data were converted into DDD values according to the Anatomical Therapeutic Chemical (ATC) classification system developed by the World Health Organization (WHO) Collaboration Centre for Drug Statistics Methodology. The WHO ATC/DDD index of 2017 was used [12]. For agents without a DDD assignment in the WHO ATC/DDD system, the maximum dosage approved by the health insurance system in Japan was adopted for DDD, and an ATC class was assigned according to its antimicrobial activity. Since DDD is the assumed average maintenance dose per day of a drug used for its main indication in adults, even special pharmaceutical forms mainly intended for children were assigned DDDs based on an adult weighing 70 kg. For combination drugs, the quantity of active substances was converted into DDD values. The DID was calculated for each agent at the fifth level of ATC classification. Population estimates for Japan were obtained from reports of the Statistics Bureau, Ministry of Internal Affairs and Communications [13].

For data analysis, cefmetazole, a parenteral cephamycin, was grouped with second-generation cephalosporins, and a few rectal and inhalation agents were grouped with oral agents. The Mann-Kendall trend test was used to statistically analyze the trend of total antimicrobial consumption. All analyses were conducted using a custom Perl script, Microsoft Excel (Microsoft Corporation, Redmond, WA, USA), and the R statistical software version 3.3.1.

3. Results

3.1. Trends and patterns of total antimicrobial consumption

During the last 13 years, there was no trend of total antimicrobial consumption in Japan (Mann-Kendall trend test: p = 0.36), with DID values ranging from 13.90 in 2008 to 15.11 in 2012, and approximately 5% fluctuation around the average of 14.41 DID (Fig. 1). The top three classes used were macrolides (J01FA), cephalosporins (J01DB + DC + DD + DE), and fluoroquinolones (J01MA) throughout the period, which constituted a mean proportion of 81%. In 2004, the most frequently used class was cephalosporins; however, this was replaced by macrolides from 2009. Between 2004 and 2016, the consumption of cephalosporins decreased by 20%, whereas that of fluoroquinolones and penicillins (J01C) increased by 47% and 37%, respectively. In 2016, the most widely used antimicrobial class was macrolides (4.56 DID, 32%), followed by cephalosporins (4.09 DID, 28%), fluoroquinolones (2.71 DID, 19%), and penicillins (1.45 DID, 10%). On average, third-generation cephalosporins comprised 83% of cephalosporins used.

3.2. Trends in oral antimicrobial consumption

Oral agents comprised a large proportion (93%) of total antimicrobial consumption in the 13 years investigated. The average oral antimicrobial consumption in Japan was 13.46 DID, ranging from 13.00 DID in 2008 to 14.15 DID in 2012 (Table 1). The use of the three major classes of oral antimicrobials (macrolides, cephalosporins, and fluoroquinolones) was identical to the total antimicrobial use, and constituted 83% of the mean.

Macrolide consumption peaked in 2011, whereas the consumption of fluoroquinolones increased by 47% from 2004 to 2016 but plateaued in 2012 (Fig. 2a). Between 2004 and 2016, cephalosporin (J01DB + DC + DD) consumption declined by 22%, whereas the consumption of penicillin, as well as sulfonamides and trimethoprim (J01EE), increased by 25% and 254%, respectively. The consumption of tetracyclines (J01A) was stable. In 2016, the most widely consumed antimicrobial class was the macrolides (4.56 DID, 34%), followed by cephalosporins (3.58 DID, 27%), fluoroquinolones (2.67 DID, 20%), penicillins (1.22 DID, 9%), tetracyclines (0.80 DID, 5.9%), and sulfonamides and trimethoprim (0.31 DID, 2.4%). The consumption of all three generations of cephalosporin declined year by year, wherein third-generation cephalosporins formed the majority of those consumed throughout the period (Fig. 2b). In 2016, third-generation cephalosporins (3.22 DID) accounted for 90% of the oral cephalosporins used.

The top 10 ranking oral agents in 2016 and their 13-year trends are shown in Table 1 and Fig. 3a. The sum of DID values of the top 10 oral agents (10.72 DID) accounted for 80% of all oral agents in 2016. Clarithromycin, the most consumed agent, accounted for 25% (3.28 DID/13.38 DID) of all oral agents used and 72% (3.28 DID/4.56 DID) of oral macrolides used in 2016. Other macrolides in the top 10 of oral agents in 2016 were azithromycin (0.65 DID, 5%) and roxithromycin (0.36 DID, 3%). Among cephalosporins listed in the top 10 oral agents in 2016, cefcapene (1.51 DID, 11%), cefditoren (1.14 DID, 9%), and cefdinir (0.35 DID, 3%) are third-generation cephalosporins. The commonly used fluoroquinolones in 2016, including levofloxacin (1.45 DID, 11%) and garenoxacin (0.55 DID, 4%), are respiratory fluoroquinolones. Between 2004 and 2016, the consumption of clarithromycin and azithromycin increased by 15% and 9%, respectively, and the use of both levofloxacin and amoxicillin increased by 34%, whereas minocycline and roxithromycin consumption decreased by 13% and 5%, respectively. Cephalosporin consumption decreased (cefcapene 13%, cefdinir 55%), except for