

PhVWP Assessment report

Antipsychotics and cerebrovascular accident

SPC Wording for Antipsychotics

in relation to:

Risk of cerebrovascular accidents (CVA), in particular when used in dementia patients.

as agreed following the PhVWP in September 2005

Section 4.4

An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. <...> should be used with caution in patients with risk factors for stroke.

SCIENTIFIC BASIS FOR PHVWP CONCLUSIONS

1. BACKGROUND

A meta-analysis of randomized placebo-controlled clinical trials in elderly patients with dementia showed a three-fold increase (compared with placebo) in the risk of CVAEs for risperidone when used in elderly patients with dementia. A pooled analysis of randomized placebo-controlled clinical trials of olanzapine in elderly patients with dementia showed that there was a similar risk with olanzapine and a two fold increase in all-cause mortality. On the basis of these data action was taken in March 2004 throughout the EU to add warnings about the potential for risperidone and olanzapine to increase the risk of CVAEs. At that time there was insufficient evidence to include other antipsychotics in the recommendations.

An epidemiological study using the General Practice Research Database (GPRD) was initiated by UK Medicines and Healthcare products Regulatory Agency (MHRA) to assess the evidence for any increased risk of CVAEs in elderly patients with dementia exposed to risperidone compared to similar patients exposed to other antipsychotics. Since 2004 there have also been a number of published epidemiological studies examining the risk of CVA with antipsychotics.

This report summarises the evidence considered by the European Pharmacovigilance Working Party (PhVWP) in coming to its conclusion on the need for class wording in relation to a possible risk of CVA associated with antipsychotics.

2. GPRD STUDY

The GPRD study was carried out by staff in the Post-Licensing Division of the MHRA. The protocol was approved by the Scientific and Ethical Advisory Group of the GPRD. A matched case-control design was used to compare the risk of CVAEs in a cohort of 10,544 elderly demented patients prescribed an antipsychotic. Controls were matched to cases on age (+/- 2 years), gender and had to be active patients for the entire period of cohort membership of the matched case. The study period was from 1/1/1993 to 31/12/2003.

2.1 Methods

Exposure status was defined from the issuing date of prescriptions as recorded in the database. If a CVAE occurred within 60 days of a prescription being issued this was defined as an exposed event. Multivariable conditional logistic regression was used to analyse the data adjusting for history of hypertension, history of diabetes, history of lipid lowering agents, history of atrial fibrillation and prior or current prescription of anti-coagulants. Prior prescription of anti-coagulants was defined as the final anti-coagulant prescription occurring at more than 90 days prior to the index event. Current prescription of anticoagulants was defined as the first prescription occurring before the index event and the last prescription occurring no more than 90 days prior to the index event. All variables were included in the initial model and variables not reaching the 10% level of significance and not changing the adjusted odds ratio by more than 10% were removed in a step-wise manner.

2.2 Results

There were 10,544 eligible patients identified for the study cohort. The mean age of the study population was 82.6 years and 68% of the cohort was female. Within the cohort, 1058 cases and 1058 matched controls were identified, a further 21 cases were identified for whom no suitable matched control could be found.

The univariate analyses did not show any significant association of CVAE risk with history of lipid lowering agents, prior anticoagulation, history of atrial fibrillation, or history of hypertension. Whilst hypertension is a known risk factor for stroke, in the specific cohort of elderly patients with dementia studied, 70% of the cohort had a prior history of hypertension therefore the majority of matched patient sets are likely to be concordant for hypertension status. Consequently a lack of power may explain the lack of a statistically and/or clinically important odds ratio associated with a prior history of hypertension in this study either in the

univariate analysis or after adjusting for other potential confounders (OR 1.0; 95% CI 0.9, 1.3). There was some association of CVAE risk with current anti-coagulation therapy (OR = 1.6; 1.2 – 2.1) and history of diabetes (OR 1.4; 1.0 – 1.8).

The adjusted odds ratios associated with history of lipid lowering agents, prior anticoagulation, history of atrial fibrillation, and history of hypertension were not significant at the 10% level in the multivariable analyses and did not materially change the odds ratios. These variables were therefore omitted from the analysis.

There was weak evidence of an increased risk of CVAEs in patients exposed to risperidone compared to all other antipsychotics (adjusted OR 1.4; 0.9, 2.1). There was also evidence of an increased risk of CVAEs for patients exposed to risperidone compared to those unexposed to antipsychotics (adjusted OR 2.1; 1.4, 3.2).

2.3 Discussion

Patients with severe dementia are known to be at higher risk of cerebrovascular adverse events than the general population. The cohort incidence rate for cerebrovascular adverse events in this study cohort was 6.5 per 100 person years (1058 CVAEs in 16,220 patient years). The weak evidence of an increased risk of CVAEs with risperidone compared to all other antipsychotics in the study should be interpreted carefully, particularly with the possibility of confounding by indication. However, this increased risk is in line with results from randomised clinical trials and suggests that there may be an increased risk of CVAEs for patients exposed to risperidone compared to other antipsychotics. There is limited power to differentiate between specific antipsychotics due to low exposure to some drugs.

2.4 Conclusions

This study provides estimates of the increased risk of CVAEs associated with risperidone and other antipsychotics used in elderly demented patients. However, confounding cannot be ruled out as a possible explanation for the results. Notably the background incidence of CVAEs in elderly demented patients is approximately 7 per 100 person years. This is not a rare event and therefore any increase in risk in this population due to antipsychotics will lead to a high burden of disease.

3. PUBLISHED STUDIES

A search of the published literature (2004-2005) was carried out using the Medline and Embase databases. Two epidemiological studies were identified which addressed the issue of the risk of stroke associated with antipsychotics.

Herrmann et al. Atypical Antipsychotics and Risk of Cerebrovascular Accidents. (Am J Psychiatry, June 2004)

Herrmann et al. carried out a retrospective population-based cohort study by linking administrative healthcare databases in Ontario, Canada. The study examined the association between atypical antipsychotic use and stroke in the elderly over a period of 5-years (1 April 1997 – 31 March 2002) and included 11,400 anti-psychotic naïve subjects over the age of 65 years. Three cohorts – users of typical antipsychotics (N=1,015), risperidone (N=6,964), and olanzapine (N=3,421) – were identified and compared.

During 13,318 person-years of follow up, there were 92 admissions for stroke (typical antipsychotic users: N=10; risperidone users: N=58; olanzapine users: N=24). The crude stroke rate per 1,000 person-years did not significantly differ among the patients treated with typical antipsychotics (5.7), risperidone (7.8), and olanzapine (5.7). Relative to typical antipsychotic users, model-based estimates (time-to event analyses using Cox proportional hazard models) adjusted for covariates (hospitalizations, procedures, drug utilization hypothesized to be associated with the risk of stroke, demographic characteristics) revealed a relative risk ratio for stroke of 1.1 (95% CI=0.5-2.3) with olanzapine use and 1.4 (95% CI=0.7-2.8) with risperidone use. Relative to olanzapine, users of risperidone were not at significantly increased risk of stroke-related hospital admission (adjusted risk ratio 1.3, 95% CI=0.8-2.2).

The author's conclude that olanzapine and risperidone use was not associated with a statistically significant increased risk of stroke compared with typical antipsychotic use in the elderly.

Comments

- This study included a relatively large cohort of patients who were followed for a lengthy period of time.
- Whilst the risk between atypical and typical antipsychotic use is not statistically significant, the point estimates for the relative risk are consistently greater than one.
- The study population is not restricted to elderly patients with dementia, although the authors comment that, based on epidemiological studies, it is likely that the vast majority of antipsychotic users in the study were being treated for dementia related behavioural disturbances as opposed to schizophrenia.
- In this study there was no matching for vascular risk factors (including history of previous stroke, diabetes, hypertension, hyperlipidaemia, atrial fibrillation) and it is unclear how well subjects were treated for these vascular risk factors.
- Administrative databases are limited by the inability to directly measure compliance and appropriateness of use.
- Whilst diagnostic codes for admissions due to stroke were used, other important cerebrovascular adverse events (e.g. transient ischaemic attacks and mild strokes) not resulting in hospital admission were not captured.
- The study provides no information on the risk with clozapine and quetiapine due to the relatively small numbers of prescriptions written during the observation period.
- One of the authors receives research support and speakers honoraria from Janssen-Ortho, Eli Lilly, Novartis, Pfizer and AstraZeneca – manufacturers of atypical antipsychotics.

Sudeep, Herrmann et al. Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. (BMJ, January 2005)

Sudeep et al conducted a population based retrospective cohort study to compare the incidence of admissions to hospital for ischaemic stroke among older adults with dementia who received atypical or typical antipsychotics. The study was carried out using 5-years (1 April 1997 – 31 March 2002) of data from administrative healthcare databases in Ontario, Canada. The study involved 32 710 antipsychotic naïve subjects aged ≥65years with dementia.

Two cohorts were identified: atypical antipsychotic users, N=17 845 (risperidone (N=13 503), olanzapine (N=3459) and quetiapine (N=883)); and typical antipsychotic users, N=14 865 (haloperidol, fluphenazine, thiothixene, pimozide, trifluoperazine, flupenthixol, zuclopenthixol, thioproperazine, chlorpromazine, thioridazine, mesoridazine, lozapine, perphenazine, promazine, pericyazine and chlorprothixane) users. Users of injectable/depot formulations and patients with other psychotic disorders such as schizophrenia were excluded from the analysis.

The results of the main analysis are provided in the table below:

Main analysis (full cohorts)	Atypical antipsychotic cohort (n=17 845)	Typical antipsychotic cohort (n=14 865)
No (%) of new admissions for ischaemic stroke	284 (1.6)	227 (1.5)
Mean (SD) duration of follow up (days)	227.2 (264.0)	250.1 (335.4)
Crude event rate (no of events per 1000 person years)*	25.5	22.3
Unadjusted hazard ratio (95% CI)	1.06 (0.89 to 1.27)	1.00
Adjusted hazard ratio (95%	1.01 (0.81 to 1.26)	1.00

CI)§		
------	--	--

*(No of events/total No of days per 365 days)x1000

§Adjusted for age; sex; low income status; residence in long term care; frequency of medical contact; year of entry to cohort; history of stroke in past 5 years; history of atrial fibrillation; hypertension; diabetes mellitus; acute myocardial infarction in past three months; congestive heart failure; number of distinct drugs; chronic use (≥ 2 consecutive prescriptions) of antipsychotics; and baseline use of warfarin, antiplatelet drugs, antihypertensive drugs, angiotensin converting enzyme inhibitors, lipid lowering drugs, antidiabetic drugs, and hormone replacement therapy.

The subgroup analyses were all consistent with the main analysis. The risk of stroke for patients receiving risperidone (adjusted hazard ratio 1.04, 0.82 to 1.31), olanzapine (0.91, 0.62 to 1.32) and quetiapine (0.78, 0.38 to 1.57) was not significantly different from that of patients receiving typical antipsychotics. Chronic users (two or more consecutive prescriptions) of atypical antipsychotics were not at increased risk compared to users of typical antipsychotics. However, a higher rate of stroke was found in those subgroups with established risk for stroke such as atrial fibrillation and prior stroke than in the main analysis.

The author's conclude that atypical antipsychotic use was not associated with a statistically significant increased risk of stroke compared with typical antipsychotic use in elderly patients with dementia.

Comments

- This study included a relatively large cohort of patients who were followed for a lengthy period of time.
- The study is controlled for various confounding factors although important confounders may have been unmeasured and unrecognized.
- As with all observational studies it is possible that not all baseline differences could be adjusted for.
- The authors could not adjust for all of the important factors affecting the risk of stroke such as smoking history, presence and severity of hypertension, lipid status and specific valvular heart conditions.
- Some strokes may not have been captured if they did not lead to hospital admission or if they led immediately to death (ascertainment bias).
- The study does not capture other cerebrovascular adverse events such as transient ischaemic attack.
- There is no cohort of non-antipsychotic users – the authors comment that this is because preliminary data showed several important baseline differences between patients receiving antipsychotics and those not receiving antipsychotics.
- One of the authors receives research support and speakers honoraria from Janssen-Ortho, Eli Lilly, Novartis, Pfizer and AstraZeneca – manufacturers of atypical antipsychotics.

3.1 Discussion

The two epidemiological studies presented are relatively large retrospective cohort studies conducted using the same healthcare databases in Ontario, Canada. The first study (Herrman et al. 2004) examined the association between atypical antipsychotic use and stroke in the elderly and concluded that olanzapine and risperidone use was not associated with a statistically significant increased risk of stroke compared with typical antipsychotic use. The second study (Sudeep et al. 2005) examined the association between antipsychotic use and stroke in elderly patients with dementia and concluded that the use of atypical antipsychotics is not associated with a greater risk of stroke than use of typical antipsychotics in this population.

The crude stroke rates observed in these studies are low compared to those observed in the randomized controlled trials upon which the CSM advice of 2004 regarding atypical antipsychotics and increased risk of CVAEs in elderly demented patients, is based. This would seem to suggest the possibility of some kind of diluting factor.

Sudeep et al (2005) comment that in light of the findings of this study, the choice of atypical or typical antipsychotic to manage behavioural and psychological symptoms of dementia (BPSD) should not be based on concerns about the risk of stroke. However, it should be noted that, whilst this review of the literature does not include efficacy studies, the randomised controlled trials for risperidone considered by CSM in 2004 showed, at best, a moderate efficacy in the treatment of BPSD.

4. OVERALL DISCUSSION

The published studies reviewed here, taken together with the GPRD study do not provide strong evidence that the risk of stroke in elderly patients with dementia evident in clinical trial data for olanzapine and risperidone does not extend to other atypical and conventional antipsychotics. In these studies the risk of cerebrovascular events associated with conventional antipsychotics was not significantly different from that of olanzapine and risperidone (for which there is clinical trial evidence of an increased risk of cerebrovascular events in elderly patients with dementia).

The PhVWP considered that the available data support the inclusion of warnings about a possible increased risk of cerebrovascular adverse events in patients with dementia in the SPCs for all conventional and atypical antipsychotics.

5. REFERENCES

1. Herrmann N, Mamdani M, Lanctot KL. Atypical Antipsychotics and Risk of Cerebrovascular Accidents. *Am J Psychiatry* 2004; 161:1113-5.
2. Sudeep SG, Rochon A, Herrmann N, Lee PE et al. Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. *BMJ*, doi:10.1136/bmj.38330.470486.8F (published 24 January 2005).