IMPACT OF LEGISLATIVE CHANGES ON PATTERNS OF ANTIPSYCHOTIC PRESCRIBING AND SELF-POISONING IN SCOTLAND: 2000-06

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(Received October 6, 2006; Accepted October 23, 2006)

ABSTRACT — Recently, national guidelines have advocated greater use of atypical rather than typical antipsychotics in the treatment of schizophrenia. In addition, there have been safety concerns regarding the potential cardiotoxicity of certain antipsychotics taken in overdose. This has led regulatory authorities in the United Kingdom to restrict the use of thioridazine. The overall impact of these legislative changes on patterns of antipsychotic prescribing has received comparatively little attention. Therefore, we sought to examine the effects on community prescribing practices, and to determine whether this was accompanied by changes in patterns of antipsychotic poisoning.

Between 2000-03, there was a rapid decline in the use of typical antipsychotics, whereas the use of atypical antipsychotics increased. The prevalence of atypical and typical antipsychotic prescribing has been approximately equal between 2003-06. During the same study period, hospital admissions due to typical antipsychotic poisoning also declined, however, the effects lagged behind changes in prescribing practice by 2-3 years. These data indicate that legislative changes that restrict the use of thioridazine and other typical antipsychotics are associated with a measurable reduction in the number of hospital admissions due to overdose with these agents.

KEY WORDS: Antipsychotic, Epidemiology, Poisoning, Thioridazine

INTRODUCTION

Schizophrenia imposes a significant healthcare burden due to the life-long nature of the illness and levels of disability encountered (Harding, 1987). Conventional, so-called 'typical' antipsychotics are associated with frequent adverse effects, which limit their clinical utility. Newer 'atypical' antipsychotics appear to be equally effective, but associated with a different adverse effect profile that is generally more acceptable to patients. For this reason, atypical antipsychotics are perceived to be better tolerated, and associated with improved quality of life compared to typical antipsychotics (Silva de Lima *et al.*, 2005). The National Institute of Clinical Excellence (NICE) have recently advocated the use of atypical agents in new onset psychosis, and for patients who experience significant adverse

effects or have an inadequate response to typical antipsychotics (National Institute for Clinical Excellence, 2002).

The American Academy of Poison Control Centers has indicated that fatalities after atypical antipsychotic ingestion are uncommon, and the effects are generally benign even after massive overdose (Trenton *et al.*, 2003; Baca-Garcia *et al.*, 2002). Nonetheless, significant cardiotoxicity may arise from inhibition of the inward rectifier potassium (IKr) channel (Witchel and Hancox, 2000), which manifests as QT prolongation and arrhythmia, including torsade de pointes (Lin *et al.*, 2004). Arrhythmia is more likely in the presence of other factors that inhibit IKr current, for example hypokalaemia, hypomagnesaemia, and chronic heart failure (Stollberger *et al.*, 2005). Recently, thioridazine and droperidol emerged as more likely to cause exten-

sive QT prolongation than other antipsychotics (Reilly *et al.*, 2000), and are associated with a greater risk of arrhythmia after overdose (Isbister *et al.*, 2006; Buckley *et al.*, 1995). In view of these safety concerns, the Medicines and Healthcare products Regulatory Agency (MHRA) restricted the use of thioridazine in the United Kingdom in 2000 and, shortly after, droperidol was withdrawn from the market by its manufacturer (MHRA, 2000).

Implementation of NICE guidelines, and licence restrictions on thioridazine have led to substantial changes in patterns of antipsychotic prescribing in Scotland and England (Bateman *et al.*, 2003). Early data indicate that the mortality related to antipsychotic poisoning in England and Wales has declined (Griffiths and Flanagan, 2005). A key objective underlying the restriction of thioridazine was to protect patients from the potentially toxic effects after acute ingestion. It remains unclear if altered community prescribing practices have led to changes in the patterns of antipsychotic overdose. Therefore, the present study was designed to examine patterns of hospital attendance after ingestion of specific antipsychotic agents, and to compare these to prevalent prescribing practices in the local community. The study is timely, because a sufficiently long period after the legislative changes has now elapsed so as to allow any impact on patterns of antipsychotic poisoning to be observed.

MATERIALS AND METHODS

Hospital admission data

Cases were identified from a local register of patients admitted to the Toxicology Unit of the Royal Infirmary of Edinburgh. We performed a retrospective review of patients admitted between April 2000 and March 2006 inclusive. Our local policy is that patients attending the Emergency Department after drug ingestion are admitted to our Toxicology Unit for ongoing medical care and psychiatric review. Patients may be admitted to the High Dependency Unit if non-invasive ventilatory support is likely to be required, and to the Intensive Treatment Unit if invasive ventilatory support, haemodialysis or other critical care intervention is likely to be required. Patients who were admitted to any of these clinical areas were included in the study.

Prescribing data

Data on community prescribing of antipsychotics was obtained from the Lothian Health Board records,

which pertains to the same patient population as served by our hospital (approximately 785000). These data are expressed as the number of prescription items for each antipsychotic drug each year for the Lothian area.

Statistical analyses

The absolute number of annual hospital admissions was expressed with respect to the number of prescription items issued during the same period, for both atypical and typical antipsychotics. Annual admission numbers were expressed per 1000 prescription items, and presented as mean $\pm$ 95% confidence interval. These values were compared using paired two-tailed Student's *t* tests (Mitchell, 2000), using StatsDirect statistical software version 2.2.2 (StatsDirect Ltd., Cheshire, UK). *p*-values <0.05 were accepted as statistically significant. Hospital admission numbers related to atypical and typical antipsychotics were also expressed as a proportion of all antipsychotic overdoses, so that variation in admitting practices from the Emergency Department could be accounted for between years.

RESULTS

The number of annual prescription items for antipsychotic drugs in the Lothian region is shown in Table 1. Between 2000-2003, atypical antipsychotic prescribing became more prevalent, whereas typical antipsychotic prescribing became less prevalent. However, after 2003, the proportion of atypical and typical antipsychotic agents prescribed has remained constant, and is near equal.

The number of patients admitted due to antipsychotic poisoning during the same period is shown in Table 2. The proportion of patients who had ingested atypical antipsychotics progressively increased during the study period, accompanied by a corresponding decline in poisoning by typical antipsychotics (Fig. 1). Changes in the pattern of hospital admissions after antipsychotic poisoning appeared to mirror changes in community prescribing, albeit that a considerable lag period was noted (Fig. 2). Overall, the number of hospital admissions associated with atypical antipsychotic overdose was low, representing 1.5 (95% CI 1.33-1.68) admissions annually per 1000 prescriptions. Hospital admissions after typical antipsychotic ingestion were higher, representing 3.36 (2.69-4.03, *p* = 0.007) admissions annually per 1000 prescriptions.

DISCUSSION

These data reflect striking changes in antipsychotic prescribing in Lothian region between 2000 and 2006. As expected, licence restrictions have caused a dramatic decline in thioridazine prescription numbers after 2001. Perhaps somewhat more importantly, this is reflected by a massive decrease in the number of patients admitted to hospital after deliberate thioridazine ingestion. Admissions to the Royal Infirmary of Edinburgh alone witnessed a fall in the annual incidence of thioridazine poisoning from 76 cases in 2000-01 to zero in 2005-06. Similarly, a decline in thioridazine-related mortality has been reported elsewhere, which coincides with the recent legislative changes (Griffiths and Flanagan, 2005).

Overall, antipsychotic prescription numbers have remained fairly constant. However, this belies a substantial increase in the utilisation of atypical antipsychotics, and a decrease in the prescription of typical antipsychotics, including, for example, chlorpromazine. These patterns are likely to reflect incorporation of NICE guidelines into local prescribing policy. The changes in prescribing practice had evolved over 2-3 years and, when established, the proportions have remained comparatively stable over the past 3 years.

Different trends were noted in the patterns of hospital admissions during the same time. Whilst the proportion of patients admitted due to atypical antipsychotic poisoning also increased during the study period, this lagged behind changes in prescribing patterns by at least 2-3 years. Therefore, hospital admis-

Table 1. Number of scripts issued for typical and atypical antipsychotics in Lothian Health Board area between 2000 and 2006, shown for 1st April through 31st March.

	2000-1	2001-2	2002-3	2003-4	2004-5	2005-6
Benperidol	—	37	41	66	32	51
Chlorpromazine	—	19701	19843	18353	17774	17149
Droperidol	—	28	0	0	0	0
Flupenthixol	—	88	68	69	105	136
Fluphenazine	—	116	86	77	70	54
Haloperidol	—	3807	3513	3005	3793	3896
Loxapine	—	55	52	22	0	0
Methotrimeprazine	—	456	610	628	718	627
Oxypertine	—	6	0	0	0	0
Pericyazine	—	330	354	329	317	330
Perphenazine	—	57	48	56	49	34
Pimozide	—	254	188	118	105	74
Promazine	—	731	591	543	423	434
Sulpiride	—	4322	3961	3327	3562	3757
Thioridazine	—	3190	2011	1479	1144	359
Trifluoperazine	—	2758	2573	2359	2207	1860
Zuclopenthixol	—	480	416	321	337	401
Typical antipsychotics:	<i>48906</i>	<i>36416</i>	<i>34355</i>	<i>30752</i>	<i>30636</i>	<i>29162</i>
Amisulpiride	—	718	921	1247	2512	1200
Aripiprazole	—	0	0	0	52	265
Clozapine	—	3	3	1	5	9
Olanzapine	—	8768	10452	12811	12352	12166
Quetiapine	—	856	1313	2114	3719	4688
Risperidone	—	11149	13558	14940	10305	8954
Sertindole	—	2	0	0	0	0
Zotepine	—	5	1	21	5	0
Atypical antipsychotics:	<i>13674</i>	<i>21501</i>	<i>26248</i>	<i>31134</i>	<i>28950</i>	<i>27282</i>
All antipsychotics:	<i>62580</i>	<i>57917</i>	<i>60603</i>	<i>61886</i>	<i>59586</i>	<i>56444</i>

sions due to antipsychotic poisoning may not be linked to contemporaneous prescribing data, and patterns of community prescribing may need to be established for at least several years before stable patterns of poisoning can be evaluated. One possible explanation for this effect is that patients may have stockpiled drugs, especially because these may have been prescribed over a long duration before legislative changes were introduced. Therefore, patients might still have access to medications for a significant amount of time after the prescription has been terminated. After drug discontinuation, patients might gain access to a further supply by other means, for example direct purchase via the Internet. Unfortunately, we are unable to evaluate this possibility in our patient population because the prescribing data are not patient-linked.

Significantly higher numbers of patients were admitted to hospital after ingestion of typical rather than atypical antipsychotics. After accounting for differences in prescription numbers, typical agents represented a substantially higher proportion of patients admitted to hospital after antipsychotic overdoses than expected. If confirmed, this finding might suggest a lower risk of suicidal behaviour, or less toxicity after overdose in patients treated with atypical agents. This is reassuring, from a safety perspective, given that the use of atypical antipsychotics has recently become more prevalent. However, the design of the present study does not consider potentially important differences between patients who were treated with typical or atypical antipsychotics, for example disease severity, previous suicidal behaviour, and the extent of hos-

Table 2. Number of adult patients admitted to the Royal Infirmary of Edinburgh after suspected self-poisoning with typical or atypical antipsychotics during 2000-2006, shown for 1st April through 31st March.

	2000-1	2001-2	2002-3	2003-4	2004-5	2005-6
Benperidol	0	0	0	0	0	0
Chlorpromazine	48	113	115	81	60	60
Droperidol	0	0	0	0	0	0
Flupenthixol	0	0	0	4	0	0
Fluphenazine	0	1	0	0	0	0
Haloperidol	13	8	7	7	7	3
Loxapine	0	0	0	0	0	0
Methotrimeprazine	0	0	0	0	0	0
Oxypertine	0	0	0	0	0	0
Pericyazine	0	2	2	1	1	1
Perphenazine	0	1	0	0	0	0
Pimozide	0	0	1	1	0	0
Promazine	1	1	0	0	0	0
Sulpiride	10	10	4	13	3	2
Thioridazine	76	14	8	1	1	0
Trifluoperazine	1	6	3	4	4	0
Zuclopenthixol	1	3	1	0	2	1
Typical antipsychotics:	150	159	141	112	78	67
Amisulpiride	1	4	2	1	2	3
Aripiprazole	0	0	0	0	0	0
Clozapine	2	6	0	3	2	1
Olanzapine	12	9	10	18	21	22
Quetiapine	3	3	4	7	9	13
Risperidone	5	10	13	19	11	8
Sertindole	0	0	0	0	0	0
Zotepine	0	0	0	0	0	0
Atypical antipsychotics:	23	32	29	48	45	47
All antipsychotics:	173	191	170	160	123	114

Patterns of antipsychotic poisoning.

pital and community psychiatric involvement. Further studies would need to be conducted in order to more fully evaluate relative safety of typical and atypical agents.

A limitation of the study is that patterns of prescribing in our catchment area may not be generalis-

able to other regions. For example, the prevalence of atypical antipsychotic prescribing is lower in the United Kingdom than in a number of other countries, for example Canada, USA, and New Zealand (Trenton *et al.*, 2003; Rapoport *et al.*, 2005; Burns *et al.*, 2006; Hanssens *et al.*, 2006; Wheeler, 2006). A potential

Fig. 1. Patients admitted to hospital after typical and typical antipsychotic self-poisoning, shown as a proportion of all antipsychotic poisoning, between 2000 and 2006, and prevalent prescribing in Lothian region during the same period.

Fig. 2. Number of patients admitted to the Royal Infirmary of Edinburgh annually between 2000 and 2006 due to atypical and typical antipsychotic poisoning, expressed per 1000 corresponding prescriptions in Lothian region.

confounding factor is that our hospital relocated within Edinburgh in 2003. This resulted in different patterns of patient flow between the Emergency Department and the Toxicology Unit, so that a small reduction in the number of patients admitted to our Unit was observed. To minimise this effect, we examined the proportion of hospital admissions due to atypical and typical antipsychotics because this is less likely to have been influenced. Another potential confounding factors is the history of drug ingestion was based on patient self-reporting, reports from companions, and circumstantial evidence such as empty drug packaging. This is an inevitable limitation of studies involving a realistic clinical setting, where laboratory confirmation of ingested drugs is rarely required in everyday practice.

In summary, antipsychotic prescribing patterns have changed substantially over recent years. Community prescribing of atypical antipsychotics has increased, and atypical and typical agents are now prescribed in near equal proportions in Lothian region. Hospital admissions due to atypical antipsychotic poisoning have also increased, albeit that these patterns appear to lag behind changes in prescribing patterns by around 2.5 years. These data show that guidelines issued at national level, and restrictions on drug licensing are capable of influencing not only prescribing practices, but also have a measurable impact on hospital admissions due to poisoning.

ACKNOWLEDGMENT

We would like to express thanks to Ross Davies of the Scottish Poisons Information Bureau for help identifying data related to antipsychotic poisoning cases admitted to the Toxicology Unit.

REFERENCES

- Baca-Garcia, E., Diaz-Sastre, C., Saiz-Ruiz, J. and de Leon, J. (2002): How safe are psychiatric medications after a voluntary overdose? *Eur. Psychiatry*, **17**, 466-470.
- Bateman, D.N., Good, A.M., Afshari, R. and Kelly, C.A. (2003): Effects of licence change on prescribing and poisons enquiries for antipsychotic agents in England and Scotland. *Br. J. Clin. Pharmacol.*, **55**, 596-603.
- Buckley, N.A., Whyte, I.M. and Dawson, A.H. (1995): Cardiotoxicity more common in thioridazine overdose than with other neuroleptics. *J. Toxicol. Clin. Toxicol.*, **33**, 199-204.
- Burns, T., Christova, L., Cooper, S., Harrison, G., McKendrick, J., Laugharne, R., Obuaya, T., McCreadie, R., O'Brien, S., Perrington, S. and Stephenson, D. (2006) Maintenance antipsychotic medication patterns in outpatient schizophrenia patients: A naturalistic cohort study. *Acta Psychiatr. Scand.*, **113**, 126-134.

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- Griffiths, C. and Flanagan, R.J. (2005): Fatal poisoning with antipsychotic drugs, England and Wales 1993-2002. *J. Psychopharmacol.*, **19**, 667-674.
- Hanssens, L., De Hert, M., Wampers, M., Reginster, J.Y. and Peuskens, J. (2006): Pharmacological treatment of ambulatory schizophrenic patients in Belgium. *Clin. Pract. Epidemiol. Ment. Health*, **2**, 11.
- Harding, C.M., Brooks, G.W., Ashikaga, T., Strauss, J.S. and Breier, A. (1987): The Vermont longitudinal study of persons with severe mental illness, II: Long-term outcome of subjects who retrospectively met DSM-III criteria for schizophrenia. *Am. J. Psychiatry*, **144**, 727-735.
- Isbister, G.K., Murray, L., John, S., Hackett, L.P., Haider, T., O'Mullane, P., Gosselin, S. and Daly, F. (2006): Amisulpride deliberate self-poisoning causing severe cardiac toxicity including QT prolongation and torsades de pointes. *Med. J. Aust.*, **184**, 354-356.
- Lin, C.H., Chen, M.C., Wang, S.Y. and Lin, C.Y. (2004): Predictive factors for QTc prolongation in schizophrenic patients taking antipsychotics. *Formos Med. Assoc.*, **103**, 437-441.
- Medicines and Healthcare Products Regulatory Agency (MHRA) (2000): MHRA (Medicines) Restricts the Use of Thioridazine. MHRA Press Release 2000/0734. London.
- Mitchell, M. (2000): StatsDirect. *JAMA.*, 284, 1988.
- National Institute for Clinical Excellence (2002): Technology Appraisal Guidance No. 43. Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia. London: National Institute for Clinical Excellence.
- Rapoport, M., Mamdani, M., Shulman, K.I., Herrmann, N. and Rochon, P.A. (2005): Antipsychotic use in the elderly: Shifting trends and increasing costs. *Int. J. Geriatr. Psychiatry*, **20**, 749-753.
- Reilly, J.G., Ayis, S.A., Ferrier, I.N., Jones, S.J. and Thomas, S.H. (2000): QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet*, **355**, 1048-1052.
- Silva de Lima, M., de Jesus Mari, J., Breier, A., Maria Costa, A., Ponde de Sena, E. and Hotopf, M. (2005): Quality of life in schizophrenia: A multicenter, randomized, naturalistic, controlled trial comparing olanzapine to first-generation antipsychotics. *J. Clin. Psychiatry*, **66**, 831-838.
- Stollberger, C., Huber, J.O. and Finsterer, J. (2005): Antipsychotic drugs and QT prolongation. *Int. Clin. Psychopharmacol.*, **20**, 243-251.
- Trenton, A., Currier, G. and Zwemer, F. (2003): Fatalities associated with therapeutic use and overdose of atypical antipsychotics. *CNS Drugs*, **17**, 307-324.
- Wheeler, A. (2006): Atypical antipsychotic use for adult outpatients in New Zealand's Auckland and Northland regions. *N. Z. Med. J.*, **119**, 2055.
- Witchel, H.J. and Hancox, J.C. (2000): Familial and acquired long QT syndrome and the cardiac rapid delayed rectifier potassium current. *Clin. Exp. Pharmacol. Physiol.*, **27**, 753-766.