Sudden Cardiac Death in Users of Second-Generation Antipsychotics

To the Editor: First-generation antipsychotics have been linked to sudden cardiac death (SCD),[1,2] but information on the relationship between second-generation antipsychotics (SGAs) and this possible adverse effect is limited. However, the latter association was recently strengthened by a retrospective large cohort study in Medicaid enrollees in Tennessee aged 30 to 74 years.[3] If the results of that study are generalizable to other populations, a considerable number of individual case safety reports with this problem would probably be found in large international pharmacovigilance data sets. Moreover, with the use of such data, certain characteristics of the affected subjects could be investigated in more detail.

Method. We reviewed international individual case safety reports of suspected adverse drug reactions (ADRs) from the World Health Organization drug safety database, VigiBase, which contains over 4.5 million records from more than 90 countries (as of March 2009).[4] Although the data are heterogeneous, at least with respect to origin (country as well as reporter of the ADR) and content (eg, quality and assessment of causality), they have been used to highlight and support emerging drug safety issues.[5–7] We analyzed all cases of SCD during SGA treatment that were identified in VigiBase on January 10, 2008. Obvious duplicates and suicides were excluded. Drugs known to prolong the QT interval were defined as drugs generally accepted by the QT Drug Lists Advisory Board of the Arizona Center for Education and Research on Therapeutics to carry a risk, a possible risk, or a conditional risk of causing torsades de pointes.[8] A disproportionality measure, the Information Component (IC), was used to identify if SCD was excessively reported for the various SGAs relative to the overall reporting rate in VigiBase.[9,10]

Results. In VigiBase, a total of 462 unique reports of SCD during SGA treatment, from 17 countries, were identified (Table 1). Clozapine was the suspected agent in most reports. Notably, the reports often concerned relatively young patients, the median age being 43 years. In 80% of the reports the SGA was the sole suspect for the reaction, and in 66% of all reports no additional drug known to prolong the QT interval was reported. The duration of treatment was 3 months or less in 43% of the reports. SCD was reported disproportionately more often for SGAs compared to the overall reporting in VigiBase, although the IC value is uncertain for the SGAs with very few reports.

Rigorous monitoring for agranulocytosis during clozapine treatment could lead to increased reporting of other ADRs as well. This might have contributed to the large proportion of reports with sudden cardiac deaths with clozapine as the suspected agent. Other reporting biases, including variable differential underreporting of suspected ADRs,[11] probably exist for these data, and

Table 1. Characteristics of 462 Cases of Sudden Cardiac Death[a] in SGA Users in the WHO Database, January 10, 2008

Antipsychotic	Unique Cases, n (n including duplicates[b])	IC (IC_{025})[c]	Age in Years,[d] Median (range)	Female,[e] n (%)	Cases With SGA as Sole Suspected Drug, n (%)	Cases Without Other Medication, n (%)	Cases With Duration of Treatment ≤ 3 Mo,[f] n (%)
Clozapine	235 (244)	2.66 (2.47)	42 (18–89)	75 (32)	202 (86)	121 (51)	38 (27)
Olanzapine	80 (85)	2.58 (2.24)	43 (16–87)	27 (34)	59 (74)	23 (29)	26 (74)
Risperidone	63 (64)	1.98 (1.59)	49 (14–95)	30 (49)	46 (73)	20 (32)	13 (52)
Quetiapine	32 (34)	2.73 (2.20)	42 (18–93)	17 (55)	24 (75)	6 (19)	11 (79)
Ziprasidone	27 (29)	3.26 (2.68)	40 (18–85)	7 (30)	16 (59)	5 (19)	3 (43)
Sertindole	13 (14)	4.22 (3.38)	42 (25–79)	4 (36)	9 (69)	4 (31)	5 (71)
Amisulpride	11 (11)	2.67 (1.70)	48 (36–89)	7 (70)	7 (64)	1 (9)	4 (100)
Aripiprazole	6 (6)	0.55 (−0.80)	56 (51–70)	1 (20)	6 (100)	3 (50)	0 (0)
Sulpiride	2 (2)	0.25 (−2.27)	41 (36–45)	1 (50)	1 (50)	0 (0)	0 (0)
Zotepine	1 (1)	1.05 (−2.68)	35 (35)	1 (100)	0 (0)	0 (0)	0 (0)
Total[g]	462 (481)	2.56 (2.43)	43 (14–95)	167 (37)	370 (80)	183 (40)	100 (43)

[a]The WHO Adverse Reaction Terminology preferred term sudden death was used; hence, reasons for death might have been other than cardiac arrhythmias.
[b]Number of reports including duplicates and suicides.
[c]The IC quoted here was computed based on all available reports; ie, duplicates and suicides have not been excluded from these calculations. Positive IC values indicate that SCD is reported in association with the SGA more often than expected in VigiBase. IC_{025} is the lower 95% credibility limit of the IC.
[d]Fifty-two cases with missing data excluded from the calculation.
[e]Twelve cases with missing data excluded from the calculation.
[f]Two hundred thirty cases with missing data excluded from the calculation.
[g]Each report can contain more than 1 drug.
Abbreviations: IC = Information Component, SCD = sudden cardiac death, SGA = second-generation antipsychotic, WHO = World Health Organization.

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comparisons between drugs should therefore be considered with great caution.

In conclusion, these data suggest that SCD in SGA users is likely to be an international problem and may occur early in treatment and in younger patients. More studies are urgently needed to investigate the association further.

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