Psychiatry Research ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Association between haemorrhages and treatment with selective and non-selective serotonergic antidepressants: Possible implications of quantitative signal detection

Maximilian Gahr [a,*], René Zeiss [a], Dirk Lang [b], Bernhard J. Connemann [a], Christoph Hiemke [c], Rainer Muche [d], Roland W. Freudenmann [a], Carlos Schönfeldt-Lecuona [a]

[a] University of Ulm, Department of Psychiatry and Psychotherapy III, Leimgrubenweg 12-14, 89075 Ulm, Germany
[b] University of Ulm, Department of Psychosomatic Medicine and Psychotherapy, Albert-Einstein-Allee 23, 89081 Ulm, Germany
[c] University Medical Center of Mainz, Department of Psychiatry and Psychotherapy, Untere Zahlbacherstr. 8, 55131 Mainz, Germany
[d] University of Ulm, Institute of Epidemiology and Medical Biometry, Medical Faculty, Schwabstr. 13, 89075 Ulm, Germany

ARTICLE INFO

Article history:
Received 19 February 2015
Received in revised form
16 June 2015
Accepted 12 July 2015

Keywords:
Haemorrhages
Depression
Pharmacovigilance
Reporting odds ratio
Signal detection

ABSTRACT

Inhibition of serotonin uptake in platelets seems to be the crucial mechanism underlying SSRI-associated haemorrhages. This effect is also present in antidepressants featuring non-selective serotonin reuptake inhibition (non-SSRI). Impact of selectivity of serotonin reuptake and/or affinity to the serotonin reuptake transporter on the bleeding risk have not yet been studied sufficiently. We retrieved country- and SSRI-/non-SSRI-specific data from the Uppsala Monitoring Centre and used a case/non-case approach to calculate substance-specific reporting odds ratios (ROR) to evaluate the statistical association of treatment with SSRI/non-SSRI and haemorrhages. Country-specific analysis revealed no clear trends towards an increased risk of bleeding related to particular agents of group SSRI/non-SSRI (sporadically ROR > 1 for citalopram, duloxetine, escitalopram, fluvoxamine, paroxetine, sertraline, St. John's wort). There was a clear trend in the total dataset towards a "reduced protective effect" (suggested by ROR < 1) on the development of haemorrhages with agents featuring comparatively high affinity to the 5-HTT and/or selective serotonin reuptake inhibition (as with escitalopram, citalopram, duloxetine or venlafaxine) in comparison to agents with lower affinity or non-selective serotonin reuptake inhibition (as with mirtazapine or doxepin). Comparison of group-specific aggregated data (SSRI vs. non-SSRI) revealed significant differences regarding the "protective effect" on the development of haemorrhages between groups SSRI vs. non-SSRI in favour of non-SSRI in nearly all countries as well as in the total dataset. Our findings provide preliminary evidence that agents with increased affinity to the 5-HTT and/or selective serotonin reuptake inhibition may be associated with an increased risk of bleeding.

1. Introduction

Bleeding events were increasingly reported as possible adverse drug reactions (ADR) of selective serotonin reuptake inhibitors (SSRI) during the past twenty years (Aranth and Lindberg, 1992; Calhoun and Calhoun, 1996). Until now numerous studies have assessed the relation between treatment with SSRI and development of haemorrhages. According to different objectives and study designs findings of these studies were partly heterogeneous (for review see: Andrade et al., 2010). Yet, there is currently convincing evidence suggesting that patients treated with SSRI feature an increased risk for the development of bleeding events (Andrade et al., 2010).

Several mechanisms underlying SSRI-associated abnormal bleedings are currently discussed (Andrade et al., 2010). The crucial mechanism seems to be SSRI-induced inhibition of serotonin uptake in platelets; this results in decrease of serotonin release from platelets in case of vascular injury with the consequence of reduced serotonin-triggered platelet aggregation and vasoconstriction (prolongation of bleeding time and reduced platelet aggregability and activity) (Serebruany, 2006; Halperin and Reber, 2007; Andrade et al., 2010). Considering pharmacologic inhibition of serotonin uptake in platelets as the allegedly most important mechanism in SSRI-associated haemorrhages (Andrade et al., 2010), not only SSRIs but also antidepressive agents with non-selective serotonin reuptake

* Correspondence to: University Hospital of Ulm, Department of Psychiatry & Psychotherapy III, Leimgrubenweg 12-14, 89075 Ulm, Germany. Fax: +49 731 50061502.
E-mail address: maximilian.gahr@uni-ulm.de (M. Gahr).

http://dx.doi.org/10.1016/j.psychres.2015.07.024
0165-1781/

inhibition (non-SSRI) may have an impact on haemostasis and thus may increase the risk of haemorrhages related to antidepressive psychopharmacotherapy (Andrade et al., 2010).

Although several hypotheses that fit to SSRI appear plausible also in the context of non-SSRI (such as amitriptyline, clomipramine, trazodone) (Andrade et al., 2010), there is a lack of systematic approaches towards the risk of bleeding related to non-SSRI. Currently, the question, whether treatment with non-SSRI is also associated with an increased risk of bleeding cannot be answered sufficiently.

In this regard we have recently performed a data mining approach within two pharmacovigilance databases (WHO-database and BfArM/AkdÄ-database in Germany) in order to detect safety signals concerning haemorrhages related to SSRI vs. non-SSRI (Gahr et al., 2015). Surprisingly, we could only detect signals for hypericum and the positive control agents (acetylsalicylic acid [ASS] and diclofenac), whereas none of the agents of group SSRI or non-SSRI was statistically associated with haemorrhages.

In the present paper we applied the same data mining approach to country-specific datasets (important pharmaceutical markets) of the Uppsala Monitoring Centre (VigiBase™) of the World Health Organisation (WHO). We retrieved numbers of spontaneous reports of ADR, and calculated and compared reporting odds ratios (ROR) of SSRIs and non-SSRI in order to assess the strength of the association between (selective vs. non-selective) antidepressive pharmacotherapy and bleeding events. Objectives of the present study were to

i. Analyze, whether safety signals in regard of haemorrhages can be detected for agents of group non-SSRI (and/or SSRI) using country-specific datasets, and
ii. Identify possible substance- and/or group-specific (SSRI vs. non-SSRI) quantitative effects regarding the statistical association with haemorrhages.

2. Methods

2.1. Database

The WHO has established the International Drug Monitoring Programme in 1968, currently representing the largest international pharmacovigilance project. As of December 2014, national pharmacovigilance centres of 120 countries participate and, in addition, pharmacovigilance centres from 28 countries are associated members (see http://www.who-umc.org). These national pharmacovigilance centres (primarily spontaneous reporting systems which are passive systems comprised of reports of suspected ADR) communicate ADR data to the Uppsala Monitoring Centre (UMC), Sweden, where ADR data are processed, evaluated and finally recorded in a particular database (VigiBase™). VigiBase™ is currently the largest and most comprehensive pharmacovigilance database in the world (see http://ww.umc-products.com). The UMC is an independent foundation and a centre for international service and scientific research (see http://www.who-umc.org) and is the name of the WHO Collaborating Centre for the International Drug Monitoring Programme. ADR reports submitted to the UMC originate from different sources such as regulatory and voluntary sources (health professionals, patients) as well as pharmaceutical companies, depending on the recording strategy of the reporting national pharmacovigilance centre. The ADR data recorded in VigiBase™ are thus heterogeneous in regard of their origin. In addition, causality assessment (that is the evaluation of the likelihood that the pharmaceutical product caused the reported ADR) is not performed by every reporting national pharmacovigilance database and therefore the ADR data of VigiBase™ are heterogeneous also in this regard. Finally, it is important to consider that the ADR data and their implications do not represent the opinion of the WHO. Recording of ADR data at the UMC has been performed since 1968.

2.2. Database query and search strategy

The above referenced database was accessed in May 2014 (index date) by preceding online applications at the WHO. Data were searched and collected using the standardised Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ). The MedDRA is a clinically validated international medical terminology thesaurus/dictionary used by regulatory authorities and exhibits a hierarchical structure of its included terms (~SMQs). It was developed in the 1990s by the International Conference of Technical Requirements for Registration of Pharmaceuticals for Humans Use (ICH) in order to provide a highly specific standardised medical terminology to allow sharing of regulatory information internationally for medical products used by humans (see http://www.meddra.org).

The SMQ-term applied for the current search was “Haemorrhages” (including all kinds of haemorrhages). Data retrieved from VigiBase™ database covered the period 1968–2014 (May 2014). Data were retrieved for the following substances: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline (group SSRI), and amitriptyline, bupropion, clomipramine, doxepin, duloxetine, hypericum/St. John's wort, imipramine, maprotiline, mirtazapine, nortriptyline, trazodone, venlafaxine (group non-SSRI). As positive controls data for diclofenac and ASS were retrieved. The absolute numbers of all ADR-reports (no SMQ-restriction) and ADR-reports related to SMQ “Haemorrhages” were obtained for each substance and in total (for all substances) as recorded at the index date. Causality assessment of the evaluated ADR reports was not performed, meaning that all levels of causality were included. Statistical analysis was performed country-specific for France, Germany, Italy, Spain, United Kingdom (UK), USA, Canada and Australia; these countries were selected due to the greatest numbers of ADR-reports within the WHO-database; though Thailand and Republic of Korea were within the ranking of the ten countries with the most ADR-reports, they were not included due to very low numbers of or absent ADR-reports related to the substances of interest.

As all ADR-reports recorded in the assessed database are reviewed by qualified personnel before definite recording the individual case narratives were not evaluated separately for plausibility.

2.3. Statistical analysis

Within the framework of pharmacovigilance the detection of signals that indicate a possible causal relationship between an adverse event and the use of a drug is of high importance for the safety assessment of drugs in the post-marketing setting (Gould, 2003; Ooba and Kubota, 2010). Data mining methods applied to databases of spontaneous reports of ADR are frequently used in quantitative signal detection (Bate and Evans, 2009). A highly disproportionate representation of the combination of a drug and an adverse event may indicate an important safety signal based upon a difference from the background frequency (Finney, 1971; van Puijenbroek et al., 2002). In our analysis we used a case/non-case approach and calculated the reporting odds ratios (ROR) as a measure for disproportionality (van Puijenbroek et al., 2002; Rothman et al., 2004) in order to evaluate the strength of the relation between treatment with a pharmacologic agent (SSRI, non-SSRI or ASS/diclofenac) and the occurrence of the event

Please cite this article as: Gahr, M., et al., Association between haemorrhages and treatment with selective and non-selective serotonergic antidepressants: Possible implications of quantitative signal detection. Psychiatry Research (2015), http://dx.doi.org/10.1016/j.psychres.2015.07.024