Antibiotic prescribing in general practice: striking differences between Italy (Ravenna) and Denmark (Funen)

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Objective: To compare antibiotic prescribing in primary care in two European populations, one in Denmark (Funen), the other in Italy (Ravenna).

Methods: Reimbursement data (1999) were retrieved from the Odense Pharmacoepidemiologic Database (Denmark) and the Emilia Romagna Health Authority Database (Italy). The extent of antibiotic use (ATC J01) was analysed as the number of defined daily doses per 1000 inhabitants per day (DDD/1000 inhabitants/day), and as annual prevalence of use. A qualitative analysis was carried out according to the Drug Utilization 90% (DU90%) approach.

Results: Antibiotic consumption was 16.5 DDD/1000 inhabitants/day in Ravenna and 10.4 DDD/1000 inhabitants/day in Funen; the annual prevalence of use was 40 and 30 subjects/100 inhabitants, respectively. Italian children received a greater amount (four-fold in DDDs) of antibiotics than Danish ones, whereas consumption was only slightly higher in Italy than in Denmark in the other age groups. In Italy, injectable antibiotics (third generation cephalosporins or aminoglycosides) accounted for 4% of total DDDs and 11% of exposed subjects. In Funen, use of injectable antibiotics was negligible. The bulk of prescription (90% of total DDDs) was made up of eight (out of 38) different antibiotics in Denmark, mainly narrow-spectrum penicillins and macrolides (1st: phenoxymethylpenicillin), and of 18 (out of 74) antibiotics in Italy, mainly broadspectrum penicillins, macrolides, fluorquinolones and cephalosporins.

Conclusions: These data show remarkable differences in antibiotic prescribing between Italy and Denmark, and suggest possible overuse and misuse of antibiotics in Italy.

Keywords: drug utilization, general practice, antibiotic prescription, international comparison

Introduction

Bacterial resistance has been a hot topic for the scientific community in the last few years. The outbreak of multidrug-resistant organisms both in humans and in animals makes interventions on the patterns of utilization of antibiotics more and more urgent, as this is a major determinant of selection and spread of such organisms.1-3

As far as prescription of antibiotics in humans is concerned, the major concerns are related to both an excessive use of such drugs and to the frequent use of newer agents in place of the more traditional, and often more effective, ones. Such a phenomenon is not easy to control because the choice of a treatment can be conditioned by multiple factors, some of which can be unrelated to clinical evidence.

As shown by several studies, particularly on hospital prescriptions, a marked variability exists among the various European countries in the choice of antibiotics.4,5 In the Nordic countries, consumption of the newer antibiotics, although increasing, is not yet as prevalent as in southern European countries such as Italy and Spain.6-9

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The aim of this study was to compare the utilization of antibiotics in primary health care in two defined European populations, one in the county of Funen, Denmark, the other in the province of Ravenna, Italy.

Materials and methods

Drug prescription data were retrieved from the Odense Pharmacoepidemiologic Database (Denmark)\(^\text{10}\) and the Emilia Romagna Health Authority Database (Italy).\(^\text{11}\) Both databases provide the following information for each reimbursed prescription: identification of the dispensed product according to the Anatomical Therapeutic Chemical (ATC) classification, number of packages and number of defined daily doses (DDDs) dispensed, code of the general practitioner (GP), code of the patient and date of prescription. In both databases, the patient code allows the reconstruction of each individual’s drug history without identification of the individual.

In the present study, we retrieved the 1999 prescription data from the County of Funen, Denmark (471,732 inhabitants in 1999),\(^\text{12}\) and from the province of Ravenna, Italy (350,434 inhabitants in 1999).\(^\text{13}\) Table 1 shows the main features of the two populations.

All drug utilization data were quantified in terms of the technical unit of comparison, DDD, and classified according to the ATC system as suggested by the WHO (release 2000).\(^\text{14}\) The extent of antibiotic use (ATC code J01) was analysed as the number of DDDs per 1000 inhabitants per day (DDD/1000 inhabitants/day; DDD/TID), according to the ATC/DDD method,\(^\text{14}\) and as annual prevalence of use (number of individuals receiving at least one prescription in 1 year per 100 inhabitants). Data were broken down by sex and age (10 year groups).

A qualitative analysis of antibiotic prescription was carried out according to the recently proposed Drug Utilization 90% (DU90%) approach.\(^\text{15}\) The individual antibiotics were ranked by extent of use (DDD), focusing the analysis on those antibiotics that accounted for 90% of the total amount of DDDs prescribed, in order to disregard occasional prescriptions. The number of different antibiotics as well as the choice of drug used was compared in the two areas.

Results

The overall antibiotic prescription in 1999 was higher in Ravenna (16.5 DDD/TID) than in Funen (10.4 DDD/TID). The annual prevalence of use was also higher in Ravenna (40 exposed subjects/100 inhabitants) than in Funen (30 subjects/100 inhabitants).

The average antibiotic use was higher in females than in males in Funen (12.0 compared with 8.6 DDD/TID), but was similar in males and females in Ravenna (16.7 compared with 16.3 DDD/TID), with women/men (W/M) ratios of 1.0 in Ravenna and 1.4 in Funen. A similar pattern was observed for the annual prevalence of use, with a higher exposure rate per 100 inhabitants in females in Funen (35 compared with 26; W/M ratio of 1.3), and similar exposures by gender in Ravenna (41 compared with 39; W/M ratio of 1.1).

Tables 2 and 3 show the analysis of individual substances by means of the DU90% approach in Funen and Ravenna, respectively. Out of a total of 86 antibiotics in the two areas,
Differences in antibiotic prescription in Italy and Denmark

Table 2. Ranking of the antibiotics making up 90% of total DDDs prescribed in Funen

<table>
<thead>
<tr>
<th>Rank</th>
<th>ATC</th>
<th>Antibiotic</th>
<th>DDD/1000 inhab./day</th>
<th>Accumulated DDD%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>J01CE02</td>
<td>phenoxymethylpenicillin</td>
<td>4.6</td>
<td>44.1</td>
</tr>
<tr>
<td>2</td>
<td>J01CA04</td>
<td>amoxicillin</td>
<td>1.3</td>
<td>57.1</td>
</tr>
<tr>
<td>3</td>
<td>J01FA01</td>
<td>erythromycin</td>
<td>1.1</td>
<td>67.5</td>
</tr>
<tr>
<td>4</td>
<td>J01CA02</td>
<td>pivampicillin</td>
<td>0.7</td>
<td>74.4</td>
</tr>
<tr>
<td>5</td>
<td>J01FA10</td>
<td>azithromycin</td>
<td>0.5</td>
<td>79.0</td>
</tr>
<tr>
<td>6</td>
<td>J01EB02</td>
<td>sulfamethizole</td>
<td>0.5</td>
<td>83.5</td>
</tr>
<tr>
<td>7</td>
<td>J01CF01</td>
<td>dicloxacillin</td>
<td>0.4</td>
<td>86.9</td>
</tr>
<tr>
<td>8</td>
<td>J01CA08</td>
<td>pivmecillinam</td>
<td>0.3</td>
<td>90.0</td>
</tr>
<tr>
<td>9–38</td>
<td>others</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>total</td>
<td></td>
<td>10.4</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 3. Ranking of the antibiotics making up 90% of total DDDs prescribed in Ravenna

<table>
<thead>
<tr>
<th>Rank</th>
<th>ATC</th>
<th>Antibiotic</th>
<th>DDD/1000 inhab./day</th>
<th>Accumulated DDD%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>J01CA04</td>
<td>amoxicillin</td>
<td>4.0</td>
<td>24.5</td>
</tr>
<tr>
<td>2</td>
<td>J01CR02</td>
<td>co-amoxiclav</td>
<td>2.6</td>
<td>40.2</td>
</tr>
<tr>
<td>3</td>
<td>J01FA09</td>
<td>clarithromycin</td>
<td>1.7</td>
<td>50.5</td>
</tr>
<tr>
<td>4</td>
<td>J01MA12</td>
<td>levofloxacin</td>
<td>0.8</td>
<td>55.4</td>
</tr>
<tr>
<td>5</td>
<td>J01FA06</td>
<td>roxithromycin</td>
<td>0.7</td>
<td>59.9</td>
</tr>
<tr>
<td>6</td>
<td>J01MA02</td>
<td>ciprofloxacin</td>
<td>0.6</td>
<td>63.8</td>
</tr>
<tr>
<td>7</td>
<td>J01EE01</td>
<td>sulfamethoxazole + trimethoprim</td>
<td>0.6</td>
<td>67.6</td>
</tr>
<tr>
<td>8</td>
<td>J01FA10</td>
<td>azithromycin</td>
<td>0.6</td>
<td>71.3</td>
</tr>
<tr>
<td>9</td>
<td>J01DA23</td>
<td>cefixime</td>
<td>0.5</td>
<td>74.6</td>
</tr>
<tr>
<td>10</td>
<td>J01MA06</td>
<td>norfloxacin</td>
<td>0.5</td>
<td>77.4</td>
</tr>
<tr>
<td>11</td>
<td>J01DA08</td>
<td>cefaclor</td>
<td>0.4</td>
<td>79.7</td>
</tr>
<tr>
<td>12</td>
<td>J01DA39</td>
<td>cefditobutin</td>
<td>0.4</td>
<td>81.9</td>
</tr>
<tr>
<td>13</td>
<td>J01CA06</td>
<td>bacampicillin</td>
<td>0.4</td>
<td>84.1</td>
</tr>
<tr>
<td>14</td>
<td>J01DA17</td>
<td>cefonicid</td>
<td>0.3</td>
<td>86.1</td>
</tr>
<tr>
<td>15</td>
<td>J01FA12</td>
<td>rokitamycin</td>
<td>0.2</td>
<td>87.6</td>
</tr>
<tr>
<td>16</td>
<td>J01DA06</td>
<td>cefuroxime axetil</td>
<td>0.2</td>
<td>89.0</td>
</tr>
<tr>
<td>17</td>
<td>J01DA41</td>
<td>cefprozil</td>
<td>0.2</td>
<td>90.3</td>
</tr>
<tr>
<td>18–74</td>
<td>others</td>
<td></td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>total</td>
<td></td>
<td>16.6</td>
<td>100.00</td>
</tr>
</tbody>
</table>

eight agents in Funen and 17 in Ravenna made up the DU90% segment. In Funen, phenoxymethylpenicillin was the most used antibiotic, representing almost half of the prescriptions, followed by amoxicillin. In Ravenna, prescription was split among a greater number of compounds, with amoxicillin and the combination of amoxicillin plus enzyme inhibitors in the first two places. In the Funen list, no injectable drug appeared, whereas one (cefonicid) was present in that of Ravenna. Moreover, no cephalosporins or fluoroquinolones were found in this segment in Funen, whereas six cephalosporins plus three fluoroquinolones made up 39% of the DU90% segment of Ravenna.

Figure 1 shows the breakdown by sex and age of both DDDs and prevalence of use. In terms of DDD, the amount of antibiotics prescribed progressively increased with age in Funen, the age groups with maximal antibiotic consumption being 70–79 years (15.5 DDD/TID) and 80+ (20.1 DDD/TID). In contrast, in Ravenna the age group 0–9 years was the highest with 23.6 DDD/TID, then prescription decreased to a minimum in young adults (20–29 years) and increased again up to 19.6 DDD/TID in the 80+ age group. In terms of prevalence of use, in Funen the rate of exposed subjects/100 inhabitants in the paediatric age group was as high as that of the 80+ class, whereas, in Ravenna, the trend was more similar to that of DDDs.

In both Ravenna and Funen, the oral route of administration was the most frequently used, both in terms of DDD consumption and prevalence of use. In Italy, however, 4% of total DDDs were represented by injectable antibiotics, and
11% of the exposed subjects were treated with such preparations. The proportion of injectable drugs in Ravenna increased progressively with age, reaching 12% of total DDDs and 25% of the exposed subjects in the age group 80+. In Funen, use of injectable antibiotics was only occasional, whereas rectal preparations were used in children (0–9 years), representing 1% of DDDs and 7% of exposed subjects.

As shown in Figure 2, the choice of antibiotics was different between Ravenna and Funen. In terms of DDD, groups such as cephalosporins (J01DA), combinations of penicillins and β-lactamase inhibitors (J01CR), and fluoroquinolones (J01MA) were used almost exclusively in Ravenna, whereas β-lactamase-sensitive penicillins (J01CE), short-acting sulphonamides (J01EB) and β-lactamase-resistant penicillins (J01CF) were prescribed in Funen but not in Ravenna. The only groups prescribed in both areas were extended-spectrum penicillins (J01CA) and macrolides (J01FA). The picture was similar when the data were expressed as prevalence of use (Figure 2, lower panel). In Ravenna, however, the ranking of ATC groups by prevalence of use was different from that by DDD, with macrolides (J01FA) and cefalosporins (J01DA) higher than extended-spectrum penicillins (J01CA).

Figures 3 and 4 show the breakdown by age and gender of the extent and prevalence of use, respectively, for the most frequently prescribed ATC groups. The most striking differences between the two areas were an increasing use of fluoroquinolones (J01MA) with age in Italy versus a similar trend of extended-spectrum penicillins (J01CA) in Funen, and a very high paediatric (0–9 years) use of cephalosporins (J01DA) in Italy.

Discussion

This study demonstrated marked differences in antibiotic prescribing in two European areas, the province of Ravenna, Italy, and the county of Funen, Denmark.

As shown in Table 1, the patient populations of the two areas are similar in terms of the main health care indicators, such as the total number of inhabitants, the number of GPs, the average number of inhabitants per GP, etc. The only significant difference is in the primary care to children, which in Ravenna is provided by paediatricians and in Funen by GPs.

The proportion of subjects exposed to antibiotics in Ravenna was higher than in Funen by about one-third, and the difference was even greater when the intensity of antibiotic use was measured through DDD. Focusing on the bulk of the use, the DU90% segment, great differences were detected, with a tendency in Italy to use a larger number of different antibiotics and a preference for those having a wide spectrum.

In a recent survey of the outpatient antibiotic sales in the European Union, Cars et al.16 reported figures of total antibiotic consumption in Denmark similar to those obtained by us in Funen (11.4 compared with 10.4 DDD/TID). In contrast, the values reported for Italy were higher than those found by us in Ravenna (24.0 compared with 16.5 DDD/TID), but are in accordance with the Italian National Statistics on drug use published by the Italian Ministry of Health.17 The difference between the European survey and our data can be explained by the broad variation among the Italian regions, with lower consumption of antibiotics in the northern regions. The choice of antibiotics reported by Cars et al.,16 however, was similar to that observed by us in both countries, with marked differences between Italy and Denmark. The pattern of antibiotic use observed in Italy was more similar to that reported for Spain,16,18 with preference for extended-spectrum penicillins, macrolides, quinolones and cefalosporins, and a negligible use of narrow-spectrum penicillins. An intermediate pattern was shown by a study of antibiotic prescribing in England and Wales.19

A simple interpretation for the greater amount of antibiotics prescribed in Ravenna is not easy to find. There are not likely to be major differences in the prevalence of infectious diseases.
Differences in antibiotic prescription in Italy and Denmark

993

diseases between the two countries accounting for the different use of antibiotics, at least for the infections commonly encountered in primary health care. The differences in the patient populations between the two areas do not seem to explain the wide variations of antibiotic prescribing. The Italian population is older than the Danish one, the greater differences being in children (age group 0–9 years, ~7% of total population in Ravenna compared with 13% in Funen) and in elderly people (age groups 60–79: 13% compared with 9%; age group 70–79: 11% compared with 7%). These demographic differences, however, do not seem to have influenced the pattern of use of antibiotics, since the age-related trend of

Figure 2. Overall prescription of antibacterial agents (1999) by ATC in Ravenna (Italy) and Funen (Denmark). Data are expressed as DDD per 1000 inhabitants per day (upper panel) and as prevalence of use (number of subjects with one or more prescription per 100 inhabitants per year; lower panel).
use was similar in the adult populations of the two areas. There are also slight differences between Ravenna and Funen in the organization of the health care systems such as the number of patients per GP and the number of beds per inhabitant, but it is unlikely that they could account for the different pattern of antibiotic use. The only marked difference is in the management of children; in Italy, primary care to children is provided by paediatricians, whereas in Denmark all individuals contact their GP directly irrespective of age. This difference in paediatric care corresponded with a prevalence of antibiotic use in Italian children which was double that in Danish ones. This difference became more striking when the intensity of antibiotic use was expressed in terms of DDD. In other words, more children were treated in Italy, and they received higher doses per therapeutic course or more frequent courses than children in Denmark.

A limitation of the present study is that it is based on reimbursement data, and this could have caused an underestimate of the actual exposure to antibiotics in the two areas. Moreover, whereas virtually all the antibiotics on the market were reimbursed in Italy in 1999, in Denmark only tetracyclines and cephalosporins were not reimbursed, these drugs being responsible for ~5% of the total amount of antibiotics sold in Denmark. Therefore, the differences in reimbursement policy could explain only partially the differences observed in the prescribing pattern, and are limited to these two drug groups.

Another limitation of this study is that reimbursement data do not provide information about the indications the drugs are prescribed for. This is a general limitation of the studies carried out using prescription databases, which, however, are widespread in the literature. Such a limitation could be overcome by means of surveys based on interviews or questionnaires, as we did in a previous study with Italian doctors.

Differences between the two countries were also observed in the selection of antibiotics. β-Lactamase-sensitive penicillins were by far the most commonly prescribed group in Denmark, but their use was negligible in Italy. There seems to be no reason why these traditional and inexpensive antibiotics should not be used. Microbial resistance seems not to be a major problem, since it has been reported that no more than 10% of pneumococci, which frequently cause infections commonly encountered by GPs, are resistant to penicillin in Italy. On the other hand, cephalosporins, fluoroquinolones, and combinations of penicillins and β-lactamase inhibitors, were among the antibiotics most frequently used in Italy, and their use was only sporadic or completely absent in Denmark. Interestingly, the curve representing the age-dependent use of cephalosporins had a U-shaped form (Figure 3), these drugs being the most frequently prescribed in Denmark.

Figure 3. Comparison of antibiotic prescription by sex and age for the most frequently prescribed ATC groups in Ravenna and Funen areas; x-axis, age groups; y-axis, DDD/1000 inhabitants/day. Squares, women; triangles, men. Filled symbols, Ravenna; open symbols, Funen.
Differences in antibiotic prescription in Italy and Denmark

Penicillins with extended spectrum (J01CA)

β-Lactamase-sensitive penicillins (J01CE)

Penicillins + β-lactamase inhibitors (J01CR)

Cephalosporins (J01DA)

Macrolides (J01FA)

Fluoroquinolones (J01MA)

Figure 4. Prevalence of antibiotic use by sex and age for the most frequently prescribed ATC groups in Ravenna and Funen areas; x-axis, age groups; y-axis, subjects per 100 inhabitants per year. Squares, women; triangles, men. Filled symbols, Ravenna; open symbols, Funen.

both children and older people. There is no evidence to indicate cephalosporins as the drug of choice in these age groups. In contrast, they are generally considered as second- or even third-choice antibiotics. Therefore, their frequent use in Italy seems not to reflect actual therapeutic needs, but rather to be induced by motivations such as pressure of patients and advertising. A more interventional attitude of Italian GPs was also shown by a recent survey carried out in two Italian regions, which showed a high proportion of patients treated unnecessarily with antibiotics. Also in other therapeutic fields, Italian GPs revealed a lower profile of appropriateness of drug use in comparison with their Danish colleagues, such as in the use of non-steroidal anti-inflammatory drugs and of lipid-lowering agents.

In conclusion, this comparative study raised more than one concern about the way antibiotics are used in primary health care. Our results cannot demonstrate whether the use of a given antibiotic was more or less appropriate in an individual patient, but suggest that in Italy there was overuse and misuse of antibiotics in a defined population, and this may represent a potential for the development and spread of bacterial resistance. Therefore, interventions are needed both at national and local levels to set a limit and to improve the quality of antibiotic prescription. Further comparative studies are also needed in order to obtain a map of the use of antibiotics in human medicine in relation to the resistance pattern.

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References


Differences in antibiotic prescription in Italy and Denmark


