

Market penetration of new drugs in one United Kingdom region: implications for general practitioners and administrators

H McGavock, C H Webb, G D Johnston, E Milligan

Abstract

Objective—To determine the use of new drugs in one United Kingdom region.

Design—Examination of data on prescribing of angiotensin converting enzyme inhibitors, new broad spectrum antibiotics, and H₂ receptor antagonists. Calculation of number of defined daily doses prescribed each month.

Setting—All general practices in Northern Ireland. **Main outcome measures**—Drug use index and market share of each drug.

Results—During 1988-91 prescribing of angiotensin converting enzyme inhibitors increased by 126%, of H₂ receptor antagonists by 46%, and of new antibiotics by 207%. The first drug on the market usually retained the largest market share. Use of oral antibiotics increased threefold irrespective of the reporting policy of the general practitioners' local laboratory.

Conclusions—The increase in prescribing of these drugs seems to be greater than can be accounted for by an increase in patients with specific indications for these drugs. This suggests that the profession has not instituted effective checks to ensure that the legitimate promotion of new products does not lead to inappropriate and wasteful use.

Introduction

Few studies of the patterns of prescribing of new drugs in general practice have been published, because regional data are unavailable to most researchers and because most research is focused on specific therapeutic groups or problems. National prescription pricing databases and pharmaceutical sales databases have occasionally been used for studies of drug use,¹⁻⁴ but we found no studies of the market penetration of new drugs.

Every few years, the drug industry produces important new drugs that are quantitatively and qualitatively different from their predecessors. Two examples are the angiotensin converting enzyme inhibitors and the H₂ receptor antagonists. These drugs were quickly accepted by the medical profession because they proved effective, safe, and relatively free from adverse reactions and side effects.

The drug industry also occasionally produces molecular variants of existing drugs—for example, the new, potent broad spectrum oral antibiotics ciprofloxacin and cefuroxime. These antibiotics have a good safety record, are easy to administer, and have side effects similar to those of all broad spectrum antibiotics.

Although these three classes of drugs improve treatment for selected patients, they are more expensive than previous drugs whose benefits are scientifically proved. They should therefore be prescribed only when specifically indicated. The drug industry has heavily promoted these products. We conducted a

study to quantify market penetration of these classes of drugs.

Methods

Since 1976 microfiche records of general practitioner prescribing in Northern Ireland have been kept monthly by the Central Services Agency, Belfast, for every drug dispensed. These records comprise the number of prescriptions issued, the quantity of medicine (numbers of tablets and capsules, volume of liquid) and the mass of drug per item or per 5 ml liquid. As there are few private practices in Northern Ireland, these data probably account for over 99% of the community dispensing of these drugs. The population of Northern Ireland is about 1 600 000.

From these records we calculated the total mass dispensed per month for each drug. This was converted into number of defined daily doses per month by using the classification of the World Health Organisation Collaborating Centre for Drug Statistics Methodology (table I).⁵

We studied prescribing data for 1988-91 for angiotensin converting enzyme inhibitors and the antibiotics. Because cimetidine and ranitidine were already well established treatments by 1988, we extended the survey back to 1986, when the market share of ranitidine was approaching that of cimetidine.

Results

The figure shows the defined daily doses per month for the angiotensin converting enzyme inhibitors. (The trends for H₂ receptor antagonists and antibiotics were similar.) Table II gives the defined daily doses prescribed for each drug in one month (December). The drug use index was calculated by taking the number of defined daily doses in December 1988 as unity.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

By 1988 captopril was a well established treatment, with 80 831 defined daily doses in December. Prescribing of this drug increased to 84 488 defined daily doses in December 1989 and to 143 268 defined daily doses in December 1991. In contrast, the competing drug enalapril was established in 1988 at 25 335 defined daily doses in December. By December 1991 the use of enalapril had increased to 40 713 defined daily doses, but the drug's market share had fallen from 24% to 16.9% (table III).

Doctors had a choice of two branded versions of lisinopril (Carace and Zestril). Zestril was first recorded in the Northern Ireland database in December 1989 at 14 593 defined daily doses. Prescription of Zestril increased more rapidly than that of the market leader, captopril, over the next two and a half years, and its use had more than trebled by December 1991. In contrast, 2419 defined daily doses of Carace were

TABLE I—Defined daily doses of drugs studied; World Health Organisation classification^a

	Defined daily dose (mg)
Angiotensin converting enzyme inhibitors:	
Captopril	50
Enalapril	20
Lisinopril	20
Quinapril	20
H ₂ receptor antagonists:	
Cimetidine	800
Ranitidine	300
Famotidine	40
Nizatidine	300
Broad spectrum antibiotics:	
Cefuroxime	1000
Ciprofloxacin	1000

Drug Utilization Research Unit, Department of Therapeutics and Pharmacology, Queen's University of Belfast, Belfast BT9 7BL
H McGavock, *director*
E Milligan, *data clerk*

Department of Bacteriology, Royal Victoria Hospital, Belfast
C H Webb, *consultant in medical microbiology*

Department of Therapeutics and Pharmacology, Queen's University of Belfast, Belfast
G D Johnston, *reader*

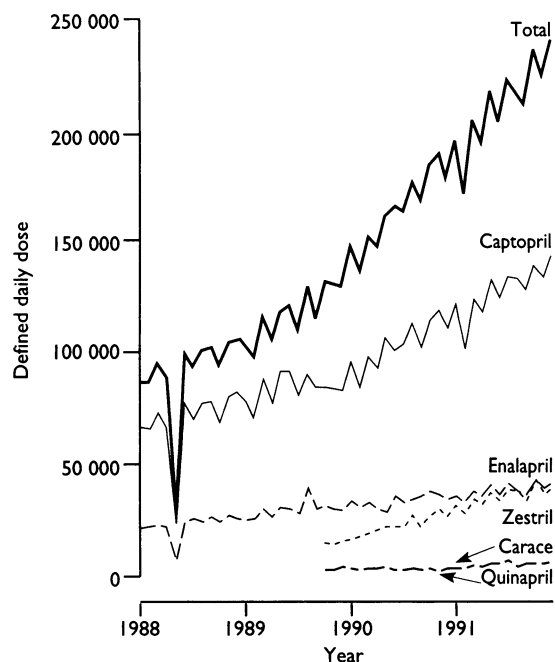
Correspondence to: Dr McGavock.

BMJ 1993;307:1118-20

prescribed in December 1988, increasing to only 5541 in December 1991. By the end of the survey the market share of Carace was only one sixth of that for Zestril. Zestril had achieved 18.4% share of the market whereas Carace had only 2.3%. A similar pattern was seen for quinapril.

H₂ RECEPTOR ANTAGONISTS

After its launch in 1978 cimetidine rapidly became established as the drug of choice for managing peptic ulceration, chronic gastritis, and reflux oesophagitis. Experience of its relative safety and freedom from side effects (combined with enthusiastic marketing) encouraged general practitioners to use it when the diagnosis had not been proved, and by 1986, 531 157 defined daily doses per month were being dispensed. A strong competitor of cimetidine, ranitidine, was introduced in 1981 and aggressively marketed. There was widespread media publicity of the drug at the same time as the launch in general practice. Ranitidine is about equally effective in healing peptic lesions and relieving symptoms as cimetidine and has a similar high relapse rate. It costs considerably more and need be prescribed only when cimetidine is contraindicated (a small proportion of patients). This information was given to all general practitioners in Northern Ireland from 1985 onwards during visits from the prescribing liaison doctor. It was then reinforced in 1987 and 1988 in a "best buys list" campaign, in which doctors were asked to consider cost effectiveness. Despite that, table II shows that the use of ranitidine increased from 461 608 defined daily doses in December 1988 to 898 026 defined daily doses in December 1991. This was almost four times its prescribing rate in 1986 (226 081 defined daily doses per month). Ranitidine



Use of angiotensin converting enzyme inhibitors in Northern Ireland, 1988-91

increased its market share from 30% in 1985 to 75% in 1991 (table III). The dispensing of cimetidine fell to 268 024 defined daily doses per month over the same period, only half its 1986 volume. The market share of cimetidine fell from 70% in 1985 to 22.5% in 1991. Famotidine and nizatidine, which were introduced later, also had decreasing market share from 1988 to 1991.

BROAD SPECTRUM ANTIBIOTICS

Ciprofloxacin and cefuroxime axetil became available within a year of each other. They were intensively marketed as antibiotics suitable for regular use in general practice. They are licensed for broadly similar indications, and taking into account the expected winter peaks and summer troughs in antibiotic prescribing both roughly trebled their prescribing volume during 1988-91. The market share of these drugs remained constant.

Discussion

We found that prescription of the three classes of drug increased rapidly over the four years studied. Prescribing was measured in defined daily doses.⁵

Doses of all drugs vary according to the age of the patient, the severity of the condition, and sometimes the idiosyncrasy of the doctor. The World Health Organisation's defined daily dose does not discriminate between any of these factors nor between duration of treatment, which is possibly even more variable. Nevertheless, it is one of the few tools available for surveying prescription pricing data to determine trends of drug use.

The drug industry has a duty to its shareholders to market the products of scientific research as effectively as possible by all legitimate means, including widespread advertising campaigns, representatives' visits, and heavy promotional activity directed at opinion formers, particularly hospital specialists. Equally, practising doctors, their collegiate bodies, and health service administrators should ensure that promotion of new products does not lead to inappropriate use. In particular, new drugs should not be allowed to replace equally effective, safe, and tolerable established treatment without good cause. There are two main reasons for this. Firstly, the safety of new products remains

TABLE II—Number of defined daily doses and drugs use index for each drug, December 1988-91

Drug	Defined daily dose (drug use index)*			
	Dec 88	Dec 89	Dec 90	Dec 91
Angiotensin converting enzyme inhibitors:				
Captopril	80 831	84 488 (1.05)	112 768 (1.4)	143 268 (1.77)
Enalapril	25 335	29 607 (1.17)	34 057 (1.34)	40 713 (1.61)
Lisinopril (Zestril)		14 593	27 925 (1.91)	43 996 (3.01)
Lisinopril (Carace)		2 419	3 544 (1.47)	5 541 (2.29)
Quinapril			2 031	6 738 (3.32)
Total	106 166	131 107 (1.23)	180 325 (1.70)	240 256 (2.26)
H₂ receptor antagonists:				
Cimetidine	327 057	307 089 (0.94)	288 008 (0.88)	268 024 (0.82)
Ranitidine	461 608	553 930 (1.2)	696 398 (1.51)	898 026 (1.95)
Famotidine	13 532	15 342 (1.13)	17 045 (1.26)	17 795 (1.32)
Nizatidine	13 584	9 631 (0.71)	9 398 (0.69)	8 009 (0.59)
Total	815 781	885 992 (1.09)	1 010 849 (1.24)	1 191 854 (1.46)
Antibiotics:				
Ciprofloxacin	6 157	9 607 (1.56)	14 879 (2.42)	18 782 (3.05)
Cefuroxime	2 792	5 840 (2.09)	7 255 (2.6)	8 647 (3.1)
Total	8 949	15 447 (1.73)	22 134 (2.47)	27 429 (3.07)

*Drug use index calculated by taking defined daily doses for December 1988 as unity.

TABLE III—Percentage of market share held by drugs

Drug name	1985	1986	1987	1988	1989	1990	1991
Angiotensin converting enzyme inhibitors:							
Captopril				76	64.4	62.5	59.6
Enalapril				24	22.6	18.9	16.9
Lisinopril (Zestril)					11.1	15.5	18.4
Lisinopril (Carace)					1.9	2.0	2.3
Quinapril						1.1	2.8
H₂ receptor antagonists:							
Cimetidine	70	53	47	40	34.7	28.5	22.5
Ranitidine	30	47	53	56	62.6	68.9	75.3
Famotidine				1.7	1.7	1.7	1.5
Nizatidine				1.7	1.0	0.9	0.7
Antibiotics:							
Ciprofloxacin				69	62	67	68.5
Cefuroxime				31	38	33	31.5

Blanks indicate that drug had not yet appeared in prescription pricing database.

suspect until sufficient clinical experience is available. Secondly, new treatments are almost always expensive, sometimes much more expensive than existing treatments.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

An excellent example is the angiotensin converting enzyme inhibitors. There are only two absolute indications for the use of these drugs—with other drugs in managing heart failure and for hypertension uncontrolled by other drugs or drug combinations. They are, however, being promoted and used for all grades of hypertension, including mild hypertension. In such cases a low dose thiazide diuretic combined, if necessary, with a selective β blocker has been proved to be effective, safe, and well tolerated—long term studies have shown a large decrease in cerebrovascular morbidity and mortality, especially in elderly people, and a smaller decrease in coronary morbidity and mortality.^{6,7} No such benefits have yet been proved for the angiotensin converting enzyme inhibitors, however likely it is that they will be seen in future. Since these drugs cost up to 30 times more than the cheapest low dose thiazide diuretic, unnecessary prescribing will waste scarce NHS resources. The aging population and a redefinition of diagnostic criteria has caused a real increase of perhaps a fifth in the rate of diagnosis of heart failure. But it is unlikely that the amount of heart failure and refractory hypertension has more than doubled in the past four years, as has prescribing of angiotensin converting enzyme inhibitors.

ANTIBIOTICS

In the case of the two antibiotics studied the companies concerned have been marketing their products for routine treatment of upper and lower respiratory tract, urinary tract, and other infections in general practice. There is little justification for using these drugs for routine treatment, and there may be specific drawbacks to their indiscriminate use. The antipneumococcal activity of ciprofloxacin *in vivo* has been disappointing,^{8,9} and cefuroxime has been commonly associated with gastrointestinal upset.¹⁰ The extra cost of these drugs is another important factor, but perhaps the most serious consequence is the inevitable development of widespread bacterial resistance and an increasing incidence of side effects to these drugs. They may ultimately become ineffective for managing life threatening illness. Doctors and their microbiological advisers are responsible for regulation of prescribing of such drugs, not the drug industry.

Laboratories come under pressure from drug industry representatives to include new products in their battery of antibiotics tested, often under the guise of a study. They may also be pressurised by general practitioners who start to prescribe a new drug and wish to have it screened. But most antibiotics are given presumptively in general practice (without any intention of determining which antibiotics the bacteria are sensitive to), and lack of data on sensitivity does not seem to inhibit prescribing. We found that the four area laboratories differed greatly in their policy on reporting sensitivity to cefuroxime and ciprofloxacin in urine and sputum cultures sent by general practitioners. But increases in prescribing of these antibiotics were similar in the four areas. The area with no consultant microbiological advice had the highest drug use index.

H₂ RECEPTOR ANTAGONISTS

One of us (HMcG) has visited general practices

throughout Northern Ireland since 1986 to audit prescribing. During these visits he advised general practitioners not to use H₂ receptor antagonists except where there is proved disease. This was both because of the risks of camouflaging serious illness, which might have been found by appropriate pretreatment investigations and because of the enormous difference in cost between H₂ receptor antagonists and simple antacids. Doctors have (almost always) defended their use of H₂ receptor antagonists on the basis of either symptoms alone or in conjunction with minimal physical signs because "there is little risk in using these drugs and investigations are expensive and often difficult to organise." But the drugs are associated with high rates of recurrence of peptic ulceration (80% within a year) and chronic gastritis after healing. This results in patients taking three or four courses a year or long term maintenance. The well tried alternative, a six to eight week course of bismuth chelate, is cheaper, heals 75% of benign ulcers, and has a relapse rate of only 30% at one year.^{11,12} In view of these facts, doctors ought to consider why prescribing of H₂ receptor antagonists is increasing.

Our results show that the first drug on the market usually continues to be the market leader. The second drug also seems to flourish, with a smaller market share. The differential between the first and second seems to persist for at least four years. Competing drugs generally take their market share from the market leaders rather than from smaller competitors.

CONCLUSION

We have shown a simple technique for revealing patterns of prescribing in a region or family health services authority. The data do not relate to individual prescribers and are thus not threatening. They do, however, highlight doctors' joint responsibility to take appropriate action when effective and legal marketing is causing unjustifiable changes in medical practice. Studies such as ours can provide evidence of these changes. We suggest that a drug use index should be monitored for all new drugs.

We thank our colleagues in the Central Services Agency and Directorate of Information Systems, Department of Health and Social Security, Belfast, for providing the microfiche films for this study. The discussion and conclusions represent only the opinions of the authors.

- 1 Hood HE, Wade OL. Use of amphetamines in general practice. *Lancet* 1968;ii:96-7.
- 2 Wade OL, Hood HE. An analysis of prescribing of an hypnotic in the community. *Br J Prev Med* 1972;26:121-8.
- 3 Elmes PC, McMeekin C. Prescribing in Northern Ireland systemic anti-infectives. *Ulster Med J* 1978;47:79-87.
- 4 Griffiths K, McDevitt DG, Andrew M, Baksaas I, Lunde PK, Bergman U, et al. Validation of observed differences in the utilization of antihypertensive and antidiabetic drugs in Northern Ireland, Norway and Sweden. *Eur J Clin Pharmacol* 1985;29:1-8.
- 5 WHO Collaborating Centre for Drug Statistics Methodology. *Anatomical therapeutic chemical classification index*. Oslo: WHO, 1993:1-122.
- 6 Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *BMJ* 1985;291:97-104.
- 7 Medical Research Council. Trial of treatment of hypertension in older adults: principal results. *BMJ* 1992;304:405-12.
- 8 Consumers Association. Ciprofloxacin—an important new antimicrobial. *Drug and Therapeutics Bulletin* 1987;25:69-72.
- 9 Hawkey PM. Where are we now with ciprofloxacin? *J Antimicrob Chemother* 1989;24:477-83.
- 10 Joint Formulary Committee. Drugs used in the treatment of infections. In: *British National Formulary*. BMA/RPSGB, London 1993;25:203-53.
- 11 Marshall BJ, Goodwin CS, Warren JR, Murray R, Blincow CS, Blackburn SJ, et al. Prospective double-blind trial of duodenal ulcer relapse after eradication of *Campylobacter pylori*. *Lancet* 1988;332:1437-42.
- 12 Rauws EAJ, Tytgat GNJ. Cure of duodenal ulcer associated with eradication of *Helicobacter pylori*. *Lancet* 1990;335:1233-5.

(Accepted 20 August 1993)