Pharmacovigilance Working Party Public Assessment Report on Neuroleptics and Cardiac safety, in particular QT prolongation, cardiac arrhythmias, ventricular tachycardia and torsades de pointes

BACKGROUND

Following the concerns about cardiotoxicity and restriction of use of thioridazine in 2000 the Pharmacovigilance Working Party (PhVWP) expressed concern about the risk with other neuroleptics and the UK initiated a class review of neuroleptics and QT prolongation. The review considered the available data on neuroleptics on the UK market (data lock point August 2001). The review assigned each drug into one of three groups according to the degree of documentation supportive of the potential for cardiotoxicity and identified core warnings for the SPC of products in each group.

Following completion of the UK review, the assessment report and advice from a UK Expert Working Group was discussed at the PhVWP to obtain consensus on core SPC wording as outlined in table 1 and 2, which could be implemented throughout the EU.

The principle of using the classification and the corresponding SPC wording described in this report has been adopted by the Committee for Medicinal Products for Human Use (CHMP) for centrally approved products.

The review of neuroleptics and cardiac safety considered by the PhVWP only included those products marketed in the UK. Following discussions at PhVWP it was decided that the proposed SPC wordings may be used as key principles for updating SPCs on a national basis, including those products marketed in other member states that were not included in the review.

This report outlines the methodology for the review and the basis for the categorisation of products into different risk categories.

SOURCES OF INFORMATION

The sources of information used in the review included experimental data, clinical trials, literature reviews, case histories, spontaneous reporting, meta-analyses and epidemiology for each drug substance. Marketing authorisation holders for each drug were also asked to provide an assessment of risk of cardiotoxicity for their products using defined preferred cardiovascular search terms, to provide evidence from line listings of cardiotoxic adverse reactions and from literature articles, clinical trials and epidemiology. The defined preferred cardiovascular search terms were:

Arrhythmia
Cardiac arrest
ECG abnormal
Heart block
QT prolonged
Torsade de pointes
Sudden death unexplained
Ventricular arrhythmia
Ventricular fibrillation
Ventricular tachycardia

METHODOLOGY OF EU REVIEW

On the basis of the available data the drugs were assigned to one of three groups depending degree of documentation supportive of the potential for cardiotoxicity.

Comparison of risk between drugs

Several factors were taken into account when considering data across different drugs:

- The 'older' drugs often have reduced reporting rates of spontaneous adverse reactions
- The 'newer' drugs have increased reporting rates
- Drugs which have been previous issues of concern have stimulated reporting rates and possibly a lower rate of usage
- The 'age' of a drug will reflect in the experimental studies and phase I clinical trials as criteria for these become more rigorous. There are often less or even no available data for older drugs which makes assessment difficult. Literature reports are often the only source of information.
- The use of a drug either in primary care or in hospital care.
- The route of administration – eg the need for rapid treatment via IV or IM routes in severely disturbed/agitated patients versus chronic oral treatment.
- Any drug metabolised by 2D6 will always carry some risk as patients are not routinely screened for genetic polymorphism of the 2D6 enzyme.
- There are problems in interpretation of QTc data where an incorrect or unknown formula has been used in correction. The CPMP guidelines indicate Bazett's correction which is not always appropriate, particularly for the atypical antipsychotic drugs.
- Comparison is based upon the following evidence-based hierarchy:
  Clinical data > weight than pre-clinical data
  Clinical cardiac event > weight than QT prolongation
  Randomised trial > open trial > epidemiology > spontaneous reports.

The drugs were differentiated into three categories depending on the degree of documentation supportive of the potential for cardiotoxicity**:**

Insufficient: no data or insufficient data to assess cardiac risk

Intermediate: Some documentation from at least one data source suggesting potential for cardiotoxic risk

Good: Evidence from one or more data sources of a clinically significant prolongation of the QT interval and/or of the occurrence of serious cardiac arrhythmias associated with treatment).

CONCLUSIONS

The PhVWP agreed on the classification of neuroleptics as shown in Table 1, and on the core SPC wording as outlined in Table 2."

Table 1

Classification of neuroleptic drugs by level of documentation supportive of cardiotoxic risk

Insufficient	Intermediate	Good
Loxapine	Amisulpride	Haloperidol
Oxypertine	Benperidol	Pimozide
Perphenazine	Chlorpromazine	Sertindole
Pipiothiazine	Clozapine	Ziprasidone
Prochlorperazine	Fluphenazine	
Promazine	Flupenthixol	
Remoxipride	Levomepromazine	
	Olanzapine	

	Quetiapine	
	Risperidone	
	Sulpiride	
	Trifluoperazine	
	Zotepine	
	Zuclopenthixol	

Table 2

Key principles of SPC wording proposed by the PhVWP

Level of Risk	Insufficient/intermediate	Good
Section 4.3		• Clinically significant cardiac disorders (eg recent acute myocardial infarction, uncompensated heart failure, arrhythmias treated with class IA and III antiarrhythmic medicinal products) • QTc interval prolongation • History of ventricular arrhythmia or Torsades de pointes • Uncorrected hypokalaemia • Other QT prolonging drugs
Section 4.4	• Caution in patients with cardiovascular disease or family history of QT prolongation • Avoid concomitant neuroleptics	• Caution in patients with cardiovascular disease or family history of QT prolongation • Baseline ECG prior to treatment (see section 4.3) • During therapy, the need for ECG monitoring should be assessed on an individual patient basis • Whilst on therapy, reduce dose if QT is prolonged and discontinue if QTc is >500ms • Periodic electrolyte monitoring recommended • Avoid concomitant neuroleptics
Section 4.5	• Concomitant QT prolonging drugs • Drugs causing electrolyte imbalance • Metabolic inhibitors (CYP….) where known	• Concomitant QT prolonging drugs ** • Drugs causing electrolyte imbalance • Metabolic inhibitors (CYP….) where known
Section 4.8*	• QT prolongation • Ventricular arrhythmias - VF, VT (rare)	• QT prolongation • Ventricular arrhythmias - VF, VT (rare)

	• Sudden unexplained death • Cardiac arrest • Torsades de pointes	• Sudden unexplained death • Cardiac arrest • Torsades de pointes

*For those products for which no data are available the wording in section 4.8 of the SPC should be accompanied by a statement that these adverse effects are class effects of neuroleptics.

** A list of drugs should be included - eg Class IA and III antiarrhythmics, arsenic trioxide, halofantrine, levomethadyl acetate, mesoridazine, thioridazine, pimozide, sparfloxacine, gatifloxacin, moxifloxacin, dolansetron mesylate, mefloquine, sertindole or cisapride. The list may have to be amended on a national basis depending on the marketing status of different products.

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