Impact of the CSM advice on thioridazine on general practitioner prescribing behaviour in Leeds: time series analysis

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SUMMARY

In December 2000, the Committee for Safety of Medicines (CSM) advised that thioridazine may prolong QT intervals risking arrhythmias. We investigated the impact on general practitioner prescribing of thioridazine using a time series analysis. Numbers of items and costs of antipsychotics and benzodiazepines prescribed in Leeds from May 1999 until April 2002 were collated. Post-advice, thioridazine prescriptions dropped by 810 items per month (95% confidence interval = 420 to 1200, P<0.001) but others increased slightly in response. Costs mimicked these changes. Fresh criteria are proposed for appraising the quality of evidence needed to inform future urgent facsimile transmissions.

Keywords: *general practitioner prescribing; long QT syndrome; prescribing advice; primary health care; psychotropic drugs; telefacsimile.*

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Introduction

IN December 2000, the Committee for Safety of Medicines (CSM) issued an urgent cascade fax to all GPs recommending that thioridazine should be restricted to second-line treatment of schizophrenia in adults and that the balance of risks and benefits is unfavourable for its previous indications (anxiety, agitation and restlessness in the elderly, moderate to severe psychomotor retardation, violent and dangerously impulsive behaviour, mania/hypomania, and behavioural disorders and epilepsy in children). The fax recommended that treatment with thioridazine should be supervised by a consultant psychiatrist (with monitoring of the patient's electroencephalogram [ECG] and electrolytes), because of concerns that thioridazine was associated with a higher risk of life-threatening arrhythmias and sudden death.[1]

Prior to December 2000, thioridazine was the most commonly prescribed phenothiazine in primary care owing to its low cost and lower incidence of extrapyramidal side-effects compared to other antipsychotics.[2]

There is often a rebound effect of urgent advice. For example, in the case of the third generation oral contraceptive 'pill scare' in 1995, there was a subsequent increase in the number of terminations of pregnancy.[3] Also, clinician workload increased as many patients had to be reviewed in a short space of time. Finally, if the evidence base for the advice is not sufficient, then patients risk being changed to different medication, the safety profile of which may be no better than that of the former treatment.

Method

Prescribing data for all antipsychotics and benzodiazepines were accessed for Leeds from May 1999 until April 2002, from a total of 444 general practitioners (GPs) from 120 practices. This included data for 19 months prior to the advice from the CSM and 16 months following the advice. The data was collated from the five Leeds Primary Care Trust prescribing advisors from the ePACT (electronic Prescribing Analysis and Cost) system. The impact of the introduction of the guidelines on number of items prescribed and their costs was modelled using linear regression (ordinary least squares) with a discontinuity at the time of the guidance. Adjustment for serial correlation was made using the Cochrane–Orcutt transformation, with the autocorrelation parameter being chosen to minimise the sum of squared errors of the transformed equation.[4] Analyses were carried out using Stata 8.1. The sensitivity of the results to adjustment for season and to use of the

HOW THIS FITS IN

What do we know?

Thioridazine and other antipsychotics have been implicated in ventricular arrhythmias and sudden cardiac death. The relative risk appears to be dose-related, with the elderly or those with pre-existing heart disease particularly at risk.

What does this paper add?

An urgent facsimile transmission from the Committee on Safety of Medicines led to an abrupt, sustained, significant reduction in thioridazine prescribing by general practitioners despite poor supporting evidence. Fresh criteria are proposed for appraising evidence to constitute a future urgent fax to general practitioners.

alternative method of Prais–Winsten transformations[5] were explored.

Results

Post-guidance, there was a statistically significant reduction in items and cost of thioridazine prescribed, a statistically significant increase in items of haloperidol prescribed (but cost increase did not reach significance) and a statistically significant increase in chlorpromazine prescribing costs (although increase in chlorpromazine items was only borderline significance). These results were broadly unchanged by adjustment for season, or by using the alternative method of Prais–Winsten transformations. The results are shown in Tables 1 and 2.

Discussion

The CSM advice regarding thioridazine resulted in a marked change in the prescribing behaviour of GPs in Leeds. This work has clearly identified trends in GP prescribing of antipsychotics both before and after the advice and demonstrated a statistically significant effect of the advice upon GP prescribing practice.

The implications of this study are that CSM guidance does influence doctors' behaviour effectively, and with immediate effect. The resulting increased workload and the absence of any demonstrable health gain from the medication changes made in this instance will continue to be debated. There is a need for greater clarity regarding the strength of evidence that triggers an urgent cascade fax from the CSM. At the time of the fax, there were no observational studies that had established a causal link between thioridazine and cardiac death. Earlier that year, a possible link was reported between thioridazine and the surrogate marker of the QT interval.[6] However, although the study showed that many psychotropic drugs prolonged the QT interval, owing to small numbers of trial participants the effect only reached statistical significance for thioridazine (the drug that most study participants were taking). The possibility of thioridazine being a causal agent for sudden cardiac deaths was also controversial, as many other drugs routinely used in primary care, such as tricycyclic antidepressants, antifungals, and antihistamines,[7,8] also prolong the QT interval.[9] Therefore, in the light of this evidence base and in response to the fax we argued that QT interval widening in itself can be a benign condition and that QT lengthening is a class effect of phenothiazines and not specific only to thioridazine.[10] We recommended thioridazine as a safe drug in young people who do not have a history of cardiac disease.

Since the cascaded fax, two large retrospective cohort studies have been published that support these recommendations. The first, of 481 744 patients,[11] concluded that in the antipyschotics studied there was a statistically significant relative and absolute risk of cardiac death when prescribed more than thioridazine 100 mg equivalent per day. There was no evidence that thioridazine causes more problems than other antipsychotics. The second, a large cohort study of almost 100 000 outpatients, found the rate of cardiac arrest and ventricular arrhythmia to be signif-

Table 1. Impact of advice on number of items prescribed.

Drug	Change in mean monthly number of items prescribed	95% CI	*P*-value
Chlorpromazine hydrochloride	160	-10 to 320	0.06
Haloperidol	120	60 to 180	<0.001
Olanzapine	60	-40 to 160	0.2
Risperidone	50	-90 to 180	0.5
Thioridazine	-810	-1200 to -420	<0.001

Table 2. Impact of advice on cost of items prescribed.

Drug	Change in mean monthly cost of drugs prescribed (£)	95% CI	*P*-value
Chlorpromazine hydrochloride	400	100 to 710	0.01
Haloperidol	150	-80 to 390	0.2
Olanzapine	3240	-3190 to 9660	0.3
Risperidone	-1080	-6010 to 3860	0.7
Thioridazine	-910	-1320 to -490	<0.001

icantly higher for haloperidol, thioridazine and risperidone compared to controls. Risperidone was shown to have the highest mortality at five cases per 1000 person years. This discussion is of importance to the issue of prescribing costs. In the year after the urgent cascade fax, the cost of primary care prescribing of atypical antipsychotics for England increased by £32 million. Over the same period, the prescribing cost of typical antipsychotics fell by just under £900 000.[12]

Our findings have implications for future urgent advice

Commentary

Wright *et al* have studied the impact of the Committee for Safety of Medicines advice on general practitioner (GP) prescribing behaviours using time series analysis.[1] The situation they find themselves in is one in which a clinical trial to evaluate an intervention cannot be carried out, but the results before and after the intervention can be observed, and it can be tested whether the intervention has an effect on subsequent outcomes. These are sometimes called 'before-and-after' studies, single case studies or 'interrupted time series'.[1,2] Examples include the effect of seat belt legislation on deaths due to car accidents, the effect of NHS Direct on consultation to a GP, and the effect of GP telephone triage on numbers seeking same-day appointments.[3-5] Usually, observations are made at regular intervals, such as weekly or annually. The 'case' might be the whole country for seat belt legislation, or a general practice for same-day appointments.

An important question for the analysis is whether the data are serially correlated. This means that the data are not independent. It is very important to distinguish single case studies and repeated measures. In the latter, more than one case (usually an individual) is studied, and observations within an individual will be correlated simply because individuals differ in their overall mean. Thus, if you knew one observation from an individual, then knowing that the next observation came from that individual means that you would be better able than by chance to predict the next observation from that person. There is an analogy here with cluster randomised trials, whereby subjects within a cluster will be correlated.[6] In the single case design, the subject effect is given, and we are interested in the correlation of the differences of the observations from the model. It is not inherently obvious that the errors should be correlated, simply because they are measured serially in time. Imagine measuring a person's weight with a scale, which has some random inaccuracy in it — perhaps due to the room temperature. Simply because it over-reads one day does not mean it will over-read the next. To reduce the effect of the random error and to get a good estimate of a person's weight, we need to make a number of measurements and take an average. In this case, no time series methods are needed despite the fact that the data are a time series! The main reason for serial correlation in a single case design is that we have the wrong model. Suppose we wish to test the effect of a diet on a person's weight, and we make repeated measures before the diet, and repeated measures after. If we believe that the effect of the diet is simply to reduce weight by a fixed amount, and yet the person continues to lose weight, the errors from the model will get greater and greater, and will be predictable, that is, a large error one week will be followed by a larger error in the subsequent one.

The effect of serial correlation is to render the usual statistical model invalid. This is because one assumption for a statistical model is that the error terms are independent. If the errors are not independent, the usual estimate of the confidence interval for the treatment effect will be too narrow, and as a consequence spurious statistical significance may be inferred. One way of testing whether the errors are independent is to use what is known as the Durbin–Watson test, which is available in many statistical packages.[7] Jiwa *et al* used this method to check for serial correlation, and we were reassured that there was none.[5] If it is present, there are a number of ways of accounting for serial correlation in an analysis. The traditional method, known as Box–Jenkins analysis, is really more suited for economic or industrial applications, where there are at least 50 observations to the series.[7] A more convenient method is to use time series regression models, which are also available in a number of computer packages.[8,9]

There are a number of possible models to use and three conventional ones are (*a*) a change in slope, (*b*) a change in level, or (*c*) a combination of a change in slope and a change in level. The equations for these are given in Supplementary Appendix 1. Wright *et al*[1] assume simply a change in level, whereas Munro *et al*[4] assumed a change in slope. A sensible scheme would be to plot the data first to decide which model to fit. A simple method of allowing for serial correlation is known as the Cochrane–Orcutt method.[9,10] This makes some strong assumptions about the nature of the serial correlation, which are described in Supplementary Appendix 1, but in many cases these are justified.

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Supplementary information

Additional information accompanies this paper at http://www.rcgp.org.uk/rcgp/journal/index.asp

from the CSM. We recommend that if there is emerging evidence of a possible poor safety profile of a drug from case reports or case series, then an urgent fax would not be an appropriate means of communicating with practitioners. Rather, updating the relevant 'cautions' or 'contra-indications' sections of prescribing formularies would be more time- and cost-effective. The mode of an urgent cascade fax should be reserved for disseminating the findings of well-designed observational studies with clear outcomes of clinical significance. Clearly, the CSM has a duty of care to protect the public from unsafe medicines and to inform clinicians. Therefore, waiting for the results of prospective cohort or randomised controlled trials could be unethical. We would contend that the well-designed, case-control study or historical cohort study of a medicine's safety should become the 'gold standard' for sources of information to inform a decision by the CSM on the appropriateness of an urgent facsimile communication. Further research is necessary to quantify the impact of an urgent CSM fax on clinician workload, patient morbidity and anxiety regarding 'urgent' changes of medication. This is a vital part of the risk/benefit equation.

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