ORIGINAL RESEARCH ARTICLE

Drug Safety 2009; 32 (5): 441-447
0114-5916/09/0005-0441/$49.95/0

Effect of Date of Drug Marketing on Disproportionality Measures in Pharmacovigilance

The Example of Suicide with SSRIs Using Data From the UK MHRA

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Abstract

Background: Warnings concerning an increased risk of suicide in patients treated with selective serotonin reuptake inhibitors (SSRIs) re-emerged in early 2003, culminating in the broadcast of a television programme in the UK. In the following months, cumulated proportional reporting ratios showed that the most recently marketed drug, escitalopram, had a much higher proportion of reports of suicide to other adverse drug reactions (ADRs) than the other drugs in the class.

Objective: To study the reporting patterns over time concerning suicide with the six SSRIs marketed in the UK as of March 2003 and their potential effect on disproportionality signal detection.

Methods: Monthly cumulated numbers of reports were obtained from the UK Medicines and Healthcare products Regulatory Agency (MHRA), from the time of the first marketing of the drugs concerned and monthly for the 2 months prior to and the 9 months following the broadcast of the television programme (broadcast date: 11 May 2003), and the monthly ratio of suicide to other reports was computed for each SSRI individually and for all SSRIs combined.

Results: Of the six SSRIs studied, five (citalopram, paroxetine, fluoxetine, sertraline and venlafaxine) had been marketed for several years and escitalopram for only a few months. At the end of the analysis period, 1.42% (4/281) of all ADR reports for escitalopram were of suicide versus 0.58% for the other five drugs combined (146/25 197). For all SSRIs combined, suicide represented 0.5% (123/24 315) of reports before the broadcast of the television programme, and increased to 2.3% (27/1163) following the programme. For escitalopram, suicide represented 1.1% (1/89) of all ADR reports before the television programme and 1.6% (3/192) afterwards. For the five other drugs

combined, suicide represented 0.5% (122/24 226) of ADR reports before the television programme and 2.5% (24/971) afterwards (varying from 1.4% to 4.7% for the various drugs). The post-programme events represented 68% of all reports and 75% of suicides for escitalopram, whereas for older drugs they represented 3.6% of reports and 13% of suicides.

Conclusion: For older drugs, the events reported during the high-reporting post-television programme period were diluted by years of low reporting. For escitalopram, although the television programme had little absolute impact on the number of reports, because the drug had been on the market for such a short period of time, a large relative effect was observed. Differential effects related to time on market on cumulated reporting of adverse drug reactions should be taken into account when analysing spontaneous reporting databases with automated signal generation methods after an alert has changed the spontaneous reporting patterns. Proper use of measures of disproportionality requires thorough knowledge of potential biases and careful analysis of reporting patterns. We found no obvious differences between SSRIs once these were taken into account.

1. Background

Regulatory decisions concerning drug safety issues often derive from signals detected from spontaneous reports of adverse drug reactions (ADRs).[1-3] To improve the detection of signals in increasingly larger databases, automated measures of disproportionality are proposed and/or used.[4-6] For instance, the proportional reporting ratio (PRR),[7] or the reporting odds ratio[5,8] are intended to identify potential alerts in spontaneous reporting databases by comparing the ratio of reporting of one event relative to other reports with the same drug, to that with other drugs. All methods follow essentially the same scheme, with more or less sophistication.[4] Classically, the comparison group comprises all other reports in the database, or reports related to other drugs of the same pharmacological or therapeutic class. The disproportionality measures usually consider all events to the date of analysis.[8] A signal is generated when a threshold value is reached, defined for each particular automated method.[4,6,9-11]

However, all these approaches rely on the spontaneous reporting of ADRs by healthcare professionals. The factors influencing the spontaneous reporting of ADRs are quite elusive,[12-17] and are related to the severity of the reaction, the physician's knowledge of the reaction, and to a series of external factors including time from marketing[18,19] or market size,[20] to such an extent that very similar chemical products may have very different risk profiles, relating to different marketing strategies.[21-23] External events can also influence reporting, including notoriety bias, in which a case has a greater chance of being reported if the subject is exposed to a factor known, thought or likely to cause the event of interest.[20] Notoriety bias can also affect drugs other than those directly involved in alerts.[24]

These biases could lead to spurious estimates of disproportionality measures and thus to the generation of false positive signals if they affect the drug of interest and those of the comparison group differently, whether the database as a whole or drugs from the same pharmacological class are involved. Moreover, even if all the studied drugs are similarly affected by notoriety at a given time, false positive signals could be generated if this notoriety effect on reporting becomes differentially diluted among prior reports for older drugs compared with more recently marketed drugs.

The use of the selective serotonin reuptake inhibitors (SSRIs) to treat depression has been associated with suicidal ideation and suicides for a number of years. In fact, suicide with antidepressants has been reported since the very earliest use of these drugs.[25,26] Nevertheless, there is still disagreement as to whether there is an association with the drugs themselves and/or with the underlying disease, as well as whether a difference exists between drugs from the same class. On 11 May 2003, the British Broadcasting Corporation (BBC) broadcast a television programme about the effects of one of the SSRIs, paroxetine, and the risk of suicide.[27] This was a follow-up to a previous programme[28] that had resulted in a large number of letters and testimonials. The new programme resulted in a large number of reports of suicide, and a month later a warning about the risk of suicide with paroxetine was released by the Medicines Control Agency (MCA; now the Medicines and Healthcare products Regulatory Agency [MHRA]).[29]

As this particular risk was suspected in users of SSRIs, we performed regular monitoring of the reporting of suicides and repeated measurement of the proportional reporting of suicides compared with other ADRs. This monitoring indicated that escitalopram, not paroxetine, appeared to be associated with an approximately 2.5-fold higher risk of suicide compared with other drugs of the same class. This might seem to warrant consideration of further regulatory scrutiny, including action such as, at least, a warning. Since there was no particular reason to suspect this drug of being associated with higher risk than the others in the class, our aim was to identify the factors involved in this apparent difference in safety by examining the reporting patterns over time and their potential effect on disproportionality measures.

2. Methods

Reports of suspected ADRs are collected in the UK by the MHRA via the Yellow Card Scheme. Since January 2005, both healthcare professionals and patients can report ADRs. The reported information is entered into the Adverse Drug Reaction Online Information Tracking (ADROIT) database. Suspected ADRs are classified using Medical Dictionary for Regulatory Activities (MedDRA) terms and these terms are used in the database.

We obtained from the MHRA, for the six SSRIs marketed in the UK as of March 2003 (citalopram, paroxetine, fluoxetine, sertraline, venlafaxine and escitalopram), the cumulated number of reports of all ADRs and suicides that were entered in the ADROIT database from marketing until March 2003, and the monthly number of reports for the 10 following months (April 2003 to January 2004). It was not possible at the time to obtain cumulated report statistics per month before March 2003. Thus, data for March 2003 included all previous reports over the market lifetime of these drugs in the UK. From this, the monthly numbers of reports were derived and compared over 11 months, from March 2003 to January 2004 inclusive. That is, 2 months before and 9 months after the airing of the television programme warning of the risk of suicide in SSRI users. Reporting ratios were calculated as the ratio of reported suicides to all other reports for each drug. They were computed using cumulated data to show how these would appear on systematic automated computation, and for the periods before and after the television programme.

Reporting ratios are expressed as percentages. Disproportionalities of reporting were studied by using the PRR and the PRR 95% confidence intervals, which were estimated according to the standard methods.[7,8] All analyses were performed using Microsoft Office Excel software (Microsoft, Redmond, WA, USA).

3. Results

Table I shows each SSRI studied and their dates of first marketing in the UK. Of the six drugs in the class, five had been marketed for several years and one, escitalopram, was first marketed only 9 months before the alert.

Table II shows the monthly cumulated reports and suicide reporting ratios. The cumulated reporting ratios do not vary much over time

Table I. Selective serotonin reuptake inhibitors considered in the analysis and date of first marketing authorization (MA) in the UK

Drug	Date of first MA in the UK
Escitalopram	10 Jun 2002
Citalopram	17 Mar 1995
Paroxetine	28 Oct 1991
Fluoxetine	25 Nov 1988
Sertraline	30 Sep 1997
Venlafaxine	5 Aug 1997

(figure 1) except for escitalopram, the most recently marketed. The PRR of escitalopram versus the other drugs together was 2.46 (95% CI 0.90, 6.68), which could raise concerns.

Monthly reporting ratios of suicides, however, show a clear increase that preceded the broadcast of the television programme. This may be related to the earlier programme broadcast, and the increase subsequently returned to near baseline (figure 2). Comparison of pre- to post-programme reporting ratios for individual drugs (figure 3) shows that the drug with the highest post-programme reporting was paroxetine, which was the main drug that the television programme featured. However, fluoxetine, which was considered and reported as being 'safe', was minimally affected by the changes in reporting patterns. Before the broadcasting of the television programme, there was little difference between drugs in the rates of reporting of suicides.

Of all the reports of suicide with escitalopram, 75% were reported after the broadcast

Table II. Monthly cumulated number of all case reports, and suicides with six selective serotonin reuptake inhibitors in the Medicines and Healthcare products Regulatory Agency ADROIT (Adverse Drug Reaction Online Information Tracking) database from March 2003 to January 2004

Drug	Cumulated number of reports[a]										
	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan
Escitalopram											
Reports	89	93	113	130	141	159	168	224	245	260	281
Suicides	1	1	2	3	3	2[b]	3	3	4	4	4
Ratio (%)	1.12	1.08	1.77	2.31	2.13	1.26	1.79	1.34	1.63	1.54	1.42
Citalopram											
Reports	1684	1696	1717	1731	1756	1771	1772	1810	1832	1857	1875
Suicides	6	7	9	9	9	9	9	9	9	9	9
Ratio (%)	0.36	0.41	0.52	0.52	0.51	0.51	0.51	0.50	0.49	0.48	0.48
Paroxetine											
Reports	8707	8720	8739	8781	8831	8854	8866	8883	8906	8927	8942
Suicides	28	29	30	34	37	38	38	39	39	39	39
Ratio (%)	0.32	0.33	0.34	0.39	0.42	0.43	0.43	0.44	0.44	0.44	0.44
Fluoxetine											
Reports	7943	7956	7966	7978	7989	8004	8005	8038	8058	8067	8090
Suicides	61	62	62	62	62	62	62	62	62	63	63
Ratio (%)	0.77	0.78	0.78	0.78	0.78	0.77	0.77	0.77	0.77	0.78	0.78
Sertraline											
Reports	2406	2413	2421	2428	2438	2452	2452	2462	2469	2480	2491
Suicides	14	15	15	15	15	15	15	15	16	16	16
Ratio (%)	0.58	0.62	0.62	0.62	0.62	0.61	0.61	0.61	0.65	0.65	0.64
Venlafaxine											
Reports	3486	3515	3541	3570	3612	3642	3649	3712	3746	3768	3799
Suicides	13	14	14	17	17	18	18	18	18	18	19
Ratio (%)	0.37	0.40	0.40	0.48	0.47	0.49	0.49	0.48	0.48	0.48	0.50

a Data for March 2003 included all previous reports over the market lifetime of these drugs in the UK.

b In one report, the patient did not die as a result of the attempted suicide and was thus reclassified between July and August.

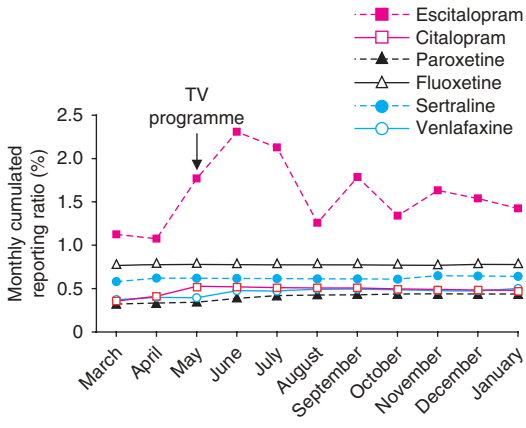

Fig. 1. Monthly cumulated reporting ratio of suicide to all other reports of adverse drug reactions reported to the Medicines and Healthcare products Regulatory Agency, for six selective serotonin reuptake inhibitors, from March 2003 to January 2004.

compared with 1.6% for fluoxetine and 26.3% for venlafaxine. PRRs for escitalopram versus the other five SSRIs were 2.06 (95% CI 0.28, 14.87) before the programme, 0.75 (0.22, 2.57) after and 2.46 (0.90, 6.68) overall. This overall rate does not fall between the two other rates, because of the imbalance of reporting of suicides and other ADRs before and after the concern regarding escitalopram versus the five other drugs combined.

Of the six SSRIs, five had been marketed for several years and escitalopram for only a few months. At the end of the analysis period, 1.42% (4/281) of all ADR reports for escitalopram were of suicide versus 0.58% for the other five drugs combined (146/25 197). For all SSRIs combined, suicide represented 0.5% (123/24 315) of reports before the broadcast of the television programme, and increased to 2.3% (27/1163) following the programme. For escitalopram, suicide represented 1.1% (1/89) of all ADR reports before the television programme and 1.6% (3/192) afterwards. For the five other drugs combined, suicide represented 0.5% (122/24 226) of ADR reports before the television programme and 2.5% (24/971) afterwards (varying from 1.4% to 4.7% for the various drugs). The post-programme events represented 68% of all reports and 75% of suicides for escitalopram, whereas for older drugs they represented 3.6% of reports and 13% of suicides.

4. Discussion

Escitalopram had only been marketed for a few months when the television broadcast and subsequent MHRA alert for paroxetine[30] occurred, whereas the others had been marketed for much longer. For this new drug, the post-television broadcast events represented 68% of all reports and 75% of suicides, whereas for older drugs the post-programme period represents, at most, 10% of all reports, and 1.6–26.3% of reports of suicides.

Only escitalopram, the recently marketed drug, appeared associated with an almost 2.5-fold higher overall relative rate of reporting of the serious event. This could be due to under-reporting of other ADRs with this newly known drug that were known to be class effects. However, another explanation could be provided by the fact that the launch of escitalopram was at a similar time to the high reporting period, whereas for the other drugs, the events reported during the high reporting period were preceded by years of low reporting leading to a diluting effect. The erratically higher reporting of suicides with escitalopram compared with other drugs before the television programme may be related to the Weber effect[18] of recent marketing, or to the earlier television programme and a previous

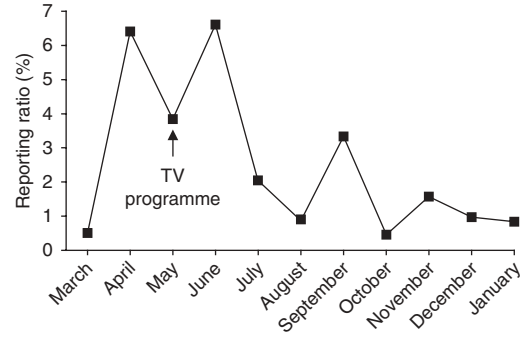

Fig. 2. Monthly reporting ratio of suicide relative to all case reports, for the six selective serotonin reuptake inhibitors combined, in the Medicines and Healthcare products Regulatory Agency Adverse Drug Reactions Online Information Tracking (ADROIT) database.

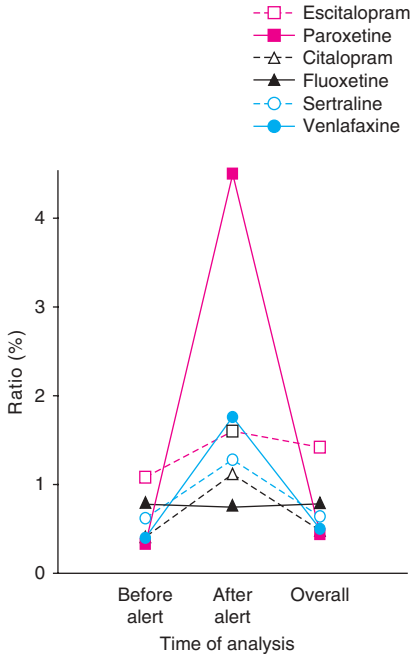

Fig. 3. Ratio of reports of suicide among all reports with each selective serotonin reuptake inhibitor in the Medicines and Healthcare products Regulatory Agency Adverse Drug Reactions Online Information Tracking (ADROIT) database, before and after the airing of the television show.

dilution episode. Because the usual mode of calculation takes into account all reports for a drug without consideration of the duration of marketing, this situation led to the dilution of the high reporting period for older drugs into the years of low reporting. This dilution completely masked the object of the television programme, i.e. the clearly higher reporting of suicides with paroxetine, which was 2- to 3-fold higher than for the other SSRIs. For escitalopram, although the television programme had little absolute impact on the number of reports, because the drug had been on the market for such a short period of time, a large relative effect was observed. Changes in reporting ratios over time must be carefully considered, especially when there are intercurrent reporting stimulants.[24] The use of PRRs and other measures of disproportionality requires thorough knowledge of potential biases and careful analysis of reporting patterns before any conclusion can be drawn. Automated alert measures should be tempered by the careful analysis of data. It seems difficult to draw further conclusions from reported data once an alert has been identified and a warning publicized other than the analysis of the effects of warnings on reporting attitudes or patterns.

If an alert is identified and publicized, the changes in reporting patterns and attitudes are such that measures of disproportionality become extremely difficult to use.[20] This is clearly what happened in the situation we describe here, which illustrates again that disproportionality measures are essential signal-generating instruments that should only be used in a stable system. This dilution effect could be added to the list of biases and errors that have to be scrutinized when analysing spontaneous reporting data, disproportionality measures and related safety signals.[29]

5. Conclusions

The differential between new and older drugs that can be observed by using disproportional methods for signal generation might in some cases be explained by the relative importance of reports notified during a high reporting period among all reports for a given drug, leading to a dilution effect. Proper use of measures of disproportionality requires thorough knowledge of potential biases and careful analysis of reporting patterns.

Acknowledgement

This study emerged from discussions with persons within the Lundbeck Laboratory concerning a possible signal involving their drug, escitalopram. Lundbeck provided the MHRA data, but the design and analysis of the present work was done in our department completely independently from Lundbeck. There was no funding for the work. The authors have no conflicts of interest to declare.

We would like to thank all MHRA and MHRA collaborators for the accuracy and the availability of the data.

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