European Surveillance of Antimicrobial Consumption (ESAC): outpatient systemic antimycotic and antifungal use in Europe

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Objectives: To assess the total outpatient systemic antimycotic and antifungal use in Europe, and to identify the antimycotic and antifungal substances most commonly used.

Methods: Within ESAC (www.esac.ua.ac.be), using the anatomical therapeutic chemical (ATC) and defined daily dose (DDD) classification, data on outpatient use of all 14 antimycotics (12) and antifungals (2) for systemic use (ATC J02 and D01B, respectively), aggregated at the level of the active substance, were collected for 2007. Use was expressed in DDD (WHO ATC/DDD, version 2008) per 1000 inhabitants per day (DID). Only countries for which data on both J02 and D01B use were available were included in the analysis.

Results: In 20 European countries (data for Cyprus and Estonia include hospital use), total outpatient systemic antimycotic and antifungal use varied by a factor of 6.7 between the country with the highest (3.03 DID in Belgium) and the country with the lowest (0.45 in Croatia) use. Terbinafine, ketoconazole, itraconazole and fluconazole represented >94% of the total outpatient antimycotic and antifungal use in all countries. Terbinafine use represented >50% of the total systemic antimycotic and antifungal use in 16 out of 20 countries (not in Croatia, Italy, Luxembourg and Bulgaria).

Conclusions: We present for the first time a standardized and validated data set of outpatient systemic antimycotic and antifungal use in Europe. Our study demonstrates a variation of antimycotic and antifungal use in Europe, as striking as that of antibiotic use. The ESAC data facilitate the auditing of antimycotic and antifungal prescribing, and the evaluation of the implementation of guidelines and public health policies to promote their judicious use.

Keywords: antimycotic use, antifungal agents, drug consumption, pharmacoepidemiology, ambulatory care

Introduction

Outpatient antibiotic use in many parts of the world has been described in detail. However, data on the use of other antimicrobials, such as antimycotics and antifungals, are scarce. Published information on antimycotic and antifungal use is mainly limited to one country, to hospitals or to market and sales data using different denominators for expressing the use. In 2005, data on the consumption of antimycotics and antifungals were collected for the first time within the ESAC project, which was at that time given grant support by DG SANCO of the European Commission and is currently funded by the European Centre for Disease Control and Prevention (agreement number 2007/001). ESAC is an international network of surveillance systems aiming to collect comparable and reliable data on antimicrobial use in Europe. This article presents the first outpatient systemic antimycotic and antifungal use results of the ESAC project in 20 European countries in 2007.

Methods

In 2007, 36 countries participated in the ESAC project, including all 27 EU countries, 4 applicant countries (Bulgaria, Croatia, Romania and Turkey), 3 of the 4 members of the European Free Trade Association (Iceland, # The Author 2010. Published by Oxford University Press on behalf of the British Society for Antimicrobial Chemotherapy. All rights reserved. For Permissions, please e-mail: journals.permissions@oupjournals.org
Norway and Switzerland), Israel and Russia. In the ESAC project, data on antimicrobial use for ambulatory care aggregated at the level of the active substance were collected and expressed in defined daily doses (DDD) per 1000 inhabitants per day (DID), according to the anatomical therapeutic chemical (ATC)/DDD classification (WHO, version 2008).18 The number of inhabitants in the European countries was based on the midyear population in the country.19 The ATC J02 and D01B classes, antimycotics and antifungals for systemic use, respectively, include 14 unique substances (Table 1). In addition to a description of their use, seasonal variation and correlation between antimycotic and antifungal and antibiotic use were analysed.

Outpatient antimycotic and antifungal data were collected from 20 countries. We included also Estonia and Cyprus, although these countries were only able to provide total antimycotic and antifungal use data, i.e. ambulatory care and hospital care data. Antimycotic and antifungal use data were reimbursement data in Austria, Belgium, the Czech Republic, Hungary, Italy and Luxembourg, and distribution or sales data in the other countries.

Seasonal variation was calculated as the difference between the use in the second and third quarters (summer quarters) and the first and last quarters (winter quarters), expressed as a percentage of winter use:

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\frac{\text{DDD (summer quarters)/DDD (winter quarters)} - 1}{} \times 100
\]

Only data from countries that could provide quarterly data for J02 and D01B between 2005 and 2007 were included in the analysis. The correlation between antimycotic and antifungal use (ATC J02 and D01B) on the one hand and antibiotic use (ATC J01) on the other hand was assessed using Spearman’s coefficient for non-parametric correlation. All P values were based on two-tailed tests of significance (P<0.05). Statistical analysis was performed using SPSS software, version 15.0 for Windows (SPSS, Inc., Chicago, IL, USA). Data sources, validity of the data collection, details of the methodology used as well as the associated problems were described and discussed in detail elsewhere.6,17

Results

For only 4 of the 14 substances assigned an ATC code, the use in 2007 represented >1% of the total outpatient antimycotic and antifungal use in Europe, while no use was recorded for 4 substances (Table 1).

Figure 1(a) shows the total outpatient antimycotic and antifungal use by showing the use of the different substances in 2007 for 20 European countries expressed in DID. Total outpatient systemic antimycotic and antifungal use varied by a factor of 6.7 between the country with the highest (3.03 DID in Belgium) and the country with the lowest (0.45 DID in Croatia) use. The proportional use of antimycotics and antifungals in ambulatory care is shown in Figure 1(b). Terbinafine, ketoconazole, itraconazole and fluconazole represented >94% of total outpatient antimycotic and antifungal use in all countries. Terbinafine, overall the most frequently used antifungal in outpatients, was the most used substance in Norway, Finland and France (>80%), in Denmark, Slovenia, Austria, Sweden and the Netherlands (70%), in Estonia, Slovakia and Portugal (60%), and in Hungary, Cyprus, Belgium, the Czech Republic and Latvia (50%). Itraconazole was the most used antifungal substance in outpatients in Luxembourg, Croatia and Italy (52.35%, 47.81% and 44.50%, respectively), and ketoconazole in Bulgaria (61.98%).

In 12 countries for which these data were available, outpatient systemic antimycotic and antifungal use represented 90.45% (Denmark) to 97.06% (Hungary) of the total antimycotic and antifungal use (Austria, Belgium, the Czech Republic, the Netherlands, Portugal and Slovenia could not provide hospital care data, and for Estonia and Cyprus no separate data on ambulatory and hospital care were available). Overall, 12 countries (Belgium, Denmark, Finland, Italy, Luxembourg, the Netherlands, Portugal, Croatia, Hungary, Latvia, Sweden and Slovakia) were able to provide quarterly outpatient data for J02 and D01B for 2007. Additionally, Italy and Portugal also provided quarterly data for 2005, and Belgium, Denmark, Italy, the Netherlands, Portugal, Latvia and Sweden also for 2006. In all countries, antimycotic and antifungal use was higher in the summer quarters than in the winter quarters. In 2007, the variation ranged from 7.39% in Italy to 26.72% in Slovakia (Figure 2).

There was no statistically significant correlation between outpatient antimycotic and antifungal and outpatient antibiotic use in 2007 (Figure 3). Excluding Cyprus and Estonia from this analysis did not change the outcome of the results (Spearman’s ρ=0.288, P=0.247).

Discussion

This study describes a striking variation of systemic outpatient antimycotic and antifungal (ATC J02 and D01B) use in Europe. The variation factor between the country with the highest and the country with the lowest use was 6.7, whereas this variation factor for systemic outpatient antibiotic use was 3.8.11 Thus, the variation factor is 1.8 times higher for systemic antimycotic
and antifungal use (ATC J02 and D01B) than for systemic antibiotic use (ATC J01).

It is likely that similar determinants could explain the large differences in the consumption of antibiotics, antymycotics and antifungals among European countries. These determinants include sociocultural differences, and differences in education, healthcare organization, resources and utilization, pharmaceutical market and regulatory practices, as well as in the knowledge of antimicrobials.

However, we found no statistically significant correlation between outpatient antymycotic and antifungal and outpatient antibiotic use. For instance, the Netherlands, one of the lowest outpatient antibiotic-prescribing countries in Europe,\textsuperscript{11} showed a relatively high outpatient antymycotic and antifungal use. Although mycosis can be a side effect of systemic antibiotic use, e.g. vulvovaginal candidiasis,\textsuperscript{20} the major indications for systemic antymycotic and antifungal use in outpatients, such as onychomyicosis, failure of topical treatment or frequent relapse.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Outpatient systemic antymycotic and antifungal use in 20 European countries in 2007. Use of the different substances in DID (a) and as a percentage of the total use in DID, ranging from the country with the highest D01B use to the lowest (b). *Total antymycotic and antifungal use data for Estonia and Cyprus.}
\end{figure}
of superficial mycosis and systemic mycotic infections, are probably not influenced or related to previous or concomitant use of antibiotics.

Data on the number of mycotic infections in the participating countries might be very helpful to interpret outpatient antimycotic and antifungal use, but such data are not readily available. Unpublished data from the Achilles foot-screening project—a large epidemiological study conducted in 16 European countries in patients presenting themselves at general practice or dermatologist offices during 2 chosen weeks in 1997 and 1998—indicated a lower prevalence of onychomycosis in Western European countries (Belgium, Germany, Luxembourg, the Netherlands and the UK) than in Central/Eastern European countries (the Czech Republic, Hungary, Poland and Russia) (T. Burzykowski, Hasselt University, Centre for Statistics, Diepenbeek, Belgium, personal communication). These findings suggest that the prevalence of onychomycosis is not highly correlated with systemic antimycotic and antifungal use.

In all countries (except Croatia, Italy, Luxembourg and Bulgaria), terbinafine was the most commonly used substance. All Northern European countries (Norway, Finland, Denmark and Sweden) have a relatively high use of terbinafine.

Figure 2. Seasonal variation of outpatient systemic antimycotic and antifungal use in 12 European countries. Data by quarter (Q) for 2005, 2006 and 2007.

Figure 3. Correlation between outpatient antibiotic use and outpatient antimycotic and antifungal use in 2007. *Total antimycotic and antifungal use data for Estonia and Cyprus.
In general, high terbinafine use could possibly be explained by the longer treatment recommendations (e.g. Norwegian guidelines for onychomycosis of toenails recommend daily treatment with terbinafine for 12 weeks, but second choice would be daily treatment with itraconazole for only 1 week). High terbinafine use in the Netherlands may also be explained by advertising campaigns in the lay media, initiated by a pharmaceutical company. Indeed, a nationwide information campaign that included television advertisements was organized in 2000, advising people with onychomycosis to visit their general practitioner. After the launch of this campaign, the rate of prescription of terbinafine increased considerably, whereas a slight decrease in prescriptions of itraconazole was observed.21 Similar campaigns ran in e.g. Belgium, where terbinafine use increased by >20% between 2003 and 2005 (data provider: National Institute of Health and Disability Insurance). Despite widespread criticism of the campaign, in particular among GPs, and in spite of various legal proceedings, the campaign website is still available at www.infomycose.info.22

Amphotericin B is mainly used in hospitals. Therefore, Estonia and Cyprus (total use) are the only countries with considerable use of these substances in our analysis.

Similar to outpatient use of antibiotics that was previously reported to represent 90%–94% of the total antibiotic use,22,26 outpatient systemic antifungals and antifungals use represented 90%–97% of the total antimycotic and antifungal use in countries that provided separate data for ambulatory and hospital care.

Analysis of seasonal variation showed higher use of antimycotics and antifungals in the summer quarters, which is in contrast to the seasonal variation seen for outpatient antibiotic use.6 Aesthetic reasons could drive the treatment of dermato- and onychomycoses when wearing more skin-revealing clothes and shoes during summer. In addition, hyperhidrosis and retained moisture are also considered to be important factors that promote the development of infections caused by dermatophytic fungi.23,24

ESAC data on systemic outpatient antimycotic and antifungal use must be interpreted with caution and is subject to bias. For instance, underreporting due to over-the-counter (OTC) sales is possible in countries with data collection systems based on reimbursement data (Australia, Belgium, the Czech Republic, Hungary, Italy and Luxembourg). Datasets based on distribution data are less vulnerable to this source of bias, as they cover the sales of both prescribed and OTC systemic antimycotics and antifungals. Topical antimycotics and antifungals can also be purchased without prescription, and several guidelines recommend topical use as first line of therapy in dermatomycosis. ESAC collects only data on the use of systemic antimycotics and antifungals, not topical. But for instance in Belgium, data from IMS Health Benelux [provided and processed by APB (General Pharmaceutical Society)] showed that the topical use in DDD represents almost 75% of the total antifungal and antifungal use.

Another source of potential bias is the proper determination of the mix between ambulatory and hospital care, as described in detail by Vander Stichele et al.17 Also, as described by Davey et al.25 for antibiotics, expressing antimycotic and antifungal use data in DDDs may not be adequate to compare prescribing patterns between countries, because of differences in the dosage and length of treatment for these substances.

We have shown that differences in outpatient antibiotic selection pressure account for the geographic variation of antibiotic resistance in Europe.2 However, with the exception of oropharyngeal candidiasis in HIV-infected patients, there is no documented link between antimycotic and antifungal consumption and the development of resistance.26 In general, antifungal and antimycotic resistance is low, and involves only Candida species (no resistance in moulds or dermatophytes).

In conclusion, the ESAC project represents the first set of publicly available standardized and validated supranational data on systemic antifungal and antifungal use in Europe. The ESAC data allow the evaluation of guidelines and policies, and the monitoring of professional and public strategies to encourage appropriate prescribing of antimycotics and antifungals.

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Transparency declarations

None to declare.

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