Modelling the market uptake of new drugs following listing for subsidy in Australia. A report from the Drug Utilisation Subcommittee of the Australian Pharmaceutical Benefits Advisory Committee

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The market uptake of five drugs following subsidy listing in Australia during the period 1990 to 1992 has been modelled using the sigmoid $E_{\max}$ model for drug-receptor binding. Utilisation trends for simvastatin, omeprazole, budesonide, fluoxetine and moclobemide in defined daily dose (DDD) per 1000 population per day were smoothed by expressing as rolling annual averages. The results indicate good fits of the model to the data except for omeprazole, with good estimates of uptake rate and eventual maximum utilisation. Substantial differences between the drugs occurred in uptake rate which may be related to public education campaigns on asthma and coronary heart disease occurring during the release period. The very slow uptake of omeprazole relative to other drugs is likely to be due to restrictions on subsidised use. Modelling the market uptake rate and eventual utilisation of new drugs is useful as an aid to regulatory, quality use of medicines and financial decisions and allows comparisons between drugs to investigate factors important in market uptake.

Keywords drug utilisation market uptake pharmacoepidemiology drug subsidy

Introduction

In Australia, about 90% of the community use of prescription medication is through two government drug subsidy schemes: the Pharmaceutical Benefits Scheme (PBS) and the Repatriation Pharmaceutical Benefits Scheme (RPBS). Listing on the PBS/RPBS is usually required for market success.

Both government and the pharmaceutical industry are keenly interested in predicting the usage and resulting financial implications of new drugs before, or at an early stage after, they are listed for subsidy. Traditional methods for forecasting the use of a new product have relied on the history of previous launches of similar products into the same market, and a comprehensive analysis of the product and its potential within this market.

We report on a novel approach to predict the rate of uptake and maximum usage of drugs recently listed for subsidy in Australia. Drug 'binding' at a

population level is modelled by application of an expression similar to that used for drug-receptor binding analysis.

Methods

Source of data

Since July 1989, estimates of community prescription drug use have been available through a database co-ordinated by the Drug Utilisation Subcommittee (DUSC) at the Department of Human Services and Health [1]. DUSC collects and analyses data on drug utilisation in Australia for use by the Pharmaceutical Benefits Advisory Committee, which advises the Minister as to the drugs to be subsidised, for inter-

national comparisons and to assist in the quality use of medicines. Statistics on the Australian use of medicines are published at regular intervals [2].

The measurement units are either prescription volumes or the WHO approved unit for drug utilisation studies—the defined daily dose (DDD) per 1000 population per day. The defined daily dose is established on the basis of the assumed average dose per day of the drug, used for its main indication by adults. Use of the DDD allows for comparisons independent of differences in price, preparation and quantity per prescription [3].

Trends in the use of individual drugs of interest are followed in various units of time, although 12 month blocks are preferred to adjust for the supply distortions that are introduced by the PBS safety net provisions. Once the cash-based safety net level is reached, subsequent prescriptions on the scheme are either free or available at a greatly reduced co-payment. The safety net period is the calendar year and the low level of use at the beginning of the year, and high use at the end, are due to stockpiling of medication towards the end of the year once this safety net level is reached [4].

The drugs selected for study were simvastatin, omeprazole, fluoxetine, budesonide and moclobemide introduced onto the subsidy scheme in the 4th quarter 1990, 3rd quarter 1990, 2nd quarter 1991, 3rd quarter 1991 and 2nd quarter 1992 respectively.

Data analysis

Quarterly utilisation data were expressed as rolling annual averages to smooth out fluctuations due to the safety net effect. Data were fitted by the sigmoid $E_{\max}$ model for drug concentration-response relationships [5]. The data were fitted to the model using the programme 'Siphar/D' (Simed, Créteil, Cedez-France) with no weighting of the data and utilisation at the zero time point fixed to zero. Goodness of fit was assessed by the coefficients of variation of the calculated parameters and by the distribution of residuals.

In the context of drug utilisation data, the expression used is

$$u = \frac{U_{\max} \cdot T^n}{TU_{50}^n + T^n}$$

where u is the utilisation (DDD/1000 population/day) at each time, $U_{\max}$ is the maximum utilisation, T is the time (in quarter years) after introduction to the market, TU_{50} is the time to achieve 50% of maximum utilisation and n is the steepness of the uptake slope.

Results

In looking at time trends for a number of new drugs, it seemed that the profile (particularly when smoothed by expressing as a rolling 12 month average) was a sigmoidal curve that might fit to the standard Hill expression as applied to drug-receptor binding [5]. The transformation of the data to a rolling annual average enhanced the sigmoidicity of the utilisation vs time curves and moved them to the right. It does, however, still allow comparisons between drugs and drug groups. Using the raw data, either as monthly or quarterly averages, introduced large safety net related fluctuations [4] which made simple fitting strategies very inaccurate.

Table 1 shows the derived parameters for the five drugs when modelled using data available up to the June quarter 1993. Figure 1a shows the uptake of the five drugs and the fit of the model to the data, and Figure 1b shows the modelled uptake of the drugs with normalised maximum utilisation. The fits of the model to the data were good in all cases except for omeprazole, with parameter coefficients of variation less than 12%.

Uptakes of moclobemide and fluoxetine were slower than those for simvastatin and budesonide (longer TU_{50} and lower n value). The results indicate

Table 1 Parameter estimates for uptake of new drugs

Drug	Data period (quarter years)	$U_{\max}$ (DDD/1000/day)	TU_{50} (quarter years)	Slope (n)
Budesonide	8	16.2 (10.9)	4.9 (11.5)	2.2 (11.8)
Omeprazole	12	25.6 (166.1)	89.2 (11.6)	1.6 (3.9)
Moclobemide	5	1.8 (12.3)	6.0 (11)	2.0 (4.4)
Fluoxetine	8	3.1 (11.4)	9.8 (10.3)	1.9 (3.8)
Simvastatin	12	6.2 (1.6)	4.4 (1.7)	3.1 (4.4)
Simvastatin	10	6.2 (2.9)	4.4 (2.6)	3.1 (5.9)
Simvastatin	8	6.2 (6.7)	4.4 (5.5)	3.1 (9.1)
Simvastatin	7	6.8 (14.7)	4.7 (11.3)	2.9 (12.2)
Simvastatin	6	20.9 (23.0)	9.7 (14.6)	2.2 (3.0)
Simvastatin	5	20.9 (78.2)	9.8 (45.7)	2.2 (6.4)

Figures in parentheses are the coefficients of variation expressed as a percentage.

Figure 1 Market uptake of new drugs. a) shows the utilisation data expressed as rolling annual averages (points) and the modelled utilisation (lines). ∇ budesonide, $\diamond$ simvastatin, $\triangle$ moclobemide, $\circ$ fluoxetine, $\square$ omeprazole. b) shows the modelled market uptake for the five drugs with maximum utilisation normalised to the same value to allow comparison of uptake rates. Model parameters are in Table 1. --- simvastatin, — budesonide, -.-.- moclobemide, fluoxetine, omeprazole.

a maximum market for fluoxetine about twice that for moclobemide. The uptake for omeprazole was slow and utilisation was still on the upswing in June 1993. Because of this, the CVs for the calculated parameters are very high indicating a large uncertainty in the fit. Also shown in Table 1 are the model parameters for simvastatin with data points successively removed. The results indicate that the fit remains robust even at quite an early stage after the introduction of the drug, becoming unreliable at the point 18 months after listing for subsidy.

Discussion

Modelling the market uptake of new drugs at a relatively short time after their introduction is feasible. The derived parameters for all the drugs except omeprazole were realistic and had acceptable coefficients of variation.

The comparison of the rates of uptake shown in Figure 1b indicates quite marked differences between drugs. The drugs with the most rapid uptake (simvastatin and budesonide), as judged by shorter TU_{50} and higher n values, were both indirectly the subject of extensive public health education campaigns. In the early 1990s, the National Heart Foundation of Australia strongly promoted high cholesterol levels as a major risk factor in coronary heart disease, while

recent messages from the National Asthma Campaign have emphasised the need for preventative therapy of asthma.

The fit for omeprazole was poor either because the model is not appropriate in this case or because the drug is still in an early stage of market uptake. This may be due to the tight restrictions initially imposed on subsidy use which were successively relaxed over the period of the study, so that utilisation is still curving upwards as long as 3 years after its introduction.

The model fits the data well and allows comparison of market uptake of different drugs in terms of standardised parameters, time to 50% maximum utilisation, steepness of uptake and maximum utilisation. That the expression used is the same as for drug-receptor binding analysis is coincidental but interesting. The model was able to predict the maximum utilisation of simvastatin at a stage where utilisation was 72% of the eventual maximum utilisation but not at earlier times. The ability to model and compare the rapidity of uptake and maximal use of new drugs will be useful in investigating factors important in market uptake and in making financial and regulatory decisions. It may also help to assess the impact on eventual utilisation of factors such as regulatory changes or the introduction of new indications and/or competitors (e.g. further SSRIs in the case of fluoxetine). We are currently investigating the application of such techniques to a wider range of new drugs.

References

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