Trends in hospital antibiotic prescribing after introduction of an antibiotic policy

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Trends in antibiotic prescribing in Grampian were monitored prospectively for seven years from 1986 using computerised ward stock lists and laboratory data relating to all in-patient and out-patient treatments in all Grampian hospitals serving a population of 500,000. The main outcome measures were the number of antibiotics available for routine and restricted uses, annual expenditure and defined daily doses (DDDs) of high expenditure antimicrobial agents. An antibiotic committee introduced a policy and formulary in the third year of the study which had only limited success in controlling prescribing. During the period of the study 30 new antibiotics were considered for inclusion in the hospital formulary, but only seven were incorporated, and all for restricted use only. Despite this, expenditure on antibiotics has more than doubled since 1986, two thirds of the increase being due to the use of new drugs. There was also an increased use of older antibiotics (DDDs increased by 33%), often for no clear reasons, and an overall increase of 46% in DDDs. Antibiotics have increased from 11.9–18.7% as a proportion of the drug budget. These findings highlight the current difficulty in controlling prescribing budgets, the increasing use of antibiotics and the consequent spread of resistance.

Introduction

Antibiotics are the largest single group of drugs used in UK hospitals (Widdison, Pope & Brown, 1993) and control of expenditure on them must form a major part of any attempts at pharmaceutical budgeting. As prescribing costs have escalated (McGavock et al., 1993), many audits of antibiotic use have demonstrated major over-use of these valuable drugs (Simmons & Stolley, 1974). Rational prescribing of antibiotics makes economic sense, but there is also a clear causal relationship between antibiotic use and antibiotic resistance (O'Brien et al., 1985; Levy, 1990; Cohen, 1992; Murray, 1994). Attempts to control antibiotic prescribing have considered both acquisition costs (Coleman et al., 1991) and quality of use (Johnson et al., 1982), although little information is available on the long term effects of such controls. Short term savings can undoubtedly be achieved and there is confidence that control measures can be efficacious (Working Party Report, 1994). Data on the effects of new drugs on the overall prescribing of antibiotics in the UK are lacking.

In 1986, in line with its policy for other drug categories (Jappy et al., 1989) Grampian
Medicines Committee formed an Antibiotic Committee to draw up an antibiotic formulary and policy for use throughout all hospitals in Grampian, in an attempt to improve the quality of prescribing and control escalating prescribing costs. This paper describes the use of antibiotics in all Grampian hospitals during the two years before the introduction of the policy and during the first 5 years of its operation.

**Methods**

The Antibiotic Committee was under the chairmanship of a consultant microbiologist and included a second microbiologist, an infectious diseases physician, a clinical pharmacologist/general physician, a general surgeon (all consultants), a general practitioner and pharmacy manager. At a later date a further two senior pharmacists, a community prescribing adviser and a further two consultants, a haematologist/oncologist and an infectious diseases/respiratory medicine specialist, were added.

A policy was implemented in April 1988 after widespread consultation with users. It was published in booklet form and widely distributed to all wards, doctors and medical students. The document contained a core list of antibiotics (the formulary) and a reserve list (Table I) informally policed by pharmacy and microbiology staff through ward pharmacist intervention. The recommendations within the policy were categorised as first choice in uncomplicated infection, second choice following primary failure or pending culture results in serious infection, and choice of agent where penicillin allergy was present. The three choices were given for each indication. Guidance was also given on surgical prophylaxis, avoidance of endocarditis and artificial joint infection during invasive procedures, and for avoidance of some other potentially serious infections, such as herpes simplex infections in immunocompromised patients and pneumocystis pneumonia in AIDS patients. Dosage, route of administration and duration of prescription were only commented on in general terms; for example, restriction of prophylaxis to a maximum of three doses for any surgical operation. A second edition of the policy was introduced in April 1991 again following widespread consultation. It contained an expanded section on prophylaxis and minor changes reflecting the introduction of new antibiotics over the preceding three years.

The Antibiotic Committee has functioned throughout, meeting quarterly to consider the introduction of new antibiotics, educational issues and specific prescribing problems.

<table>
<thead>
<tr>
<th>Table I. Grampian antibiotic formulary—reserve list</th>
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<tbody>
<tr>
<td><strong>Cefoxitin</strong>—im/iv</td>
</tr>
<tr>
<td><strong>Ceftazidime</strong>—im/iv</td>
</tr>
<tr>
<td><strong>Chloramphenicol</strong>—oral/iv</td>
</tr>
<tr>
<td><strong>Ciprofloxacin</strong>—iv</td>
</tr>
<tr>
<td><strong>Clindamycin</strong>—oral/im/iv</td>
</tr>
<tr>
<td><strong>Colistin</strong>—oral/im/iv/nebulised</td>
</tr>
<tr>
<td><strong>Co-trimoxazole</strong>—oral/iv</td>
</tr>
<tr>
<td><strong>Fluconazole</strong>—iv</td>
</tr>
<tr>
<td><strong>Ganciclovir</strong>—iv</td>
</tr>
<tr>
<td><strong>Imipenem</strong>—iv</td>
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</tbody>
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These antimicrobial agents were only to be used under the guidance of a member of the Department of Clinical Microbiology and Infection.

†Subsequent additions to the list.
The introduction of new agents were considered following receipt of a written request from a hospital consultant stating the specific reasons for wanting an antibiotic included in the policy. During each year a minimum of three clinical meetings or grand rounds were held to publicise the formulary and policy, or to discuss specific clinical cases and new antibiotics. Occasional meetings were also held at ward level.

The Pharmacy department at Aberdeen Royal Infirmary (ARI) was responsible for the supply of all antibiotics to hospitals throughout the Grampian area, Orkney and Shetland (population 42,000). Consequently, all the data on antibiotic consumption (in-patients and out-patients) included that from both the Island Health Boards and Grampian. Data on antibiotic consumption, mainly expressed as defined daily doses (DDD) was obtained from the pharmacy stock order computer. Each acute ward was served by a clinical pharmacist who closely monitored individual prescriptions in discussion with the ward medical staff. Approaches to the duty consultant microbiologist could be made at any stage. The use of non-formulary drugs was severely restricted, primarily because they were not stocked in pharmacy, could only be obtained on a named patient basis and then only after approval by a consultant in microbiology or infectious diseases. Antibiotic susceptibility test results for non-formulary agents were not reported and requests to use these drugs were extremely rare.

The Department of Clinical Microbiology offered a clinically orientated service giving advice on diagnostic and therapeutic matters. Antibiotic susceptibility reporting on significant clinical isolates was unrestricted, a minimum of eight agents being reported. Several audits of prescribing were carried out by pharmacy and microbiology staff.

Results

Antibiotic expenditure more than doubled from £427,000 in 1986/87 to £1,014,000 in 1992/93, which was equivalent to a mean annual increase of 15.8% both before and after introduction of the policy. There was an actual temporary slowing of this annual increase to 2% in the third year of operation of the policy. As a percentage of the total drug bill antibiotic expenditure increased from 11.9 to 18.7%. There was no inflationary antibiotic price increase due to successful re-negotiation of contrast prices. Acute services, bed occupancy and deaths did not change significantly over the study period, although acute in-patient discharges increased by 15.4% and out-patient attendances by 17.4%. Long stay bed numbers halved to approximately 2000 due to community care policies.

Forty-one oral and/or systemic antibacterial, antifungal and antiviral drugs were made available in the policy, 13 of them for restricted use only. During the first five years of the policy a further 30 agents were considered for inclusion but only seven were incorporated, five of them for restricted use only: teicoplanin, imipenem, zidovudine, ribavirin and ganciclovir. Fluconazole and ciprofloxacin were also introduced, the oral formulations for general use and the iv preparations for restricted use. Three older antimicrobial agents were removed from the policy.

Ciprofloxacin, fluconazole, imipenem and teicoplanin soon became widely prescribed after addition to the formulary, despite being on the restricted list (Table I). Other antimicrobial agents such as co-amoxiclav, cefuroxime and cefotaxime, which were already very commonly prescribed before introduction of the policy, continued to be increasingly used.
The changes in use of the high expenditure antimicrobial agents, expressed as data on DDDs for the last year studied (1992/93) and the reference year (1986/87), are shown in Table II. Total DDDs per 1000 patient days at ARI for the agents shown were 627 in 1992/93, an increase of 46% from 1986/87. Consumption of the 12 antimicrobial agents shown in Table II, which were available in 1986/87, increased by 33%. Those agents introduced subsequently accounted for 9% of DDDs shown in Table II in 1992/93, but represented 66% of the increased costs. Only two antibiotics, cephadine and amoxycillin had a reduction in use over the study period. With the exception of penicillin, for which both oral and iv formulations were available, the great majority of prescriptions were for oral preparations.

Audit

Several audits were carried out including one on the prescribing of oral ciprofloxacin in a geriatric unit which was a high user of this antibiotic. During the three months before the audit, 89 prescriptions for oral ciprofloxacin were written. During the three months of the audit this fell to 40 prescriptions, but rose to 79 in the three months immediately after the audit. Use was considered appropriate in all but three cases during the audit period.

The use of antimicrobial agents on the reserve list of the formulary was audited for 104 prescriptions. Ninety-five per cent of prescriptions were considered microbiologi-
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Figure 1. Expenditure on ciprofloxacin, 1988–93. Oral (only 250 mg tablets available, ---) and iv (100 mg vials, ..., 200 mg vials - - -: 400 mg vials not available) formulations are included.

cally and clinically appropriate, although about half of these did not conform to the policy. Fifty-two prescriptions were recommended by microbiology but only 24 of these conformed to the policy. Twenty-two prescriptions neither conformed to the policy nor had been prescribed following advice from pharmacy or microbiology.

The high use of ciprofloxacin (Figure) was altered by an educational campaign, which resulted in a significant switch to the oral formulation. This change in usage has now been maintained for six years.

An audit of surgical antibiotic prophylaxis (Table III) suggested significant, unnecessarily prolonged, duration of administration. For 37 of 74 orthopaedic operations and 29 of 38 general surgical operations more than three doses of antibiotic were given, yet in only 16 of 66 such operations were specimens sent for culture, and in only four cases were these specimens positive. In this and a repeat audit, performed

Table III. Audit of surgical antibiotic prophylaxis (n = 112 operations, 105 patients)

<table>
<thead>
<tr>
<th></th>
<th>Orthopaedics</th>
<th>General surgical</th>
</tr>
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<tbody>
<tr>
<td>Number of operations</td>
<td>74</td>
<td>38</td>
</tr>
<tr>
<td>Number given prophylaxis</td>
<td>69</td>
<td>38</td>
</tr>
<tr>
<td>Number &gt; 3 doses given</td>
<td>37</td>
<td>29</td>
</tr>
<tr>
<td>Number with specimen sent for microbiology (number positive)</td>
<td>5 (1)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Number of iv antibiotic courses administered (number of doses received in excess of recommended three)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cefuroxime</td>
<td>53 (120)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>cefotaxime</td>
<td>3 (3)</td>
<td>8 (56)</td>
</tr>
<tr>
<td>co-amoxiclav</td>
<td>16 (27 iv + 191 po)</td>
<td>22 (144 iv + 19 po)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>—</td>
<td>22 (215 iv)</td>
</tr>
</tbody>
</table>
two years later after sustained feedback (data not presented) a mean of nine prophylactic antibiotic doses were given.

Discussion

There is little information available on the effects of long term attempts at antibiotic control nor on the usage patterns of new antibiotics. In assessing the impact of the antibiotic policy in our study no firm conclusions can be drawn as there was no control hospital. Clearly though, any beneficial effects on controlling levels of use were limited, as the use of existing antimicrobial agents rose by 33% and new drugs caused an increase of 66% in antibiotic expenditure.

The usages of anti-Gram-positive agents flucloxacillin, teicoplanin and vancomycin have increased markedly. Increased glycopeptide use is due to the well described increases in antibiotic-resistant, Gram-positive pathogens causing infections in immunocompromised patients (Moellering, 1992, Martino et al., 1995), and of cases of *Clostridium difficile* diarrhoea (Riley et al., 1994). Isolation of *C. difficile* has increased five-fold during the period of operation of the policy (data not shown). The heavy use of teicoplanin does not reflect its restricted status, but more probably its ease of administration and probable safety. Similarly, another restricted agent, fluconazole, has become widely used due to its lack of toxicity. There is little doubt that the threshold for treatment of possible invasive mycosis has now been lowered (Mangino, Moser & Waites, 1995). In common with other agents such as teicoplanin and ciprofloxacin, higher dosages of fluconazole than were originally recommended are being increasingly used (Ansari, Gould & Douglas, 1990; Bauernfeind, 1993).

Introduction of acyclovir for prophylaxis of herpetic infection in neutropenic patients with leukaemia in 1990 accounted for a large part of the increased use of this antiviral agent. Acyclovir accounts for 80% of antiviral expenditure. Grampian has a low prevalence of HIV infection which is reflected in the low usage of zidovudine.

Imipenem use increased rapidly after its introduction as a second line antibiotic for the treatment of serious infection in neutropenic and intensive care unit (ICU) patients. After outbreaks of infection due to multiply-resistant *Klebsiella* spp. and *Acinetobacter* spp. (Gould, MacKenzie & Thomson, 1995), probably caused by high levels of cephalosporin use, prescribing of imipenem increased further, and it is now a first line treatment for serious sepsis in certain units.

Ciprofloxacin became widely used despite its use being restricted. There has been discussion about increasing the use of oral antibiotics in hospital to save on costs and reduce the hazards to patients (Ehrenkranz et al., 1993). Table II shows, perhaps surprisingly, that with the exception of penicillin prescriptions, all antibiotics were mainly prescribed as oral preparations where these were available. The prospective audit of ciprofloxacin use in a geriatric unit suggested most prescribing was appropriate, although the audit clearly influenced prescribing. The heavy use of ciprofloxacin, is reflected in increased resistance amongst clinical isolates (Kern et al., 1994) although this is largely confined to bacteria such as *Pseudomonas* spp. against which this antibiotic has relatively weak activity. However, we have recently also described only the second ever ciprofloxacin-resistant strain of *Haemophilus influenzae* (Gould et al., 1994).
The continued use of peri-operative prophylaxis with a mean of nine doses also gives cause for concern (Table III), but this is not a problem restricted to Grampian. Cefotaxime, cefuroxime and co-amoxiclav are the agents most commonly used for surgical prophylaxis. Their use was high at the start of the study but continued to increase. Increased surgical activity may have contributed to the increased use of prophylactic antibiotics.

The apparent increase in acute services activity as measured by a 15.4% increase in patient discharges over the study period is likely to have caused increased antibiotic prescribing, although bed occupancy has remained static. Increasing numbers of invasive and immunosuppressive diagnostic and therapeutic procedures are performed, undoubtedly increasing the incidence of infection, and this is reflected in the 5% per annum increase in specimen numbers submitted to the microbiology laboratory over the study period. However, it is still difficult to justify the greater part of the increased antibiotic use, with approximately 600 DDDs of antibiotics being administered per 1000 patient days at ARI in 1992/93 for the high expenditure antibiotics shown in Table II, a 46% increase in seven years. We believe that the major causes of inappropriate use are prolonged perioperative antibiotic prophylaxis, prolonged prophylaxis in immunosuppressed patients, use of broad spectrum treatment instead of invasive diagnostic tests to establish aetiology, and possibly a "just in case" philosophy of "spiraling empiricism" as described by Péchére (1994) and Kim & Gallis (1989).

From the results of audit we believe there is potential to increase the use of microbiologists and pharmacists in monitoring reserve list drugs to contain rising prescribing costs. Audit generally showed a good standard of prescribing antimicrobial agents on the reserve list. Successful pharmacy intervention, educational rather than prescriptive, was often a factor in these prescriptions. Forty-seven of 90 prescriptions written for indications mentioned in the policy did not comply, although almost half were on the recommendation of microbiology.

Significant cost savings could probably have been made in the remainder, by prescribing alternative cheaper, narrower spectrum agents as recommended in the policy. Co-operation and communication between ward pharmacists and the medical microbiologists were important aspects of the policy but could be further improved to restrict use of reserve list antibiotics better than was achieved during this study. Similarly, audit recommendations need to be implemented more effectively.

There are many other measures to improve the quality of antibiotic prescribing and we are investigating some of these; for example, Centralised Intravenous Administration Services (CIVAS) (Cousins et al., 1989), computer links between microbiology and pharmacy (Corkhill et al., 1984), nursing administration of iv drugs (Clark et al., 1986), use of restricted antibiotic sensitivity reporting (Langdale & Millar, 1986), and reporting the cost of antimicrobial agents on bacteriology report forms (Campo & Mylotte, 1988). Since April 1993, each ward has been responsible for the management of its own pharmacy budget through Directorates. Paradoxically though, there is a danger that some of these developments, such as CIVAS and nurse administration of iv antibiotics, could lead to prolonged and unnecessary administration.

Comparisons of our experience with other areas are difficult as there appear to be no similar data available elsewhere in the UK. Figures on notional drug costs for the whole of Scotland from InterContinental Medical Statistics (Hounslow, UK) however, suggest a similar increase in the use of many antimicrobial agents from 1990–1993 (D. Page, Common Services Agency, Edinburgh, UK, personal communication).
Recent data from the USA (Pallares et al., 1993) also confirm a trend of increasing total antibiotic consumption (of both new and old agents), and a similar high overall use of antibiotics although this study reported only on parenterally administered drugs. Pallares et al. (1993) also found an increased proportion of patients were receiving antibiotics, and there was an increased use of combination therapy. These factors are likely to have accounted for some of the increase in prescribing observed in the present study, although we have no data to support this.

The use of antibiotic policies in the UK does not seem to have increased significantly over the past 20 years (Collier & Foster, 1985; Lacey, 1979; Working Party, 1994) and published evidence of their efficacy is sparse. Our report is unusual in that it describes the effects of an antibiotic policy over a prolonged (five year) period and suggests that containment of prescribing is not easily sustainable. Our findings suggest that with control systems typical of those currently in place in the UK, the ability of a policy to contain costs rests largely with the restriction of access to new broad spectrum agents. Only seven of 30 new antimicrobial agents considered were introduced into the formulary. All new oral and the majority of new parenteral cephalosporins were excluded from the formulary. Although it is impossible to quantify, we believe that introduction of these and other agents would have further increased costs. In the future, limiting access to expensive drugs such as new preparations of amphotericin B will be crucial.

We consider that there is a viscious circle of increased antibiotic prescribing contributing to increased resistance and use of more expensive, new agents. In addition, there is an increasing tendency to practice defensive medicine (Storrs, 1996). Clearly some but not all the increased prescribing is justifiable, due not only to increased resistance but also increased patient activity and more ill patients. We need to understand the reasons for overuse of antibiotics, using better information systems and closer co-operation between pharmacists/clinicians and microbiologists to monitor use of reserve list drugs. All this costs money. While the current emphasis is very much on control of prescribing costs, there is an understandable reluctance to spend money in order to save money. Traditional control measures have gone about as far as they can without further understanding of the causes of the problems. Clinicians are often condemned for prescribing badly but most are not willfully negligent. It may be the system under which they practice which is at fault (Kritchevsky & Simmons, 1994).

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References

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