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Associations Between Venous Thromboembolism and Antipsychotics

A Study of the WHO Database of Adverse Drug Reactions

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Abstract

Background: Concern has been raised about the occurrence of venous thromboembolism (VTE) during treatment with antipsychotics. However, to date, clozapine is the only antipsychotic agent for which recurring evidence supports an association with VTE. Therefore, the aim of this study was to investigate the association between antipsychotic drugs, including clozapine and VTE.

Study design and methods: Data mining of the WHO database of adverse drug reactions (ADRs) using Bayesian statistics is in routine use for early alerting to possible ADRs. An information component measure was used to investigate the association between antipsychotic drugs and VTE reactions in the database.

Results: A total of 754 suspected cases of VTE related to treatment with antipsychotics had been reported. After excluding cases related to clozapine, 379 cases remained. A robust association was found for the second-generation antipsychotics group but not for the high-potency, first-generation antipsychotics group or the low-potency first-generation antipsychotics group. The individual compounds with statistically significant associations were olanzapine, sertindole and zuclopenthixol. A time-dependent analysis showed that the associations were positive for these drugs in 2002, 2001 and 2003, respectively. Case analyses were undertaken after excluding ten suspected duplicate reports. Of the remaining 369 cases, 91 cases were associated with olanzapine, 9 with zuclopenthixol and 6 with sertindole.

Conclusions: VTE was more often reported with the antipsychotic drugs olanzapine, sertindole and zuclopenthixol than with other drugs in the WHO database. Further studies are warranted to explain this disproportional reporting. Since the associations found were based on incomplete clinical data, the results should be considered as preliminary and interpreted cautiously.

Background

It has been increasingly recognized that antipsychotic agents may cause a number of metabolic effects such as obesity, dyslipidemia, diabetes mellitus and hyperleptinemia.[1,2] Antipsychotic drugs have also been reported to be associated with venous thromboembolism (VTE). In a number of studies

published between 1953 and 1984, several suspected cases of VTE were reported with first-generation antipsychotics.[3] The possibility of an association between treatment with antipsychotic drugs and VTE has received renewed attention during recent years.[3-12] One of these studies, a case-control study published in 2000, found a significantly increased risk of venous thrombosis during treatment with first-generation antipsychotics.[6] However, it was not possible to reliably evaluate the association between second-generation antipsychotics and thrombosis as only a limited number of patients taking these drugs were included in the study. In a recently published retrospective cohort study among nursing home residents, the rate of hospitalization for VTE was significantly increased for users of the second-generation antipsychotic drugs (risperidone, olanzapine, clozapine and quetiapine) but not for users of first-generation antipsychotics.[10] While second-generation antipsychotic drugs are often used in patients with dementia and dementia is associated with immobility, a risk factor for VTE, confounding by indication is possible and may explain the associations found. In another retrospective cohort study of patients aged ≥65 years, no significant association between the use of antipsychotics and VTE was found.[12] With the exception of clozapine, there is, to date, no evidence of a link between second-generation antipsychotics and VTE in patients <65 years of age except for a few published case reports.[13-15] Since available data on the association are very sparse, to some extent inconsistent and have several limitations, further studies investigating the association are warranted. Clozapine is, at present, the only antipsychotic agent for which recurring pharmacoepidemiological evidence of VTE exists.

Data mining of a large database of spontaneously reported suspected adverse reactions may be used to discover possible new drug safety signals.[16-18] As an important element of the WHO programme for international drug monitoring, national pharmacovigilance centres forward spontaneously reported cases of suspected ADRs to a central database maintained by the Uppsala Monitoring Centre (UMC) in Sweden.[19] To screen this database, a measure of disproportionality, the 'information component' (IC), is routinely used. The method originates from Bayesian statistics implemented in a neural network architecture and is referred to as the Bayesian Confidence Propagation Neural Network (BCPNN).[16,20] Using this approach, we investigated the occurrence of VTE related to antipsychotic drugs and examined possible predisposing factors.

Study Design and Methods

A database of spontaneously reported cases of suspected ADRs from 79 countries (at the time of the study) is maintained by the UMC. The case reports are processed and accumulated in the database, in which over 3.6 million case records at the time of the study were included. This database offers a unique resource of global drug safety information.[18] Even though the reports in the database are not homogeneous with respect to origin or the probability that the drug caused the adverse reaction, they have a confirmed use in the early detection of ADR signals. A signal is defined by the WHO as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously."[21]

The reports in the database contain information about the patient, the medication, the suspected ADRs and administrative data (type of report and source). The minimum information required for approval of a report is the reporting country and identification number provided by the National Authorities of each country, the ADR, and the name of the medication. The WHO Adverse Reaction Terminology (WHO-ART) is used for all ADRs. This categorization is hierarchical and includes medical terms clustered into body-system organ classes. Drugs can be listed as being suspected of having caused the reaction, as interacting with another prescribed drug or as concomitant medication not related to the ADR. Drugs are coded according to the WHO Drug Dictionary as maintained by the WHO Collaborating Centre for International Drug Monitoring. Drugs are grouped according to the WHO Collaborating Centre for Drug Statistics Methodology's international Anatomical Therapeutic Chemical (ATC) classification.[22]

Suspected ADR reports are entered consecutively into the database, and every 3 months a statistical analysis of the old and new reports is carried out at

the UMC using the BCPNN method.[15-18] This analysis provides a statistical indicator, the IC, which is used to filter out combinations of particular drugs and suspected ADRs that are present in the database more frequently than would be expected on the basis of chance alone. An IC value can be calculated for a specific drug-ADR combination. The IC is a logarithmic measure of association and is based on the number of case reports with a particular drug x (Cx), the number of case reports with a particular adverse reaction (Cy), the number of reports with the specific drug-ADR combination xy (Cxy) and the total number of reports (C). The higher the Cx, Cy and Cxy values are, the narrower becomes the credibility interval. The IC value can be viewed as the strength of dependency between a drug and an adverse event relative to a background of all other adverse event spontaneous reports. The credibility interval of the IC value provides a measure of the robustness of the value. An association between the drug and the reaction is considered statistically significant if the lower bound of the 95% credibility interval of the IC (IC_{025}) is greater than zero. A subset of associations upon clinical review are considered signals. The BCPNN method has been described in detail previously. [16-18,20,23] The method has been thoroughly tested and evaluated[18,24,25] and is effective in identifying early signals of possible ADRs, as evident by the publication of important signals detected using the method.[26,27] Because of the incomplete nature of the dataset, the method is used for hypothesis generation rather than for hypothesis testing.

In the present study, the BCPNN method was used with the WHO database to investigate whether there are more reports on VTE during treatment with antipsychotic drugs than would be expected on the basis of chance alone based on general reporting in this database. Additional analysis was performed to identify possible risk factors. For this analysis, the following antipsychotic drugs belonging to the ATC classification group N05 were studied: the low-potency, first-generation antipsychotics chlorpromazine, cyamemazine, melperone, levomepromazine, perazine and thioridazine; the high-potency, first-generation antipsychotics benperidol, bromperidol, clopenthixol, fluphenazine, flupenthixol, haloperidol, perphenazine, pimozide, tiotixene, trifluperidol, trifluoperazine and zuclopenthixol; and the second-generation antipsychotics amisulpride, aripiprazole, clozapine, olanzapine, remoxipride, risperidone, sertindole, sultopride, quetiapine, ziprasidone and zotepine. We included clozapine in the analyses as a positive control since recurring, albeit preliminary, evidence supports an association with VTE. The IC was calculated for the three antipsychotic groups and for each particular compound separately. Moreover, sex- and age-specific ICs were also calculated. As the risk for VTE in general is clearly increased in individuals ≥55 years of age,[28] study patients were divided into two age groups; <55 and ≥55 years of age.

As a sensitivity analysis, two VTE definitions were used: a specific definition (VTE1), where all cases reported as VTE could reasonably be expected to be VTE; and a wider definition (VTE2), where the diagnoses are less specific and might include non-VTE reactions as well. VTE1 was defined as the presence of at least one of the following WHO-ART terms on the report: 'embolism pulmonary', 'venous thrombosis', 'phlebitis deep', 'thrombophlebitis leg deep', 'thrombophlebitis deep', 'thrombophlebitis multiple deep', 'thrombophlebitis pelvic vein', 'pelvic venous thrombosis', 'thrombosis vena cava inferior', 'thrombophlebitis vena cava' and 'thrombophlebitis arm deep'. VTE2 was defined as the presence of at least one of the terms above and/or at least one of the following WHO-ART terms: 'thrombophlebitis', 'plebothrombosis', 'thrombophlebitis multiple', 'thrombosis venous arms', 'postphlebotic syndrome' and 'post-thrombotic syndrome'. All ADR reports were included in the IC analyses since duplicate reports will occur throughout the database and exclusion of duplicate reports solely from the numerator in the IC calculation would artificially deflate the IC estimates. However, possible duplicate reports were identified and omitted from the analysis of the specific cases.

Results

VTE, as defined by using the specific definition (VTE1), accounted for approximately 0.5% (16 350) of the almost 3.2 million reports in the WHO database at the time of the study. By November 2004, 754 cases of VTE during treatment with antipsychotics were identified in the database and included in the IC analyses. Of these, 375 concerned

clozapine and 379 concerned other antipsychotic drugs. After scrutinizing these reports, 20 suspected duplicate reports were found. These included ten possible duplicate reports for clozapine, eight for olanzapine, one for zuclopenthixol and one for perazine. All these were marked as duplicate reports in the database. The remaining 734 patients were included in the case analysis.

Of all VTE reports, most concerned second-generation antipsychotics (table I) and the second-generation antipsychotics group had a positive IC_{025}. In contrast, the corresponding value was negative for both the high-potency antipsychotics group and for the low-potency, first-generation antipsychotics group. Of the individual antipsychotics, olanzapine had the highest IC_{025} values in addition to the positive control clozapine. In addition, sertindole and zuclopenthixol had positive IC_{025} values; however, these associations were weaker, based on few cases (table I) and observed later (figure 1). In addition, perazine had an IC_{025} value of 0.0 (table I). When using the less specific definition VTE2, the IC values for the associations between VTE2 and clozapine, olanzapine, sertindole and the second-generation antipsychotics group were slightly lower than for VTE1 but, with the exception of zuclopenthixol, were regarded as statistically significant.

IC values for the individual drugs olanzapine, sertindole, zuclopenthixol and clozapine related to gender and age (information not always available) are presented in table II. A trend towards a higher IC value for olanzapine and clozapine in men compared with women was observed. Patient characteristics, doses and treatment durations in the VTE1 cases are presented in table III. Most patients were between 20 and 50 years old. The median ages of the patients treated with olanzapine, sertindole, and zuclopenthixol were 45, 37 and 52 years, respectively. In the VTE cases with known duration of therapy with these drugs, 60% (32/53) occurred within the first 3 months of treatment (table III). The corresponding figure for clozapine was 39% (94/242). The time intervals between the initiation of therapy with olanzapine and clozapine to occurrence of VTE are displayed in figure 2.

For cases where olanzapine, sertindole and zuclopenthixol were the suspected agents for VTE, concurrent medications with other drugs known to increase the risk of VTE were reported in eight cases (8%), three cases (50%) and zero cases (0%), respectively. The corresponding figure for clozapine was 16 cases (4%). In 86% of the cases with concurrent treatment with drugs known to increase the risk for VTE, estrogen-containing medications were reported.

The associations became significant in 2001, 2002 and 2003 for sertindole, olanzapine and zuclopenthixol (figures 1b, 1a and 1c), respectively. For comparison, the first time the IC_{025} value for clozapine and VTE1 was above zero was in 1993, when 53 cases of the association were included and IC_{025} reached 0.07 (figure 1d). A detailed analysis, including review of the individual cases, was undertaken and suggested a possible causal relationship between use of these drugs and VTE.

Discussion

The reliability of data in the WHO database is dependent on the quality of the participating national systems of spontaneous reporting of ADRs. In general, spontaneous ADR reporting is limited by factors such as provision of incomplete information and under-reporting.[29] Moreover, the reporting is influenced by several factors such as the extent of use of the drugs, the year of introduction to the market, general knowledge of the adverse effects of the drug, public attention to specific problems and health professionals' attitudes to reporting of ADRs. Despite these limitations, assessing data from spontaneous ADR reporting systems, including the WHO database, is an important and cost-effective way of detecting possible infrequent reactions,[18,19] although the method, by itself, cannot be used to establish a conclusive causal relationship between an event and a drug.

Our analyses found that in the WHO ADR database, VTE was reported more often in combination with second-generation antipsychotic drugs and with the individual drugs olanzapine, sertindole, zuclopenthixol and clozapine than would be expected based on general reporting patterns in the dataset. The disproportional reporting of the antipsychotic drugs olanzapine, sertindole, zuclopenthixol and VTE represent new ADR signals that should be investigated further. The observed disproportional reporting may have several explana-

tions in addition to there being a causal association between the drugs and the ADR. These include reporting bias, confounding by indication, other confounding factors, that the association may have arisen by chance, or a combination of these factors. Given the nature of spontaneous reporting data, it is not possible to exclude different types of bias. Confounding factors such as the underlying disease, smoking, obesity, which may in turn be associated with the antipsychotic drug treatment or immobilization could all have contributed to disproportional reporting.

For olanzapine and risperidone, an association between the drug and VTE has recently been sug-

Table I. Cases of venous thromboembolism (specific definition; VTE1) during treatment with antipsychotic drugs reported to the WHO database, with information component (IC) values[a]

Drugs	Total no. of reports for drug	VTE1		
		no. of case reports	IC value	lower 95% credibility interval of the IC value (IC_{025})
High potency, first-generation antipsychotics	**19 277**	**88**	**−0.2**	**−0.5**
Benperidol	132	2	0.8	−0.9
Bromperidol	219	2	0.5	−1.2
Clopenthixol	284	2	0.3	−1.4
Flupenthixol	1 561	9	0.2	−0.8
Fluphenazine	2 438	8	−0.6	−1.6
Haloperidol	9 428	41	−0.2	−0.7
Perphenazine	1 549	7	−0.2	−1.2
Pimozide	596	1	−1.0	−3.1
Tiotixene	847	0	−2.4	−5.3
Trifluoperazine	1 794	6	−0.5	−1.6
Trifluperidol	20	1	0.9	−1.3
Zuclopenthixol	848	10	1.0	0.2
Low-potency first-generation antipsychotics	**13 419**	**46**	**−0.6**	**−1.0**
Chlorpromazine	5 785	14	−1.0	−1.8
Cyamemazine	665	4	0.2	−1.1
Levomepromazine	2 103	6	−0.8	−1.8
Melperone	300	4	1.0	−0.3
Perazine	567	7	1.0	0.0
Thioridazine	4 330	12	−0.8	−1.6
Second-generation antipsychotics	**69 598**	**620**	**0.8**	**0.7**
Amisulpride	945	2	−1.0	−2.6
Aripiprazole	597	4	0.3	−1.0
Clozapine	36 739	385	1.0	0.9
Olanzapine	11 480	99	0.7	0.5
Quetiapine	2 857	20	0.4	−0.2
Remoxipride	319	1	−0.4	−2.5
Risperidone	15 064	91	0.2	−0.1
Sertindole	316	6	1.4	0.3
Sultopride	65	1	0.6	−1.5
Ziprasidone	1 678	13	0.6	−0.2
Zotepine	249	3	0.8	−0.6

a The table show the number of case reports and IC values prior to exclusion of suspected duplicates.

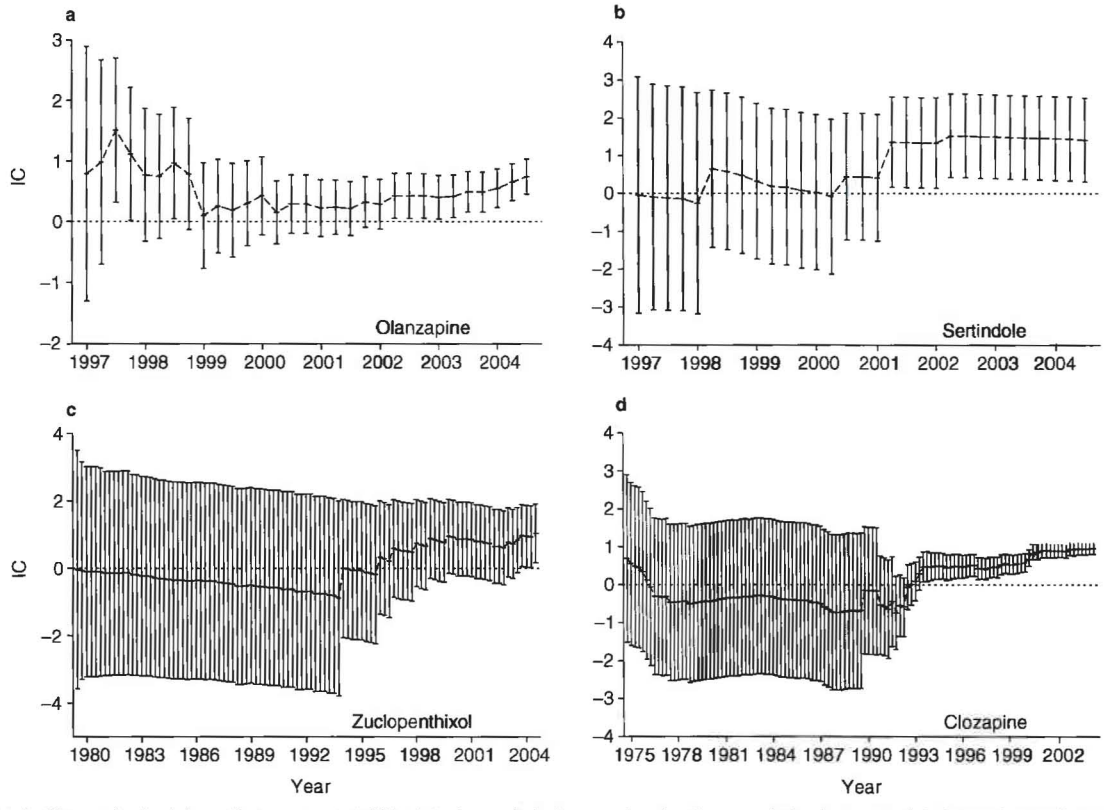

Fig. 1. Change in the information component (IC) plotted cumulatively over time for the association between: (**a**) olanzapine and venous thromboembolism (VTE)1; (**b**) sertindole and VTE1; (**c**) zuclopenthixol; and VTE1 (**d**) clozapine and VTE1. The IC values are plotted at quarterly intervals with the lower and higher bounds of the 95% credibility intervals shown.

gested in a population of nursing home residents >65 years of age.[10] That study population may be very different from younger populations using second-generation antipsychotics with regard to the presence of VTE risk factors. This, and confounding by indication, may be an alternative explanation for the associations found in that study.[10] To date, no study has been published investigating these associations in individuals <65 years old. In our study, the median age of the patients in the reported cases of VTE in users of olanzapine, sertindole or zuclopenthixol was between 37 and 52 years. The IC value was statistically significant for both olanzapine and clozapine in the younger (0–55 years) age group, but only for clozapine in the older age group (>55 years). Thus, young patients may also be at risk for this possible ADR. Regarding risperidone, we found no corresponding disproportional reporting in the WHO database. However, because of the nature of the spontaneous reporting system, a negative finding does not necessarily prove that there is no excess risk for VTE during treatment with risperidone, but only that relatively infrequent reporting occurs. For sertindole and zuclopenthixol, no data have been published supporting or challenging an association between these drugs and VTE.

As expected, the IC values were slightly higher using a more specific definition of VTE (VTE1) compared with a wider definition where other ADRs might be included (VTE2). Few additional cases were identified when the less specific definition of VTE was used, which suggests that if VTE is observed and reported it is often diagnosed as VTE1.

Approximately half of the VTE cases reported during the use of antipsychotics concerned clozapine. This association has been highlighted in case

reports,[3] ADR monitoring system reports[5] and retrospective autopsy data.[4,8] A substantial number of the clozapine reports in this study predated the recent publications reporting these associations, making reporting bias due to an increased awareness less likely as an explanation. Since patients treated with clozapine are intensively monitored for agranulocytosis, the possibility that the association between clozapine and VTE may be a result of an intense monitoring of other medical disorders cannot be excluded. However, the IC for VTE should not be affected in such cases, as the reporting of all suspected ADRs would be expected to increase. Another possible, or at least theoretical, explanation is that patients taking clozapine might be more often co-prescribed drugs that are known to cause VTE than other antipsychotics. However, a re-evaluation of these reports showed that in only 4% of the cases such exposure was present. Associations between olanzapine, sertindole, zuclopenthixol and VTE were based on relatively fewer cases than clozapine. In approximately one-sixth of these cases, olanzapine was the suspected drug. Exposure to concomitantly used drugs that are known to cause VTE was documented in only 8% of the olanzapine reports. In a few case reports, an association between olanzapine and VTE has been suggested.[13,30] However, as the relationship in the database was statistically significant before these case reports were published, reporting bias is an unlikely explanation for the positive IC value for olanzapine with VTE.

Associations between sertindole and zuclopenthixol and VTE were based on only six and ten reports, respectively. Possibly confounding drugs were present in three of the six reports where sertindole was the suspected agent, making a causal association between sertindole and VTE less likely. IC and IC_{025} values for sertindole have remained at stable high levels since 2001. In 1998, sertindole was withdrawn from the market because of suspected cardiac ADRs. The suspension was lifted in 2001, but wider use of the drug has only occurred

Table II. Cases of venous thromboembolism (specific definition; VTE1) during treatment with clozapine, olanzapine, sertindole and zuclopenthixol, with information component (IC), in relation to sex and age[a]

Drug	Total no. of reports for drug	VTE1		
		no. of case reports	IC	lower 95% credibility interval of the IC value (IC_{025})
Clozapine	**36 739**	**385**	**1.0**	**0.9**
Males	21 122	180	1.4	1.2
Females	14 052	202	1.1	0.9
0–55 y	27 871	152	0.8	0.7
>55 y	5 660	69	1.3	1.0
Olanzapine	**11 480**	**99**	**0.7**	**0.5**
Males	5 664	50	1.4	1.0
Females	5 181	46	0.4	0.0
Age 0–55 y	7 184	68	0.6	0.3
Age >55 y	2 499	18	0.5	−0.1
Sertindole	**316**	**6**	**1.4**	**0.3**
Males	153	0	−0.6	−3.5
Females	156	6	1.8	0.6
Age 0–55 y	233	4	1.0	−0.3
Age >55 y	58	2	1.2	−0.5
Zuclopenthixol	**848**	**10**	**1.0**	**0.2**
Males	484	6	1.5	0.4
Females	333	4	0.6	−0.7
Age 0–55 y	609	6	0.6	−0.5
Age >55 y	161	4	1.5	0.2

a The table shows number of case reports and IC values prior to exclusion of suspected duplicates.

Table III. Characteristics of cases of venous thromboembolism (specific definition; VTE1) during treatment with antipsychotic drugs reported to the WHO database after excluding suspected duplicates

Pt and treatment details	Drug			
	clozapine	olanzapine	zuclopenthixol	sertindole
Number of pts (m/f/unknown)	375 (176/196/3)	91 (45/43/3)	9 (6/3/0)	6 (0/6/0)
Median age, y (range)	40 (20–89)[a]	45 (20–87)[b]	52 (33–64)	37 (32–65)
Median dose, mg/d (range)	350 (12–2000)[c]	10 (3–100)[d]	150 (100–200)[e], IV or IM in four subjects; 25 mg PO in one subject	20 (4–20)[f]
Duration of drug treatment (proportion ≤3 months)	94/242 (39%)	25/44 (57%)	4/5 (80%)	4/5 (80%)
Percentage of monotherapy	201/375 (54%)	25/91 (26%)	3/9 (33%)	2/6 (33%)

a Information available in 361 cases.

b Information available in 78 cases.

c Information available in 199 cases.

d Information available in 40 cases.

e Depot formulation.

f Information available in 3 cases.

f = females; **IM** = intramuscular administration ; **IV** = intravenous administration; **m** = males; **PO** = oral administration; **pt** = patient.

very recently. We have not found any previous reports suggesting that sertindole has been associated with VTE. The association between zuclopenthixol and VTE was statistically significant only when the specific VTE definition (VTE1) was used. When using the less specific VTE definition (VTE2), the association was not statistically significant. Furthermore, no previous reports suggesting that zuclopenthixol is associated with VTE have been identified in the literature. These findings might thus be coincidental, but further investigations are nevertheless warranted. A trend towards higher IC values for olanzapine and clozapine in men compared with women was observed, suggesting a more disproportional reporting in men. However, it is possible that some VTE events in women using antipsychotic drugs may have been attributed to the concomitant use of estrogens. Thus, it remains an open question as to whether there is a true gender difference in risk.

We found no association between VTE and either low-potency or high-potency first-generation antipsychotics as a group. In contrast, an association for first-generation antipsychotics is supported by one large case-control study,[6] which found a relative risk of 7.1 (95% CI 2.3, 22.0) for current antipsychotic use compared with no antipsychotic use. Low-potency first-generation antipsychotic drugs were more strongly associated with VTE than were high-potency drugs. Separate analyses for each drug were not undertaken in that study. The reason for the discrepancy between our data and the results from the case-control study is unclear but may well reflect the differences in data sources used and the methodologies employed.

The median doses in the VTE cases were slightly higher than the defined daily dose (DDD) for clozapine (300 mg) and equal to the DDD for olanzapine (10 mg), indicating that the reaction was not dependent on excessive doses of these drugs. Due to the

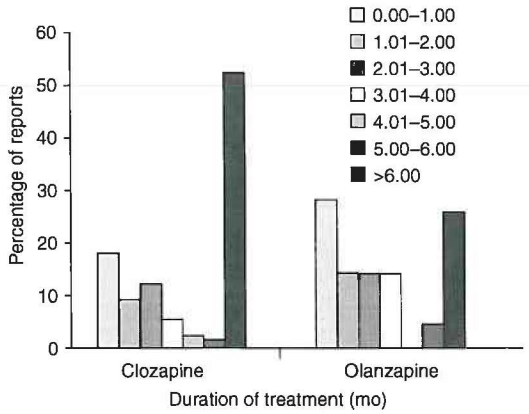

Fig. 2. Time from start of therapy to occurrence of venous thromboembolism 1 for the reports where clozapine and olanzapine were implicated as suspected drugs (data available in 64.5% of the clozapine reports and 48.3% of the olanzapine reports).

limited number of cases, no solid analysis can be made about the prescribed doses for sertindole and zuclopenthixol. In 60% of the VTE cases the event occurred within the first 3 months of treatment in the cases associated with olanzapine, sertindole and zuclopenthixol. The corresponding figure was 39% in the cases associated with clozapine. Similar findings have been reported previously.[5] However, it should be taken into account that in the majority of our reports, the treatment duration was unknown. Therefore, the results should be interpreted cautiously. Moreover, any association between a drug and an ADR is more obvious shortly after institution of treatment and thus more likely to be reported.

The mechanisms underlying the relationship between antipsychotic drugs and VTE are basically unknown but some plausible mechanisms have been suggested, such as antipsychotic-induced sedation, obesity, hyperleptinemia, presence of antiphospholipid antibodies and enhanced platelet aggregation.[3] The use of clozapine has been shown to increase platelet adhesion and aggregation.[31] Clozapine and olanzapine also have a particular propensity to induce metabolic abnormalities such as obesity and hyperleptinemia.[1] Moreover, antipsychotic drugs might predispose patients to venous thrombosis because of their sedative effects leading to immobilization and thereby venous stasis and blood pooling in the lower extremities. Significant sedation is a common ADR for many second-generation antipsychotics, particularly clozapine.[32] Increased adrenaline (epinephrine) secretion in patients having acute psychotic excitation has also been suggested as a possible factor enhancing blood coagulation,[33] although no experimental data supporting this hypothesis have been published. Moreover, the frequency of smoking among patients with schizophrenia is increased compared with the general population.[34,35] However, some studies[36] suggest that smoking is associated with a very small increased risk for VTE only, and others do not generally accept smoking as an important risk factor for VTE.[37,38] Nevertheless, disease-related factors cannot explain why positive associations were observed for clozapine, olanzapine, sertindole and zuclopenthixol only, and not for all other antipsychotics or for antipsychotics in general. In the previously mentioned large case-control study,[6] psychiatric conditions such as schizophrenia, other psychoses, affective and anxiety disorders and insomnia were not independently associated with VTE.

Conclusions

The results of the present study show that VTE was more often reported with the antipsychotic drugs olanzapine, sertindole and zuclopenthixol than with other drugs in the WHO database and are suggestive of a causal relationship between these drugs and VTE in patients aged ≥20 years. However, one should bear in mind that results generated from disproportionality analysis of spontaneous ADR databases cannot be used to establish causality. Therefore, further investigations are needed to explain this signal and studies using alternative methodologies are required to determine whether antipsychotics actually cause VTE, to identify the frequency of this possible adverse reaction, to explore the mechanism and to identify possible risk factors. Until such data are available, clinicians should be aware of VTE as a possible adverse reaction associated with use of antipsychotic agents. In patients experiencing VTE during treatment with an antipsychotic agent, it seems reasonable to reassess the risks and benefits of continued therapy with the drug.

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