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Development of neuroleptic agents: pharmacogenetics and current safety issues of regulatory concern

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Schizophrenia is a mental disease that affects approximately 1% of the population with distressing long-term consequences for the patient and society. There is consistent evidence that the principal etiology of schizophrenia involves predisposing genetic factors.

However, the search for the susceptibility genes with a view to any form of gene therapy has proved elusive. Furthermore, it is not clear whether the genes of familial schizophrenia are also involved in sporadic cases, which represent the overwhelming majority of patients with schizophrenia. For sporadic cases, genetic association studies comparing the distribution of allelic frequencies of candidate genes in patients with schizophrenia and controls have been performed, but the outcome of such

The development of safe and effective new drug treatments for schizophrenia poses a challenging task. This class of drugs is known to be associated with a wide range of serious and troublesome safety problems that include neurological, cardiac, endocrine, and metabolic side effects. Many of these drugs have a narrow therapeutic index and generate metabolites that often have their own unique pharmacological profile different from the parent compound. These features make it imperative that the optimal dose schedules for neuroleptic drugs are carefully characterized. Many of these drugs are metabolized by cytochrome P450 enzymes, which show genetic polymorphism and a bimodal distribution within the population. A significant subset of the population cannot eliminate these drugs as effectively as the majority. This brings an added dimension of complexity in characterizing the dose and individualizing therapy. Many neuroleptic agents are proarrhythmic with an adverse effect on cardiac repolarization. They are prone to prolonging the QT interval and inducing torsade de pointes. Given the potentially fatal outcome of this ventricular tachyarrhythmia, drug development programs need to ensure that the proarrhythmic potential of any new neuroleptic agent is thoroughly explored and its proarrhythmic risk characterized. The clinical use of many of these drugs is further troubled by their high potential for drug–drug interactions. These too need to be adequately investigated during development. The approval and the labeling of a new neuroleptic agent require a careful regulatory assessment of its risk/benefit ratio in comparison with the available alternatives. Their safe and effective use in routine clinical practice depends on careful attention to prescribing information, especially the contraindications, precautions, and patient-monitoring requirements.

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Selected abbreviations and acronyms

CPMP	*Committee for Proprietary Medicinal Products*
EMEA	*European Medicines Evaluation Agency*
EM	*extensive metabolizer*
EPS	*extrapyramidal symptoms*
FDA	*Food and Drug Administration*
HERG	*human ether-a-go-go*
ICH	*International Conference on Harmonization*
IKr	*delayed rectifier potassium channel*
NCE	*new chemical entity*
PM	*poor metabolizer*
SPC	*summary of product characteristics*
TD	*tardive dyskinesia*
TdP	*torsade de pointes*

studies has not been particularly spectacular. There is optimism that advances in molecular genetics will increase our understanding of the progression from genetic susceptibility to clinically overt schizophrenia. The mainstay of managing schizophrenia at present, however, is drug therapy. Indeed, if the susceptibility gene with a required degree of predictive power can be identified, but cannot be modified, there is much ethical and clinical discussion as to whether "pharmacological prophylaxis" of the potential patient with schizophrenia with atypical neuroleptics ought to be initiated at the "prodromal" stage or even earlier.

While the principles of clinical trials aimed at demonstrating the efficacy of new neuroleptic agents are relatively well established, the task of establishing their safety still remains a challenging one. This class of drugs is known to have a wide range of serious and troublesome safety problems, which include neurological, cardiac, endocrine, and metabolic side effects. Recently, developed atypical neuroleptics have succeeded in modestly reducing these risks.

The present efficacy-orientated approach is primarily responsible for the failure of clinical trials to detect the risks that are likely to be encountered during the uncontrolled use of the drug after it is approved. The number of patients exposed is not large enough nor are all the patient subgroups likely to receive the drug during its uncontrolled clinical use represented in these preapproval clinical trials. Despite very tight inclusion and exclusion criteria, clinical trials with neuroleptic drugs are among those with very high patient withdrawal rates.

It is usually the case that the subgroups excluded from clinical trials are in fact those who are at a much greater risk.

These include those patients with predisposing diseases or those receiving drugs with a potential for pharmacokinetic or pharmacodynamic interactions. Thus, the scope for detecting drug–disease or drug–drug interactions in clinical trials is also very limited. And yet, experience has shown that these are among the most important risk factors!

There are additional reasons why the safety of neuroleptic drugs should be adequately characterized. Atypical antipsychotics have revolutionized the treatment of schizophrenia, becoming the treatment of choice for patients not only during their first episode, but also throughout their life course. However, of particular regulatory interest are the reports that more than 70% of prescriptions for these drugs are written for conditions other than schizophrenia, such as affective disorders (both mania and depression), autism, geriatric agitation, substance abuse disorder, senile dementia, and pathologic aggression.[1,2] Atypical agents may be particularly suitable for the elderly, children, or adolescents, who are especially susceptible to the side effects of medications and in whom the risk of tardive dyskinesia (TD) is high.

Important lessons have already been learnt from routine clinical use of neuroleptic drugs already approved. Therefore, there is a clear prerequisite to consider and thoroughly explore the potential of a candidate new drug for the hazards known to be associated with other drugs of the same chemical, pharmacological and/or therapeutic classes. In this context, the International Conference on Harmonization (ICH) guideline[3] entitled "The Extent of Population Exposure to Assess Clinical Safety for Medicines Intended for Long-term Treatment of Non-life–threatening Conditions" is helpful. The mandatory requirement is 100 patients exposed to the new drug for at least 12 months. For the most common adverse events, ie, frequent and early-onset events, the guideline provides for 1500 patients studied over 3 months and it is estimated that this database will characterize a cumulative 3-month incidence of about 1% or more. This guideline does, however, recommend that the safety database may need to be expanded to characterize specific issues in special circumstances. Nevertheless, potentially fatal or otherwise serious adverse reactions usually have a frequency well below that which can be detected by this size of database. Clearly, alternative strategies are necessary to identify the risk and the predisposing factors.

In order to facilitate the development of new chemical entities (NCEs), including neuroleptic drugs, the European

Union's Committee for Proprietary Medicinal Products (CPMP) has issued a number of notes for guidance, including one on schizophrenia. These give a state-of-the-art scientific guidance on development strategies, all aspects of clinical trials, and the nature of the data required. In addition, there is a range of biostatistical guidance notes. These can all be accessed on the website of the European Medicines Evaluation Agency (EMEA).[4]

This paper is a brief review of some of the issues that weigh heavily during the regulatory evaluation of new neuroleptic agents. Drugs in this pharmacotherapeutic class attract particular attention since they have a narrow therapeutic index and are metabolized by enzymes that are highly polymorphic. Among the major deficiencies encountered during the evaluation of any new neuroleptic agent are the identification of the optimal dose schedule and the effect of pharmacogenetic factors on its efficacy, as well as the safety. Other issues of concern are characterization of its potential for proarrhythmias and significant drug–drug interactions.

Dosing schedule

It is not infrequently the case that the dose schedules proposed by the sponsors bear hardly any relationship to the pharmacology of the drug concerned. This applies not only to the neuroleptic drugs, but also to many other pharmacotherapeutic classes. When proposing a dose schedule, the factors most relevant are the primary pharmacological activity and half-lives of both the parent drug and its metabolites. At times, because of the potent secondary pharmacology of the drug (responsible for its toxicity), there may be a compelling need for a very shallow dose titration schedule. Two good examples of drugs requiring gradual upward titration are pimozide and sertindole.

Pimozide is an effective neuroleptic agent that has been on the market since 1971. It has a long mean half-life of approximately 55 h in most individuals. This is highly variable and may be as long as 150 h in some patients. When first approved, its starting dosage was 2 to 4 mg/day with a slow upward titration to a maximum dosage of 10 mg/day. Subsequently, the slow titration schedule was removed, the starting dosage increased to 20 mg/day and the maximum dosage was increased to 60 mg/day. Following reports of QTc interval prolongation and torsade de pointes (TdP), the recommended dosing schedule for patients with chronic schizophrenia was amended to a starting dosage of 2 mg/day. Subsequent

titration was to be slow and shallow, with increases of 2 to 4 mg in the daily dose being made at weekly intervals or longer. The maximum dosage was reduced from 60 to 20 mg/day. In 1981, trials investigating the use of pimozide in schizophrenia in the USA had to be suspended following the sudden deaths of two patients during acute titration of pimozide to 70 to 80 mg/day.[5] In the USA, pimozide is not approved for use in schizophrenia; it was approved in 1984 only for use in Tourette's syndrome.

Sertindole is one of the relatively new, atypical antipsychotic agents. It was introduced onto the market in 1995. It has powerful α-adrenoceptor–blocking activity and an acute administration of a single dose of 8 mg or more can result in marked orthostatic hypotension. Initiation of therapy with sertindole, therefore, requires a starting dosage of 4 mg/day. Sertindole is metabolized by the cytochrome P450 enzyme CYP2D6 and exhibits a high interindividual variability of metabolism. Its half-life ranges from 60 to 100 h, and a given dose requires well over 10 days for steady-state plasma concentration to be reached. Therefore, the dosing scheme approved requires that the dose should be increased in 4 mg increments after 4 to 5 days on each dose to the optimal maintenance dosage range of 12 to 20 mg/day. Depending upon individual patient response, the dosage may be increased to a maximum of 24 mg/day. Patients' blood pressure should be monitored during the period of dose titration and during the early part of maintenance treatment. The dosing section warns, *"A starting dose of 8 mg or a rapid increase in dose carries a significant risk of severe hypotension."* Despite its otherwise favorable profile in terms of extrapyramidal side effects, this shallow dose titration renders the drug worthless for use in acute situations.

In one study, all 499 labels of drugs approved by the US Food and Drug Administration (FDA) between 1 January 1980 and 31 December 1999 were examined for significant dose changes.[6] Time- and covariate-adjusted risks for dosage changes by 5-year epoch and therapeutic groups were estimated by survival analysis. Of the 499 NCEs, 354 (71%) were evaluable. Dosage changes in indicated populations occurred in 73 NCEs (21%). A total of 58 (79%) were safety-motivated, net dosage decreases. The percentage of NCEs with changes by therapeutic group ranged from 27.3% for neuropharmacologic drugs to 13.6% for miscellaneous drugs. Median time to change following approval fell from 6.5 years

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(1980-1984) to 2.0 years (1995-1999). 1995-1999 NCEs were 3.15 times more likely to change in comparison to 1980-1984 NCEs (P=0.008, Cox analysis).

When developing new antipsychotic agents, therefore, it is advisable that the dose-finding phase 2 studies explore a range of doses from 25% to at least 200% of the likely dose, and then proceed to the pivotal phase 3 studies with at least two doses. The ICH guideline on "Dose-Response Information to Support Drug Registration"[7] describes how helpful is the knowledge of the shape of individual dose–response curves, and it distinguishes these from the population curve. The guideline clearly cautions:

"Choice of a starting dose might also be affected by potential intersubject variability in pharmacodynamic response to a given blood concentration level, or by anticipated intersubject pharmacokinetic differences, such as could arise from nonlinear kinetics, metabolic polymorphisms or a high potential for pharmacokinetic drug–drug interactions"

and recommends that in utilizing dose–response information, the influences of various demographic features, individual characteristics (including metabolic differences), and concurrent drugs and diseases should be identified as far as possible.

The dosing scheme should identify the unit dose, daily frequency of administration, maximum daily dose, and the dose titration schedule. The influence of pharmacogenetics in determining the optimal dose for a subgroup of patients, discussed below, may have to be explored and justified in the regulatory submission.

Pharmacogenetic influences on drug response

The two components of a dose–response curve—pharmacokinetics and pharmacodynamics—are both subject to high interindividual variability. Although a number of factors such as age, gender, presence of comorbidity, and administration of comedications may modulate these two components, they are under powerful genetic influences. These genetic influences act by regulating the expression of drug-metabolizing enzymes (pharmacokinetic variability) or the function of various pharmacological targets (pharmacodynamic variability). The presence of variant alleles often exerts influences that far exceed those due to the other factors. It is therefore not surprising that the safety and efficacy of some drugs in an indi-

vidual patient are often determined largely by the genetic profile (genotype) of the patient.

With the completion of the Human Genome Project and advances in biotechnology, which promise the prospects of characterizing genetic variations in individual patients rapidly and cheaply, expectations are rising that therapy individualized on the basis of a patient's genotype may become a reality within the next few years. The application of pharmacogenetics during drug development and regulatory evaluation has gathered momentum as a result of this anticipated revolution in therapeutics over the course of next decade. Arising from these genetically driven interindividual differences in pharmacology, areas of new drug applications that are likely to attract close regulatory scrutiny include the investigation of genetic influences on dose–response relationships and the recommended dose schedules.

The genetic polymorphism most thoroughly characterized and also directly relevant to the use of neuroleptic drugs is that of drug-metabolizing enzyme, CYP2D6. Although CYP2D6 accounts for only 2% of the total liver cytochrome P450 content, it is responsible for the metabolism of well over 20% of the drugs eliminated by metabolic clearance.[8] It has been shown to control the oxidative biotransformation of well over 60 drugs to date, which include antiarrhythmics, β-blockers, antihypertensives, antianginals, neuroleptics, antidepressants, and analgesics, as well as a number of other miscellaneous drugs.[8,9] Similarly, clinically relevant polymorphisms have also been described for other drug-metabolizing enzymes such as cholinesterase, *N*-acetyltransferase (NAT2), dihydropyrimidine dehydrogenase (DPD), CYP2C9, CYP2C19, and thiopurine methyltransferase (TPMT). However, these seem to be far less important for neuroleptic drugs.

Studies over the last 25 years have shown that, depending on their ability to mediate CYP2D6-dependent hydroxylation of the antihypertensive drug debrisoquine, a given population may be divided into two phenotypes: extensive metabolizers (EMs) or poor metabolizers (PMs).[10] This polymorphism results from autosomal recessive inheritance, in a simple Mendelian fashion, of alleles at a single locus mapped to chromosomal region 22q13.1. Individuals heterozygous for the defective allele are EMs with some impairment in effecting this reaction, indicating a gene–dose effect. Some phenotypically EM individuals inherit alleles (eg, CYP2D6*10 and CYP2D6*17), which express enzyme with reduced or altered affinity for certain

CYP2D6 substrates.[11,12] Within the EMs, there is another subgroup, termed the ultrarapid metabolizers, resulting from multiple copies of the gene for normal metabolic capacity.[13] The CYP2D6 gene is extremely polymorphic with more than 70 allelic variants described so far.[14]

Pharmacokinetic parameter	Consequences for the PM relative to the EM
• Bioavailability	2- to 5-fold
• Systemic exposure	
Cmax	2- to 6-fold
AUC	2- to 5-fold
• Half-life	2- to 6-fold
• Metabolic clearance	0.1- to 0.5-fold

Table I. Pharmacokinetic consequences of the drug-metabolizing enzyme CYP2D6 polymorphism. PM, poor metabolizer; EM, extensive metabolizer; Cmax, peak concentration; AUC, area under the curve.

The pharmacokinetic consequences of CYP2D6 polymorphism, shown in *Table I*, are that, relative to EMs, the PMs experience far greater exposure to the parent drug,[15] while the reverse is true for the metabolites generated by this enzyme. Ultrarapid EMs metabolize CYP2D6 substrates so fast that, even at the usually recommended doses, they are exposed to rapidly accumulating levels of metabolites and manage to attain only very low plasma levels of the parent drug. The importance of this polymorphism arises from the fact that the substrates of CYP2D6 are typically the cardiovascular and psychoactive drugs, most of which have a narrow therapeutic index and are usually intended for long-term administration.

Table II summarizes the clinical consequences of CYP2D6 polymorphism. It has been shown that PMs are at risk of a number of side effects of drugs that are primarily metabolized by CYP2D6. In contrast, many EMs, including ultrarapid metabolizers, are at risk of exaggerated pharmacological effects of the metabolite and much

Clinical consequences for the PM	
• *Increased risk of toxicity*	
Debrisoquine	Postural hypotension and physical collapse
Sparteine	Oxytocic effects
Perphenazine	Extrapyramidal symptoms
Flecainide	Ventricular tachyarrhythmias?
Perhexiline	Neuropathy and hepatotoxicity
Phenformin	Lactic acidosis
Propafenone	CNS toxicity and bronchoconstriction
Metoprolol	Loss of cardioselectivity
Nortriptyline	Hypotension and confusion
Terikalant	Excessive prolongation in QT interval
L-Tryptophan	Eosinophilia-myalgia syndrome
Indoramin	Sedation
Thioridazine	Excessive prolongation in QT interval
• *Failure to respond*	
Codeine	Poor analgesic efficacy
Tramadol	Poor analgesic efficacy
Opiates	Protection from oral opiate dependence
Clinical consequences for the ultrarapid EM	
• *Increased risk of toxicity*	
Encainide	Proarrhythmias?
Codeine	Morphine toxicity
• *Failure to respond*	
Nortriptyline	Poor efficacy at normal doses
Propafenone	Poor efficacy at normal doses

Table II. Clinical consequences for poor metabolizer (PM) and ultrarapid extensive metabolizer (EM) phenotypes of the drug-metabolizing enzyme CYP2D6. CNS, central nervous system.

attenuated effects of the parent drug. CYP2D6 polymorphism has efficacy implications as well. PMs are at a risk of lack of efficacy when the therapeutic effect of a drug is mediated principally by its CYP2D6-generated metabolite.

The CPMP guideline[16] on "Pharmacokinetic Studies in Man" has included direct references to genetic factors for well over 15 years now! This guideline requires that metabolic studies should indicate whether the metabolism of a drug may be substantially modified in case of genetic enzyme deficiency and whether within the dose levels normally used, saturation of metabolism may occur, thereby resulting in nonlinear kinetics. It is therefore self-evident that if a new antipsychotic drug under development is found to be metabolized by an enzyme that is polymorphic, every attempt should be made during its development to determine whether the clinical response to it—therapeutic or toxic—is determined or heavily influenced by genetic factors. In this context, it may be noted that there is some concern arising from the evidence that clinical trial population may be biased by an inappropriate underrepresentation (or even absence) of specific genotypes, usually the PMs.[17,18] Others have argued for prescreening genotyping of subjects with a view to actively excluding specific genotypes from clinical trials.[18]

A wide range of neuroleptic drugs are metabolized by CYP2D6. However, studies investigating the relationship between CYP2D6 phenotype or genotype and response to these drugs have provided ambiguous evidence on the utility of genotyping patients to predict drug response. The author of this paper analyzed 17 studies published between 1995 and 2000, which had included over 1350 patients receiving a range of neuroleptic drugs (R. Shah, manuscript in preparation). These studies investigated the association between CYP2D6 genotype and drug levels, failure to respond beneficially, and frequency and severity of a number of adverse reactions (neuroleptic malignant syndrome, extrapyramidal symptoms [EPS], and TD). Relationship with plasma concentrations was shown for drugs with dominant CYP2D6-mediated metabolism, but large intragenotypic variability tended to obscure its clinical value. However, there was no relationship reported for failure to respond beneficially. There was a general modest trend observed towards a positive correlation between the genotype, especially the presence of *10 allele in the Japanese, and severity of TD and EPS. This discouraging finding is hardly surprising,

since many antipsychotic agents are metabolized by multiple pathways and many have active metabolites. It is, however, acknowledged that these studies were highly heterogeneous, investigating a variety of drugs, regardless of the pharmacokinetics, pharmacodynamics, and pharmacokinetic/pharmacodynamic relationships of the drugs and their metabolites. Dahl has recently reviewed the relevance of CYP2D6 and other genetic polymorphisms of drug-metabolizing enzymes in relation to clinical response to antipsychotic therapy,[11] reaching essentially the same conclusion as this author. Another important area of interest in pharmacogenetics has focused on candidate genes of the pharmacological targets that play a role in susceptibility to TD. Four published studies have investigated an association between a Ser9Gly polymorphism in exon 1 of the dopamine D_3 receptor gene (*DRD3*) and TD; three failed to show an association and one found an insignificant trend. Lerer et al[19] examined this association in a pooled sample of 780 patients (317 with TD and 463 without TD). Their findings support a small but significant contribution of the *DRD3* Ser9Gly polymorphism to TD susceptibility, which is demonstrable over and above population effects and the effect of age and gender on the phenotype.

Arising from the globalization of drug development programs, the global heterogeneity in the frequencies of various variant alleles in different populations has become an important regulatory issue. The ICH guideline[20] on "Ethnic Factors in the Acceptability of Foreign Clinical Data" recommends evaluation of the clinical trials data from one region or population for their extrapolation to another region or population. To this end, it is recommended that the submission should include (i) adequate characterization of pharmacokinetics, pharmacodynamics, dose–response, efficacy, and safety in the population of the foreign region; and (ii) characterization of pharmacokinetics, pharmacodynamics, and dose–response in the new region. The guideline recognizes the role of genetic factors and the slope of the dose–response curve in determining whether the drug is likely to show significant ethnic differences during clinical use. When interethnic differences are anticipated, bridging studies may be required.

Proarrhythmic effects of neuroleptics

The QT interval of the electrocardiogram (ECG) reflects the duration of the ventricular action potential. It is pro-

longed when there is delayed repolarization due to a reduction in outward potassium current during phases 2 and 3 of the action potential. The delayed rectifier potassium channel (IKr) is primarily responsible for mediating this repolarizing current. Four HERG (human ether-a-go-go) α-subunits assemble with miRP1 β-subunits to form IKr. In in vitro studies, blockade of HERG is predictive of the blockade of IKr. Almost all drugs (including the neuroleptics) that prolong the QT interval do so by blocking this channel. This action, when exerted in a carefully controlled manner, is the primary pharmacological mechanism by which class III antiarrhythmic drugs exert their therapeutic effect. However, QT interval prolongation, when excessive, can be proarrhythmic and can degenerate into TdP, a unique form of polymorphic ventricular tachycardia.[21] Apart from clinical manifestations resulting from impaired circulation, TdP is potentially fatal. TdP subsequently degenerates into ventricular fibrillation in about 20% of cases[22] and, not uncommonly, cardiac arrest and sudden death may be the outcome.[23] The overall mortality from TdP is of the order of 10% to 17%.[22,24] Drug-induced prolongation of QT interval is, therefore, a highly undesirable pharmacological effect as far as nonanti-arrhythmic drugs are concerned. Clinically, a number of antianginal drugs as well as noncardiovascular drugs have been shown to possess this concentration-related undesirable pharmacological activity. There are now well over 10 antianginal and 100 noncardiac drugs that have been reported to significantly prolong the QT interval and/or induce TdP.[25] Unfortunately, neuroleptic drugs feature prominently in this list. In a survey of 2194 cases of TdP in the FDA database recorded from 1969 to 1998, psychoactive drugs were held culpable in 21.9% of cases.[24] Of these 2194, 11.7% were associated with drug interactions and a further 9.2% with overdoses. Haddad and Anderson have also recently reviewed the data on antipsychotic-related QTc interval, TdP, and sudden death.[26] Patients prescribed moderate doses of antipsychotics have large relative and absolute increases in the risk of sudden cardiac death. Data from one large retrospective Medicaid study suggest that the potential adverse cardiac effects of antipsychotics are significantly greater in patients with cardiovascular disease.[27]

It is recognized that QT interval prolongation per se is not necessarily harmful. It is only harmful when the prolongation is excessive enough to degenerate into TdP. The proarrhythmic threshold for QTc interval is close to 500 ms and the risk of induction of TdP bears an exponential

relationship to the degree of prolongation above this threshold. The link between QT interval prolongation and TdP is complex and influenced by many other factors.[25] Myxedema is also associated with prolongation of QT interval, but this is not a disease that one typically associates with TdP! Not all the drugs prolonging the QT interval, or blocking the outward repolarizing potassium current to the same extent, carry the same torsadogenic risk. Drugs such as amiodarone and racemic sotalol prolong the QT interval, but their torsadogenic potential is nowhere near as high as one might anticipate. Notwithstanding, QT interval is the best surrogate marker we currently have for TdP that, by definition, is associated with and follows concurrent prolongation of the QT interval. The level of risk varies with each neuroleptic, with thioridazine being highly torsadogenic. Although ziprasidone has been shown to block the HERG channel in vitro and prolong the QTc interval in vivo in man, there have been no reported cases of TdP associated with its clinical use to date. A fuller picture will only emerge following its wider use. Other ancillary pharmacological properties of these drugs, particularly autonomic effects, no doubt, modulate their torsadogenic risk. While (+)-(S)-sotalol is highly torsadogenic, racemic sotalol is much less so because of the β-blocking activity of (-)-(R)-sotalol in the racemic drug.[28,29] Sertindole too markedly prolongs the QT interval, but its powerful α-adrenoceptor (and possibly calcium channel)–blocking activity seems to offer a relative protection against the development of TdP. In one study of 1444 patients receiving a mean (SD) daily dose of 13.4 (5.6) mg sertindole, there were 15 reports of QTc interval prolongation with no cases of TdP.[30]

The risk is further modified by a number of other factors such as bradycardia, diminished basal repolarization reserve (as in congenital QT interval prolongation syndromes), cardiac disease, or electrolyte imbalance. In one study of 313 schizophrenic men, admitted on an emergency basis during a 24-month period, serum potassium concentration in the severely agitated group was lower than that in the mildly affected group. There was a significant inverse correlation between serum potassium concentration and the level of symptoms of acute agitation. Improvement in serum level following sedation correlated with baseline acute agitation.[31] An association is documented between hypokalemia and acute psychotic decompensation in a patient with chronic schizophrenia.[32] Some recent clinical studies also indicate that hypokalemia is a

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characteristic feature in acute psychotic patients at the time of emergency admission. Since hypokalemia is one of the major causes of prolonged QT interval and TdP, it was not surprising to find that in 67 drug-free acute psychotic patients, the mean QTc interval was prolonged. The mean QTc interval of psychiatric emergency patients was longer than that of psychiatric outpatients. As psychiatric emergency patients often receive *parenteral* antipsychotics, it is evident why the QT-prolonging activity of a new neuroleptic agent should be thoroughly characterized.[33]

Mutations of potassium channels, resulting in diminished repolarization reserve and increased pharmacodynamic susceptibility to QT prolongation, are common. There is now a wealth of evidence that, in view of the low penetration of many of these mutations, the size of population with mutations of potassium channels may be substantially larger than that diagnosed by ECG recording alone. Relatively large numbers of individuals who carry these "silent" mutations of long QT syndrome genes have been identified.[34] They have a diminished repolarization reserve, but a normal ECG phenotype. They are nevertheless at an increased proarrhythmic risk, often developing TdP at therapeutic doses. It has been postulated that drug-induced long QT syndrome might represent a genetically mediated forme fruste of the long QT syndrome.

Furthermore, any cardiac disease-induced downregulation of potassium channels will also increase this susceptibility to proarrhythmias. Female gender is a particularly striking example of genetically conferred susceptibility. In view of the potentially fatal outcome (even when TdP follows the use of antiarrhythmic drugs), the regulatory focus on the effect of drugs on QT interval has shifted dramatically from one of a beneficial antiarrhythmic mechanism to that of a highly undesirable pharmacological activity. Given the wide range of drugs from diverse chemical and pharmacotherapeutic classes that are known to be associated with potential to prolong the QTc interval, it is important that all NCEs are characterized, during preclinical and clinical development, for their effect on cardiac repolarization. In December 1997, the CPMP adopted two documents of considerable significance for the development of neuroleptic drugs.

One of these was the CPMP document "Points to Consider: The Assessment of the Potential for QT Interval Prolongation by Noncardiovascular Medicinal Products."[35] This describes the preclinical and clinical trial strategy for investigation of drugs for their potential to prolong the QT interval. Clinical trials designed to inves-

tigate the QT liability of an antipsychotic agent are a major challenge in drug development. This is largely because QTc interval shows considerable spontaneous intraindividual variability and is susceptible to a number of nonpharmacological influences.

Healthy volunteer studies are the first to be undertaken during clinical development and are more robust when of crossover design. The doses used in healthy volunteer studies should be reasonable multiples of the likely recommended dose (to ascertain its dose–effect relationship), in both the absence and presence of a metabolic inhibitor. Depending on the half-life of the drug, the study should be of an appropriate duration. It is prudent to include a positive control and the study should be appropriately powered to detect not only the difference in changes in mean QTc interval, but also the frequency of outliers as defined in the CPMP document (especially those with a QTc interval of ≥500 ms or those with an increase in QTc interval of ≥60 ms from baseline). The QT interval should be carefully measured by blinded readers and the values corrected for changes in heart rate by not only the traditional Bazett's correction, but also the Fridericia correction and, if practical, by a study-specific correction formula.

Although these studies are conducted in healthy volunteers, ECGs should also be rigorously monitored in all patients in phase 2 studies and in a substantial number in phase 3 studies. The demography of these patients in terms of age, gender, comedications, and comorbidity should be representative of the ultimate target population.

The data from these clinical studies must be interpreted collectively together with preclinical in vitro and in vivo data.[25] It is important that the regulatory submission package addresses the issues on the roles of dose schedules, metabolites, stereoselectivity in cardiotoxicity, comedications (drug interactions), comorbidity, pharmacogenetic factors, and if relevant, product formulation.

Drug interactions and neuroleptics

A number of drugs such as terfenadine, astemizole, pimozide, cisapride, and others have the propensity to prolong the QT interval and induce TdP and other proarrhythmias, more often (but not always) as a result of drug interactions. Therefore, the other significant document adopted by the CPMP was its "Note for Guidance on the Investigation of Drug Interactions."[36]

During concurrent administration of a drug with its metabolic inhibitor to a normal EM, there follows the pharmacokinetic (and often pharmacodynamic) consequences that are usually observed in the PM genotype. For example, inhibition of CYP2D6 (eg, by administration of quinidine, a potent CYP2D6 inhibitor) in a normal EM genotype converts the subject into a PM phenocopy, predisposing the individual concerned to developing high plasma concentrations of, and a much greater systemic exposure to, the substrate parent drug. Apart from quinidine, a large number of other drugs are also known to inhibit CYP2D6. Among the most powerful inhibitors of CYP2D6 are fluoxetine,[37] other selective serotonin reuptake inhibitors,[38] and moclobemide.[39] The inhibition of CYP2D6 by these popular drugs is critical, given that typical substrates of CYP2D6 are cardiovascular and psychoactive drugs with narrow therapeutic index and most likely to be coprescribed to the elderly. Furthermore, one substrate of CYP2D6 may inhibit the metabolism of another CYP2D6 substrate through competition for the drug-metabolizing site. Similarly, inhibition of other cytochrome P450 enzymes by their corresponding inhibitors results in functional PMs of the metabolic pathways mediated by those enzymes. One inhibitor may inhibit more than one cytochrome P450 enzyme.

Just as administration of an inhibitor to an EM genotype converts the subject into a PM phenocopy, the administration of an inducer to a normal EM produces a phenocopy of an ultrarapid EM. Induction is usually not a feature of CYP2D6, but it is most evident with CYP3A4. Drugs such as rifampicin, phenytoin, and other anticonvulsants are powerful inducers of CYP3A4. Induction results in rapid elimination of the parent drug and rapidly accumulating metabolites. Metabolites of drugs can at times be even more powerful and/or unexpected inhibitors.

Drug interactions are probably more frequent than one might realize. It is estimated that adverse reactions, drug interactions, and contraindications account for 55.8%, 9.0%, and 5.8%, respectively, of all safety-related changes to product particulars during the postapproval period of a drug. However, it is estimated that 6.9% to 22% of adverse drug reactions are in fact due to drug interactions. One investigation from Sweden studied the CYP2D6 genotype on postmortem femoral blood from 22 cases in whom there was unexpectedly high ratio of parent drug to metabolite. None was found to be a geno-type PM. Clearly, this high ratio of parent drug to metabolite had resulted from inhibition of metabolism due to drug interactions. In contrast, there was 1 PM among the 24 other cases serving as controls (representing a PM frequency of 4.2% in this control population versus the general population frequency of 4% to 5% PMs).

Drug interactions are of particular concern for drug classes with a narrow therapeutic index or for drugs known to modulate the activity of drug-metabolizing enzymes. Consequently, there are certain major pharmacotherapeutic classes of drugs involved in clinically significant drug interactions. One survey found that cardiovascular (40%), gastrointestinal (16%), neurological (15%), hemopoietic (14%), respiratory (3%), and anti-infective (3%) drugs were the major therapeutic classes involved in drug interactions. There is little doubt that drug interactions are on the increase. A number of factors account for this rise.

In the context of neuroleptic therapy, the foremost is the extent of polypharmacy. In one survey among subjects with schizophrenia,[40] an average number of 1.54 neuroleptics were prescribed per patient, compared with 1.4 and 1.2 in other psychotic and depressed subjects, respectively. Regardless of the indication, nonneuroleptic psychotropic drugs were coprescribed in 75.4% of cases, mainly benzodiazepines (75.7%). Adjuvant drugs used in prevention or treatment of side effects were coprescribed in 46.7%, mostly anticholinergic drugs against parkinsonism (86.1%). The main finding of another survey was that 27.5% of patients with schizophrenia were discharged on an antipsychotic polypharmacy regimen. The investigators concluded that although antipsychotic polypharmacy persists today, as it has over the past 30 years, evidence-based data to support this controversial treatment strategy are lacking.[41] On the basis of their multinational study in inpatients with schizophrenia, Kiivet et al[42] concluded that polypharmacy with concomitant multiple neuroleptics, additional anticholinergic drugs, and other psychotropics is an international phenomenon. At least two neuroleptics were prescribed simultaneously on 73% of treatment days in Badajoz (Spain) and 46% in both Huddinge (Sweden) and Tartu (Estonia).

The issue of drug interactions is intricately linked with pharmacogenetics. Since PMs do not have any functional enzyme to inhibit, they are unlikely to display a pharmacokinetic interaction. Likewise, the probability of an

interaction is low in those with a high metabolic capacity such as those who are homozygous extensive or ultra-rapid metabolizers. These individuals have high functional reserve and therefore, high (almost toxic) doses of inhibitors may be required for adequate inhibition. The subjects most likely to display an interaction are those with compromised metabolic capacity (heterozygous EMs). This genotype-dependent response accounts for the recommendation in the CPMP guidance note[36] that subjects enrolled in drug–drug interaction studies should be genotyped.

The data from drug interaction studies should be presented not only in terms of the mean changes, but also in terms of each individual. Data should also be presented on metabolites and enantiomers when measured. The significance of the changes observed should be considered in terms of their clinical relevance—notwithstanding any statistical significance of these changes—bearing in mind the dose–concentration–response curves. Recommendations for labeling should be formulated in light of these considerations.

Evaluation of approvability and labeling implications

It is most unlikely that any neuroleptic NCE, however unique, will be approved these days unless its regulatory submission includes adequate studies—preclinical and clinical—characterizing the potential of the NCE to prolong the QT interval. The strategy recommended for investigating this potential is described in the CPMP document referred to earlier.[35]

Once it is concluded that the drug is likely to significantly prolong the QTc interval at clinically relevant concentrations, the approval of the drug depends on a number of factors. These include the potency and the frequency of the QTc prolongation by the drug, the likely proarrhythmic risk, the therapeutic indication supported by the data, the susceptibility of the target population to proarrhythmias, its overall safety profile, and the therapeutic benefit conferred by the NCE.[43] Availability of alternatives with superior risk/benefit ratio is also an important determinant of the approvability of the NCE concerned. The careful balance of risk and benefit leading to the approval of a drug with a serious adverse drug reaction is best illustrated by clozapine. The efficacy of clozapine in patients who had failed to respond to other drugs was sufficiently compelling that, despite a relatively

high frequency of myelosuppression associated with its use, it was approved, subject to regular hematological monitoring of the patient.

Labeling restrictions

It is not inconceivable that despite its potential to prolong the QT interval, a nonantiarrhythmic NCE may be approved, provided a carefully planned clinical development program has identified a population in whom the benefits of the drug can be shown to outweigh the small potential risk of proarrhythmias or the drug can be shown to fulfil an unmet need. For such drugs, the prescribing information (known as the summary of product characteristics "SPC" in Europe and "labeling" in the USA) would require careful crafting of the indication to reflect the population and the disease entity most likely to benefit as well as detailed information on the proarrhythmic risk with carefully selected dose regimen, appropriate contraindications, description of interactions, special precautions, and monitoring requirements during their clinical use.[43]

Reflecting the robust data on efficacy, restriction of an indication may be one way of minimizing the population likely to be exposed to the NCE. Allied to the indication is the posology of the NCE. The posology section may be required to include information on starting dose, a shallow dose titration schedule depending on the half-life of the drug and the time required to reach steady state, maximum single dose, maximum daily dose, and the duration of therapy.

The most recent example of restriction of indications is thioridazine. From July 2000, the indication for thioridazine in the US was amended by the FDA to state:

"Thioridazine is now indicated only for schizophrenic patients who fail to show an acceptable response to adequate courses of treatment with other antipsychotic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects. Thioridazine has not been systematically evaluated in controlled trials in treatment-refractory schizophrenic patients and its efficacy in such patients is unknown."

In view of the long half-life of pimozide (55 h, but may be as high as 150 h in some), its dose schedule was revised to recommended a starting dosage of 20 mg/day with a maximum dosage of 60 mg/day. Following reports

of TdP and other ventricular arrhythmias, the dose schedule of pimozide for chronic schizophrenia was re-amended to recommend an initial starting dosage of 2 mg/day (exceptionally 10 mg/day in acute schizophrenia, but even this recommendation too was subsequently removed). The dose was to be increased by a shallow dose titration (*"dose increases should be made at weekly intervals or longer, and by increments of 2-4 mg in the daily dose"*). The maximum dosage was reduced from 60 to 20 mg/day.

The section of the SPC most likely to be effective in containing a clinical risk, if the prescribing physicians adhere to it, is that on contraindications. In view of the many pharmacological properties commonly shared by these QT-prolonging drugs and the common features associated with drug-induced TdP, it is not surprising that a standard set of contraindications have evolved over time. These include those related to the pharmacokinetics of the drug (comedication with inhibitors of the metabolism of the drug and patients with hepatic and/or renal dysfunctions) and those related to enhanced susceptibility to the undesirable pharmacodynamic effect of the drug on cardiac repolarization (predisposition to hypokalemia, bradycardia, cardiac disease, and/or arrhythmias, preexisting prolongation of QT interval, and comedication with other QT-prolonging drugs).

Specific contraindications may also be applied to suit particular drugs. For example, since thioridazine is metabolized by CYP2D6, it was determined that *"thioridazine is also contraindicated in patients known to have reduced levels of cytochrome P4502D6."* Sertindole too is metabolized by CYP2D6, but in PMs of CYP2D6, an alternative pathway of elimination is that mediated by CYP3A4. Since PMs of CYP2D6 may not be routinely identified in clinical practice, it was considered essential that sertindole was contraindicated with inhibitors of CYP3A4 generally in order to specifically protect the PMs.

Special warnings and precautions may be required with regard to the use of a QT-prolonging NCE in special populations, such as patients with cardiac disease, the elderly, or patients receiving diuretics and other relevant drug classes. Statements may also be required on special monitoring requirements. These may include ECG recordings pretreatment and periodically while the patient is on treatment. Pimozide, once again, illustrates the case well. ECG monitoring is recommended at baseline, annually, and (even more frequently) in those patients receiving pimozide in excess of 16 mg/day. A

review of the need to continue treatment with pimozide is recommended in those showing certain specified ECG changes. The US labeling of thioridazine also requires serum potassium levels to be measured and normalized before starting treatment. It is also recommended that patients with a QTc interval greater than 450 ms should not receive thioridazine. It is further advised that periodic monitoring of ECGs and serum potassium levels during thioridazine treatment may be useful and thioridazine should be discontinued in patients who are found to have a QTc interval over 500 ms.

The interaction section of pimozide, for example, describes pharmacodynamic interactions associated with comedications, such as neuroleptics, risk of diuretic therapy, drugs that prolong the QT interval, drugs with arrhythmogenic potential (antidepressants, antiarrhythmics), its CYP3A4- and CYP2D6-mediated metabolic profile (including in vitro data) and the consequences of the concurrent use of the inhibitors of its metabolism. The labeling of sertindole includes an elaborate drug interactions section describing its metabolism by CYP2D6 and CYP3A4 and the probable interactions at these loci.

The undesirable effects section should include details of the QTc interval changes and arrhythmias observed in clinical trials and, if appropriate, clinical manifestations of these arrhythmias. Statements on the magnitude of the risk, risk factors, and course of action in the event of an arrhythmia may also be required if the information is available. The US labeling of perphenazine includes a reminder of the potential value of pretreatment genotyping of the elderly patients for their CYP2D6 status with a view to identifying those at high risk of adverse effects.

Finally, the overdose section should include information on acute toxicity experience in animals, any observations during clinical trials, dose for proarrhythmic risk, duration of risk, special clinical manifestations, monitoring recommendations, measures to reduce systemic exposure, and the role of dialysis.

Effectiveness of prescribing restriction

An important question in approving the drugs with "QT liability," even with a restrictive labeling, is how effective these prescribing restrictions are in containing the risk of potentially fatal TdP. Recent experiences with terfenadine and cisapride are not very encouraging.[44-46] It is also

questionable whether the patients will be appropriately monitored. It is remarkable how few patients receiving even high doses of antipsychotic agents are being monitored by ECGs as recommended in the prescribing information.[47] In evaluation of the proarrhythmic risks of a QT-prolonging drug during its routine clinical use and its approval, it has now become essential also to consider whether the prescribing information, however restrictive, is practical and likely to be adhered to.

Conclusions

The development of safe and effective new drug treatments for schizophrenia poses a challenging task. This class of drugs have a wide range of serious and troublesome side effects and usually a narrow therapeutic index with active metabolites. These features make it imperative that the optimal dose schedules are carefully characterized during drug development. Advances in genomics have raised the expectations of individualized therapy. In terms of drug development, characterizing the dose and individualizing therapy is made more complex by the polymorphisms of enzymes that metabolize many of these drugs and their pharmacological targets. Many neuroleptic agents are proarrhythmic with an adverse effect on cardiac repolarization. They are prone to prolonging the QT interval and inducing potentially fatal TdP. This makes it imperative that all new neuroleptic agents are thoroughly explored for their proarrhythmic potential. The clinical use of many of these drugs is fraught with a high potential for drug–drug interactions, which should also be adequately investigated during their development. The approvability and the labeling of any new neuroleptic agent require a careful assessment of its risk/benefit ratio and that of available alternatives. Neuroleptic drugs, like other drugs, are approved on the understanding that the risks can be managed and contained effectively by their appropriate use and supervision of the patients. Patients require to be monitored as recommended for any cardiac electrophysiological effects and for other side effects. Provided the physician adheres to the prescribing information, neuroleptics may be used safely and effectively in routine clinical practice. ❏

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Desarrollo de agentes neurolépticos: farmacogenética y aspectos actuales de seguridad de importancia para las agencias reguladoras

El desarrollo de nuevos tratamientos con fármacos seguros y efectivos para la esquizofrenia implica una tarea desafiante. Se sabe que esta clase de fármacos se asocia con un amplio margen de serios y molestos problemas de seguridad que incluyen efectos neurológicos, cardíacos, endocrinos y metabólicos. Muchos de estos fármacos tienen un estrecho índice terapéutico y generan metabolitos que a menudo tienen un perfil farmacológico específico el cual difiere del compuesto madre. Estas características determinan en forma imperativa que los esquemas de dosis óptimas para los neurolépticos sean cuidadosamente individualizados. Muchos de estos fármacos son metabolizados por enzimas citocromo P450, las que tienen un polimorfismo genético y una distribución bimodal dentro de la población. Un subgrupo significativo de la población no puede eliminar estos fármacos en forma tan efectiva como la mayoría. Esto conlleva un aspecto adicional de complejidad al tener que caracterizar la dosis e individualizar la terapia. Muchos agentes neurolépticos son proarrítmicos, con un efecto adverso en la repolarización cardíaca. Ellos son proclives a prolongar el intervalo QT y a inducir "torsade de pointes." Dada la evolución potencialmente fatal de esta taquiarritmia ventricular, los programas de desarrollo de fármacos requieren asegurar que el potencial proarrítmico de cualquier nuevo agente neuroléptico sea completamente explorado y se caracterice su riesgo proarrítmico. El uso clínico de muchos de estos fármacos se complica además por su alto potencial de interacciones fármaco-fármaco. Esto también requiere ser adecuadamente investigado durante el desarrollo. La aprobación y rotulación de un nuevo agente neuroléptico requiere de una cuidadosa evaluación por las agencias de regulación de su relación riesgo-beneficio en comparación con las alternativas terapéuticas disponibles. Su empleo seguro y efectivo en la práctica clínica rutinaria depende de una atención cuidadosa a la información para prescribir, especialmente respecto a contraindicaciones, precauciones y requisitos de monitoreo del paciente.

Développement des neuroleptiques : pharmacogénétique et aspects réglementaires actuels concernant la sécurité d'emploi

Le développement de nouveaux traitements médicamenteux sûrs et efficaces pour la schizophrénie est un défi. Cette classe de médicaments est connue pour être associée à un large éventail de problèmes sérieux et gênants concernant la sécurité d'emploi tels que des effets indésirables neurologiques, cardiaques, endocriniens et métaboliques. Un grand nombre de ces médicaments ont un index thérapeutique étroit et génèrent des métabolites qui ont souvent leur propre profil pharmacologique original et différent de la molécule mère. Ces particularités imposent que les schémas posologiques optimaux soient soigneusement définis. Un grand nombre de ces médicaments sont métabolisés par les enzymes du cytochrome P450, qui montrent un polymorphisme génétique et une distribution bimodale dans la population. Un sous-groupe important de la population ne peut pas éliminer ces médicaments aussi efficacement que la majorité. Cela apporte une dimension supplémentaire dans la complexité pour déterminer la dose et personnaliser le traitement. Beaucoup de neuroleptiques sont arythmogènes avec un effet indésirable sur la repolarisation cardiaque et sont susceptibles d'allonger l'intervalle QT et d'induire des torsades de pointes. Étant donné l'issue fatale possible d'une telle tachyarythmie ventriculaire, les programmes de développement d'un médicament doivent garantir que le potentiel arythmogène de tout nouveau neuroleptique a été complètement exploré et ses risques arythmogènes définis. Par ailleurs, le risque élevé d'interactions médicamenteuses perturbe l'utilisation clinique d'un grand nombre de ces médicaments. Celles-ci doivent aussi être correctement explorées pendant le développement. L'approbation et l'étiquetage de conditionnement d'un nouveau neuroleptique demandent une évaluation réglementaire soigneuse du rapport bénéfice/risque à comparer aux choix existants. L'innocuité et l'efficacité en pratique clinique de routine des neuroleptiques dépendent de l'attention vigilante portée à l'information contenue dans leurs fiches signalétiques respectives, en particulier concernant les contre-indications, les précautions d'emploi et la surveillance du patient.

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