Modelling of escalating outpatient antibiotic expenditures

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Objectives: To model the relative role of old and newly introduced antibiotics in shaping increased antibiotic use.

Methods: Grouped data covering nationwide consumption and expenditure for out-of-hospital antibiotics in Greece (1990–1999) were used. The antibiotic formulations were categorized into ‘common old formulations’, ‘old formulations with intermittent sales’, ‘recast formulations’ and ‘new substances’. The effect of each category was investigated based on index and pricing analyses.

Results: We estimated a 143\% net increase in out-of-hospital antibiotic use during 1990–1999. The increase was 59\% when all formulations of antibiotic substances available by 1990 were considered. A rapid turnaround of formulations of old substances was noticed with 669 formulations marketed during the decade. Sixteen new antibiotic substances were first introduced after 1990 and by 1999 they accounted for 34.9\% of total out-of-hospital antibiotic expenditures. Three new antibiotics (a macrolide and two cephalosporins) accounted for over 90\% of this amount. For all three, other less expensive alternatives were available.

Conclusions: In the studied setting, out-of-hospital antibiotic use has been expanding in a highly substance-specific and non-rational fashion that is accelerated by the introduction of new drugs.

Keywords: antibiotic use, expenditure, model

Introduction

Escalating consumption and misuse of antibiotics in the community setting is a key reason for the development of bacterial resistance worldwide.\textsuperscript{1–3} Pharmacoeconomic approaches are necessary to understand the evolution of expenditures for out-of-hospital antibiotics (OA). Some key questions may be posed. What is the contribution of pricing, inflation and increased consumption in escalating OA costs? Moreover, what is the contribution of new antibiotic agents to this phenomenon? In order to address these questions, we used nationwide data (with appropriate grouping to satisfy confidentiality issues) on the outpatient consumption of antibiotics (anti-biotics (OA)). Some key questions may be posed. What is the contribution of pricing, inflation and increased consumption in escalating OA costs? Moreover, what is the contribution of new antibiotic agents to this phenomenon? In order to address these questions, we used nationwide data (with appropriate grouping to satisfy confidentiality issues) on the outpatient consumption of antibiotics (anti-biotics for systemic use, ATC J01 classification) from a European country during the last decade (1990–1999). Expenditure for OA in Greece has accounted for between 11\% and 16\% of the annual drug expenditure during this decade. OA annual expenditure per capita in Greece has reached a level of over US$20. Although cost may not be a perfect proxy for use, it is an important parameter in health care and our analysis highlights how escalating expenditures may be an important determinant in antimicrobial chemotherapy from a community-wide perspective.

Materials and methods

Data and adjusting factors

The project was commissioned and data were supplied by Prof. Moutsopoulos, President of the Hellenic Organization for Medicines (EOF). These data originated from Pharmetrica S.A., a subsidiary company of EOF and they are comprehensive sales data from the pharmaceutical industry. We used group data covering consumption and expenditure for OA in the period 1990–1999. Exports to other countries were generally excluded but parallel exports are included (they are considered to be relatively steady and estimated at 3–4\% of total expenditure).

In this study, we present only group/summary data without formulation-specific information, since the diffusion of information on the consumption or expenditure of specific antibiotic formulations is prohibited by confidentiality agreements. Greece has had a relatively stable population during this decade based on data from the National Statistical...
Service. In 1990, the population was 10 160 551 and in 1999 it was 10 538 086, an increase of 3.7%.

Inflation rate estimates were obtained from the Bank of Greece: the consumer price index (CPI) for the years 1990 (base year) to 1999 are 100, 120, 139, 159, 176, 194, 209, 221, 231 and 237, respectively. The Laspeyres price index was provided for the purposes of this study using the 142 antibiotic formulations that had sales in each year during the decade 1990–9 (fixed basket) and it is a weighted index [weighted by defined daily dose (DDD) consumption in 1990].

However, alternative indices, such as the Paasche index, might be used when DDD data are available for each year, since current year estimates of DDD are needed for its calculation. Price of a specific formulation for a specific year is defined by the total expenditure of the formulation divided by the number of formulations sold, i.e. it is a price cost per formulation.

**Adjusted use index**

Given the fact that there are a large number of antibiotics and each antibiotic substance is marketed under a large variety of different formulations that are not necessarily interchangeable, overall expenditures may give a better index of antibiotic use, if appropriately adjusted for inflation and for changes in antibiotic pricing. We define the adjusted use index as the ratio \( R_{E/P} \) of the deflated expenditures (E) over the deflated price index (P) between the year x and the baseline (1990) values. The price index is estimated as above. Both the expenditures and the price index are adjusted for the inflation rate. The adjusted use index is strictly pertinent to the 142 antibiotic formulations that go into the calculation of the price index. However, it may also be extrapolated to other broader groups, or to the whole OA expenditures, since a price index cannot be formally estimated for formulations that do not have sales in each year during the time period of interest.

**Antibiotic categories**

It is important to estimate separately the contribution of old and newly introduced antibiotics and formulations thereof to the OA market. One could categorize antibiotics and formulations in the following four groups: (a) formulations of antibiotics that were available in 1990 and had sales each year during the whole decade (‘common old formulations’ that are considered in the calculation of the price index); (b) formulations of antibiotics that were available in 1990 but did not have sales for each year during the decade (‘old formulations with intermittent sales’); (c) formulations that did not have any sales in 1990, but that pertained to antibiotic substances that were available already before 1990 (‘recast formulations’); and (d) new antibiotics that were introduced for the first time after 1990, including all the subsequently introduced formulations of each of these substances (‘new substances’).

Analyses were conducted with SAS (SAS Institute, Cary, NC, USA) and SPSS (SPSS, Inc., Chicago, IL, USA) software.

**Results**

As shown in Figure 1, after adjusting for inflation, the expenditures for OA increased by 24% between 1990 and 1999. An important question is whether pricing of the antibiotics is responsible for this increase. A weighted price index, adjusted for inflation, was calculated using a basket of antibiotic formulations that were in sales each year during the whole decade (1990–9). Interestingly, the price index shows a marked decline over time (Figure 1), suggesting that old antibiotics at least are becoming relatively more inexpensive. The deflated price of these antibiotics per unit dose in 1999 was only 51% of the respective price in 1990. This decrease in price per unit dose was mainly because of government intervention that removed several taxes and which resulted in a 23% decrease in retail price and the imposing of a reimbursement list in 1997. The remainder was the result of downward pricing of existing formulations by the industry.

Thus, the increase in expenditure is more prominent if one takes into account the decreasing adjusted price index. The ratio \( R_{E/P},1999 \) of the deflated expenditures (E) over the deflated price index (P) between 1999 and the baseline (1990) is 2.43, i.e. it shows a 143% net increase during the decade, once both inflation and price changes are taken into account.

A total of 142 formulations of 44 antibiotics had annual sales throughout the decade (common old formulations). There were 202 old formulations of 44 antibiotics with intermittent sales and 275 recast formulations of 39 antibiotics that appeared during the decade. No antibiotic substance was completely withdrawn during this period, i.e. even if some formulations were withdrawn, at least one other continued to be marketed. Conversely, 16 new antibiotic substances (seven cephalosporins, three macrofides, two quinolones and four other antibiotics) were introduced in the decade being studied, in a total of 50 formulations. Figure 2 shows the contribution of each of these four categories to the total annual OA expenditure.

Deflated expenditures for the 142 common antibiotic formulations that were maintained in the market during the whole decade seemed to decrease over time. However, if one were to take into account the concurrently decreasing price index, the \( R_{E/P},1999 \) is 1.35, suggesting a net 35% increase in price- and inflation-adjusted expenditures over the decade. The \( R_{E/P},1999 \) is 1.59, if we also add the formulations with intermittent sales and the recast formulations. Thus old antibiotics show characteristics of a product with medium elasticity: decreases in price are associated with an even larger increase in consumption and expenditure. This behaviour is surprising given the unavoidable competition from newer agents. There is considerable turnover in the available formulations, but formulations that do not have a continuous presence in the market are relatively small contributors in the overall expenditures.
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The rapid increase in expenditures is also associated with an influx of a few selected new antibiotic substances into the market. By 1999, ‘new’ substances (those that were first marketed after 1990) accounted for over one-third (34.9%) of the total OA expenditure. The three new antibiotics with highest expenditures were clarithromycin (introduced in 1993), cefprozil (introduced in 1994) and loracarbef (introduced in 1995). In 1999, about 90% of the cost of new substances was attributed to these three expensive new antibiotics. Five of the eight top expenditure antibiotics in 1999 were introduced into the market after 1987. Each of these five antibiotics (two macrolides, two cephalosporins and one quinolone) cost 4- to 20-fold more per unit dose compared with amoxicillin, erythromycin or co-trimoxazole. At the same time, the two leading antibiotics in terms of expenditures for 1990 (amoxicillin and cefaclor) have maintained their inflation-adjusted expenditures largely unaltered during the decade with a small decrease for amoxicillin and a small increase for cefaclor (both changes within less than 20% of the 1990 expenditures).

Discussion

Our study shows that the OA market is one where increased demands are continuously generated and this leads to increased expenditures in a highly substance-specific and non-rational fashion that is accelerated by the introduction of new drugs. A few expensive newly-introduced agents account for a continuously increasing share of the total cost, despite their high pricing, suggesting that these agents may have very high elasticity, i.e. their consumption is not inhibited by their high cost. It is unknown whether the high cost is actually part of the advertisement process for making these substances seem top choices. These agents have been promoted and rapidly accepted as essential, irreplaceable choices among physicians and health consumers. The newer macrolides and newer cephalosporins are contributing more extensively to overall antibiotic expenditures. At the same time, the total expenditure for the two leading older substances (amoxicillin and cefaclor) has not been curtailed, suggesting that the new substances largely create a new market on top of the existing market of these old substances.

Newly introduced macrolides, cephalosporins and quinolones are largely used for outpatient treatment of generally mild conditions, typically of the respiratory tract (acute otitis, acute sinusitis and acute bronchitis), that often may not need any antibiotics at all. These antibiotics have few or no indications for which some other much less expensive antibiotic could not be used instead (e.g. co-trimoxazole, erythromycin, amoxicillin or ampicillin). Thus, the market of OA is highly product-specific, and attracted by new agents that have high elasticity, i.e. their consumption does not seem to be curtailed by their high prices. High elasticity may be representative of health care systems with generous reimbursement practices with few or no restrictions for expensive antibiotics and limited co-payment. It is unknown whether the elasticity of new agents may vary under different reimbursement conditions and during changes in the reimbursement system. This should be worth studying in different settings.

Such an expanding market for antibiotic use does not seem to be a rational evolution for populations where the use of antibiotics is probably already exaggerated and out of proportion to their real indications. Although we have targeted data from a specific European country for this analysis, antibiotic misuse is a worldwide concern. Similar analyses may be carried out to model the use of old and new antibiotics in various settings. One group of investigators recently examined the variation in OA use across the 15 member states of the European Union in 1997. There was very large heterogeneity in the consumption (in DDDs) per 1000 inhabitants per day, ranging from 9 in the Netherlands to 37 in France. Greece was in the middle with 23 DDDs per 1000 inhabitants per day. Moreover, there was substantial heterogeneity in the relative contribution of various antibiotic classes to total consumption. In this regard, Greece had the highest consumption of cephalosporins (4.68 versus 0.02 for Denmark, which had the lowest figure), whereas the highest consumption of macrolides and broad-spectrum penicillins was seen in France, and Portugal had the highest consumption of quinolones. Differential marketing and differences in health care and the reimbursement systems of each country may be responsible for this heterogeneity.

Despite the observed heterogeneity, it is almost certain that the vast majority of these antibiotics should not have been prescribed. One study found that even in the Netherlands, the country with the lowest rates of OA consumption, only 23% of the antibiotic prescriptions for acute otitis media were in accordance with Dutch guidelines. Therefore there seems to be room for substantial curtailing of OA consumption. Rational use of antibiotics could lead to large drops in the expenditure associated with their use, in addition to the anticipated advantages of reducing bacterial resistance and optimizing antimicrobial efficacy, when antibiotics are truly indicated.

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