Chapter C

Withdrawal of Terodiline: A Tale of Two Toxicities

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INTRODUCTION

Apart from drug-induced prolongation of the QT interval, and its subsequent degeneration into torsade de pointes, it is difficult to think of another type of pharmacological adverse drug reaction that has been responsible for the withdrawal of so many drugs from the market over the last two decades. Withdrawal of prenylamine in 1988, followed by that of lidoflazine in 1989 and terodiline in 1991, was to herald a similar misfortune for many other drugs such as terfenadine, astemizole, cisapride, sertindole, grepafloxacin, droperidol, thioridazine and levacetylmethadol. A number of other drugs, such as pimozide, halofantrine, lumefantrine and mizolastine to name just four, had severe prescribing restrictions placed on their clinical use for similar reason, while others such as moxifloxacin, gatifloxacin and ziprasidone have had their approval greatly delayed in some Member States of the European Union (EU) because their ‘QT-liability’ was determined to adversely affect their risk–benefit ratio. Not surprisingly, many drugs have recently had their clinical development terminated, some at a fairly advanced stage, as a result of their potential to prolong the QT interval (Shah, 2002).

Withdrawal of terodiline has a number of important lessons for drug development and pharmacovigilance. Firstly, from a regulatory perspective, terodiline is almost too perfect an example of drugs whose more potent secondary pharmacological effects, observed as adverse drug reactions during their originally intended clinical uses, have led to their clinical re-development for completely different indications. In the case of terodiline, this concerned its potent anticholinergic side effect observed during its approved use as an antianginal agent. Terodiline illustrates how such a strategy can be eclipsed by the virulent appearance of additional secondary pharmacological effects that are not fully explored. With terodiline, this additional activity was its adverse effect on cardiac repolarization and QT interval duration on the surface electrocardiogram (ECG). Indeed, terodiline might therefore be described as a ‘pharmaceutical boomerang’. It serves as a reminder of the limitations of drug development programmes in characterizing a relatively rare, but potentially fatal, clinical hazard. Secondly, it emphasizes both the perils...
of failing to appreciate the problems associated with other members of the same chemical, pharmacological or therapeutic class of drugs (prenylamine in the case of terodiline), and the necessity of applying all available techniques to characterize a potential class-related safety issue when developing a new drug. This is particularly unfortunate, since drug-induced QT interval prolongation is a concentration-dependent type A adverse drug reaction that can be investigated during preclinical and clinical phases of drug development, and therefore ought to be predictable. Finally, the post-marketing identification of the proarrhythmic risk associated with terodiline through a spontaneous reporting system emphasizes the strengths of systems such as the United Kingdom (UK) Yellow Card Scheme in comparison with formal post-marketing surveillance studies that had continued to assert its cardiac safety.

This chapter will focus on a comparison between terodiline and prenylamine with a view to providing a framework of some of the major issues that need to be considered when preparing the pre-marketing Safety Specification of a new drug, as required by the International Conference on Harmonization (ICH) E2E guideline, and discussing the potential risks that require further evaluation. In this context, it will also discuss the ICH E1A guideline on the clinical safety dataset required to assess the safety of medicines intended for chronic use, and the recently adopted ICH S7B and ICH E14 guidelines on pre-approval investigation of drugs for their potential to prolong QT interval.

Drugs-Induced QT Interval Prolongation and Pharmacovigilance Planning (ICH E2E)

The ICH E2E guideline on Pharmacovigilance Planning came into operation in the EU in June 2005, and is intended to assist in planning pharmacovigilance activities, especially in preparation for the early post-marketing period of a new drug (Anon, 2004). The guideline includes a section on Safety Specification that should be submitted at the time of marketing authorization application.

In the context of drug-induced proarrhythmias, the guideline recommends that the preclinical elements that should be considered for inclusion in the Safety Specification of a new drug are its potential to prolong the QT interval and for drug interactions.

The Safety Specification also requires a discussion on populations that have not been studied or have only been studied to a limited degree in the pre-approval phase. The implications of this with respect to predicting the safety of the product in the marketplace should be explicitly discussed. Among the populations to be considered are the elderly, those with relevant co-morbidity (such as hepatic or renal disorders), patients with disease severity different from that studied in clinical trials, those who carry known genetic mutations of relevant drug-metabolizing enzymes and/or pharmacological targets, and patients of different racial and/or ethnic origins.

In addition to providing a detailed account of important information that is missing from the regulatory submission, the Safety Specification requires a summary of the important risks identified to be associated with a drug, any important potential risks and outstanding safety questions which warrant further investigations during the post-approval period to refine an understanding of its risk–benefit profile. With regard to potential risks that require further evaluation, the evidence that led to the conclusion that there were (or might exist) these potential risks should be presented. It is anticipated that for any important potential risk, there will be a further (post-approval) evaluation of the drug to characterize the association.

The ICH E2E also emphasizes that the Safety Specification should identify risks believed to be common to the pharmacological class of the new drug concerned.

Re-Birth of Terodiline

Terodiline was first marketed in 1965 as an antiangiinal agent (‘Bicor’) in Scandinavia, a relatively small market (Wibell, 1968). This period of original marketing of terodiline in the 1960s is worthy of note because it antedates (a) any serious regulatory or clinical interest in drug-induced prolongation of the QT interval and (b) the first description of torsade de pointes as a unique
proarrhythmia associated with prolonged QT interval (Dessertenne, 1966). Moreover, the re-development of terodiline in the early 1980s coincided with increasing number of reports of QT interval prolongation and torsade de pointes in association with two other antianginal drugs, prenylamine (Picard, Auzepy and Chauvin, 1971; Oakley et al., 1980; Abinader and Shahar, 1983) and lidoflazine (Kaden and Kubler, 1977; Hanley and Hampton, 1983). These two drugs ceased to be available for clinical use in the UK – prenylamine in 1988 and lidoflazine in 1989.

Because of the potent anticholinergic properties of terodiline, urinary retention proved to be a frequent and troublesome side effect during its use as an antianginal agent. Terodiline was therefore re-developed in the early 1980s for clinical use in urinary incontinence due to detrusor instability. In isolated airway preparations from rats, terodiline had also been shown to block the bronchoconstrictor effect of acetylcholine. The shift in the acetylcholine dose-response curve induced by terodiline indicated that its anticholinergic property might also explain its observed ciliospasm and myotonic effect (Iravani and Melville, 1975). It is therefore not surprising that in the period intervening between these two indications, terodiline was also being investigated for use in chronic obstructive airways disease (Castenfors, Hedenstierna and Glenne, 1975), presumably in an attempt to harness the same, otherwise unwanted, pharmacological property observed during its use as an antianginal agent.

Terodiline was first introduced in the United Kingdom under the brand name of ‘Terolin’ (later changed to ‘Micturin’) in July 1986 for use in urinary frequency, urgency and incontinence in patients with detrusor instability and neurogenic bladder disorders. In the EU, it was also approved in Denmark, Ireland, Luxembourg, Belgium, the Netherlands, Spain and West Germany, but not in France, Greece, Italy or Portugal. Overall, the drug was approved in 20 countries worldwide and marketed in a number of these, but the major markets were the UK, Sweden and Japan. The recommended dose in the United Kingdom was 12.5–25 mg twice daily in young adults and otherwise healthy elderly patients, but 12.5 mg twice daily in frail elderly patients. In general, the doses used in Sweden were lower than those used in the United Kingdom, and the dose approved in Japan was half the UK recommended dose.

**TERODILINE-INDUCED PROARRHYTHMIAS**

One of the earliest suspicions of the proarrhythmic potential of terodiline arose from the sudden unexpected death of a previously healthy 20-year-old man, following an overdose in 1987 (Cattini et al., 1989). Forensic toxicological analysis revealed the presence of a very high blood level of terodiline. His blood and urine levels were greater than 10 µg/mL. No other drugs or metabolites of terodiline were detected. At post-mortem, his organs did not reveal any natural disease. Although the death was suspected to have followed inhalation of vomitus, the probability of a proarrhythmic event preceding aspiration could not be excluded. Although the maximum steady-state serum concentrations of terodiline following 10–15 days of continuous twice-daily dosing with 25 mg are of the order of 0.5 ± 0.23 µg/mL, peak serum concentrations following single oral doses of 12.5 and 25 mg are only 0.066 and 0.105 µg/mL respectively. Based on this kinetics, Boyd (1990) has estimated that this patient might have ingested close to 168 tablets (of 12.5 mg each) as a single dose.

The first proarrhythmic reactions to clinical doses of terodiline were also reported to have occurred in 1987, when there was one case of ventricular tachycardia and one of bradycardia. These reports were followed by an additional one report each of these two reactions in 1988. Following its post-approval routine clinical use, the first three reports of torsade de pointes in association with terodiline were notified to the marketing authorization holder during 1988 and 1989, and the fourth report in 1990 (Wild, 1992). Beginning in early 1991, additional reports of QT interval prolongation and torsade de pointes began to appear (Andrews and Bevan, 1991; Connolly et al., 1991; Davis, Brecker and Stevenson, 1991; McLeod, Thorogood and Barnett, 1991). These events, reported individually to the Medicines Control Agency (MCA, the competent UK authority that preceded the current Medicines and Healthcare products Regulatory Agency), did not raise any immediate concern at first because of the confounding factors associated with some of the reports. By May 1991, however, the marketing authorization holder was aware of 10 cases of torsade de pointes when
the MCA was alerted of the potential hazard signalled collectively by these reports.

Additional reports followed, and by 21 July 1991 there were a total of 21 reports – 14 reports of ventricular tachycardias (including 13 of torsade de pointes) and 7 of bradyarrhythmias. None had a fatal outcome. Therefore, the Chairman of the then UK advisory body, the Committee on Safety of Medicines (CSM), wrote to all the doctors and pharmacists in the United Kingdom warning them of this potentially fatal adverse reaction (Anon, 1991a). On the basis of these reports, the prescribers were advised that the drug should not be used in the presence of risk factors such as age greater than 75 years, ischaemic heart disease, co-prescription with cardioactive drugs, diuretics, antidepressants and antipsychotic agents, hypokalaemia and patients with any cardiac arrhythmias including ECG evidence of (pre-existing) prolongation of QT interval. Age per se was not regarded as an absolute contraindication.

After this warning, there followed an avalanche of reports. An additional 48 case reports followed within the next 6 weeks, and by September 1991 there were a total of 69 reports of terodiline-induced serious cardiac arrhythmias. The majority of these 48 additional reports were retrospective cases with the onset of terodiline-associated proarrhythmia antedating the warning letter. Clearly, there were cases of cardiac effects of terodiline, but these were simply not reported because the association might have appeared too implausible to the prescribing community. However, after the alert, the real magnitude of the potential risk started to become apparent.

These 69 reports consisted of 50 reports of tachycardias and 19 reports of bradyarrhythmias and heart blocks. Amongst these 69 cases were 14 cases of sudden or unexplained deaths (13 in the tachycardia group). Fifty-one cases had recovered and there was no information on outcome in the remaining 4 reports (but assumed non-fatal). Among the 55 non-fatal reports were 24 cases of torsade de pointes, 5 ventricular fibrillation, 7 unspecified ventricular tachycardia, one of multifocal ventricular ectopics and 18 of bradyarrhythmias.

Patient demography and pattern of drug usage was essentially similar in the tachycardia and bradyarrhythmia groups. Of the 50 patients with tachyarrhythmias, 40 were females and 43 were aged 61 years or more. A dose of 25 mg daily or less was taken by 25 (56%) of the 45 patients with tachyarrhythmias in whom the dose was stated. Information on duration of treatment was available in 40 of these 50 patients. It was less than 1 month in 8 cases, up to 2 months in 10 cases, up to 6 months in 8 cases and more than 6 months in the remaining 14 cases. A dose of 25 mg or less was taken by 11 (65%) of the 17 patients with bradyarrhythmias and heart blocks in whom the information on dose was available.

A further analysis of predisposing factors in these 69 reports of terodiline-induced cardiotoxicity confirmed previous conclusions on potential risk factors: (a) an age greater than 75 years, (b) concurrent use of cardioactive medication (n = 33), (c) concurrent use of diuretics (n = 27), (d) concurrent use of antidepressants or antipsychotic agents and (e) hypokalaemia (n = 8). Ischaemic heart disease was present in 13 patients, and other cardiovascular pathologies were present in 39 patients. In 12 cases (18%), however, there were no clinically identifiable risk factors at all.

While the regulatory action was under consideration, the marketing authorization holder withdrew the drug voluntarily from the market worldwide on 13 September 1991 (Anon, 1991b).

Interestingly enough, at the time of its withdrawal, only 3 reports had come from Sweden (daily doses were 37.5, 50 and 50 mg), 1 from the Netherlands (dose unknown) and none from Japan. There were no reports of cardiac arrhythmias from Denmark, Germany or Ireland. There was no information from Luxembourg. The drug was not marketed in Belgium, France, Greece, Italy, Spain or Portugal. Following its withdrawal, there were isolated reports of terodiline-induced torsade de pointes published from Denmark and Norway, and additional ones from the Netherlands. There was also one report of sudden unexpected death from Germany.

At the time of its withdrawal, about one million patients had been treated with terodiline worldwide, including about 450 000 in the United Kingdom. Even assuming a generous spontaneous reporting rate of 20%, the incidence of the risk was estimated at 1 in 1300 patients exposed. This remarkably high cardiotoxic potential of terodiline, uncovered through a spontaneous reporting system, is in sharp contrast to the generally reassuring safety profile that was being asserted on the basis of observations from
post-marketing surveillance studies (Hall et al., 1993; Inman et al., 1993).

LIMITATIONS OF FORMAL POST-MARKETING SURVEILLANCE STUDIES

A general practice based Prescription Event Monitoring (PEM) study profiled the safety of terodiline in 12,457 patients, treated between November 1986 and September 1987 (Inman et al., 1993). Of these patients, 72.5% were females. The mean age was 65.6 (range 5–98) years in males and 63.3 (range 5–102) years in females. Incontinence (47.8%), frequency (16.9%), bladder irritability (7.7%) and urgency (6.6%) accounted for the majority of the indications for use of terodiline in females. In clinical practice, 62.2% of the patients were receiving a maximum daily dose of 25 mg, 18.2% were receiving 50 mg and a minority had used other regimes, including some up to 100 mg per day. Terodiline was reported to have been effective in 56% of the patients. Cardiovascular events reported during the first 6 months and at any time during and after treatment with terodiline, but not considered to be adverse reactions to it, included dizziness (n = 135 and 255, respectively), syncope (41 and 105), hypotension (15 and 30), atrial fibrillation (8 and 30), tachycardia (8 and 17), bradycardia (2 and 10), arrhythmias (2 and 8), ventricular fibrillation (0 and 3), heart block (0 and 2) and cardiac arrest (0 and 2). Even in a subsequent survey (initiated in 1990) of co-prescribing of various cardiactive medications, it could not be established whether the excess of syncope, arrhythmias, bradycardia, hypotension and other cardiovascular events was due to drug combinations or the presence of co-existing cardiovascular disease. Of all the events reported in the cohort, only 51 events were suspected to be actual adverse reactions to terodiline and these included 2 cases of dizziness. No case of cardiovascular collapse attributable to torsade de pointes could be found.

Even a retrospective study, undertaken in the aftermath of the powerful signal from the spontaneous reporting system and the withdrawal of terodiline from the market, failed to better quantify the risk of cardiotoxicity of terodiline. In this study using the VAMP database (Hall et al., 1993), a preliminary open study identified a total of 9176 terodiline-treated patients. A total of 77 (0.8%) of these 9176 patients had an ECG investigation during the study period. There was only one confirmed case of torsade de pointes in a 41-year-old female who had hypokalaemia at the time of the event. Apart from a 50 mg daily dose of terodiline, she was concurrently receiving a tricyclic antidepressant. Altogether, a total of 59 patients were found to have had a cardiac arrhythmia during the follow-up period. This open study estimated the risk of terodiline-induced torsade de pointes to be 1.1 per 10,000 patients. A retrospective but limited inquiry into the nature of arrhythmias in the 59 patients with cardiac arrhythmias elicited information in only 19 patients. These included 6 bradycardia, 4 heart blocks, 3 ventricular tachycardias, 2 ventricular conduction defects, 2 extrasystoles, 1 ‘tachy-brady syndrome’ and 1 cardiac arrest. None had previously been reported to the CSM through the yellow cards and 16 of the 19 practitioners concerned agreed to complete a yellow card.

In another retrospective cohort extension of the above VAMP study, 5705 terodiline-treated patients were compared with 9604 controls. It concluded that there was no significant difference in the risk of developing an arrhythmia in the terodiline-treated patients compared with that in the controls. The relative risk compared with controls was estimated at 1.1 (95% CI: 0.64–1.90). Even the patients reporting symptoms suggestive of cardiac arrhythmias (syncope, collapse, blackouts) were not overly represented in the terodiline-treated cohort. Only dizziness and falls were reported significantly more frequently in the terodiline-treated patients (5.13% vs. 3.35%).

Both these studies had failed spectacularly if it was intended that they would test or strengthen what is frequently, and deprecatingly, termed merely a ‘hypothesis’ when reports of serious reactions are gathered through a spontaneous reporting system.

The failure of formal post-marketing surveillance studies to detect or quantify the risk of drug-induced QT interval prolongation, with or without torsade de pointes, associated with some potent torsadogens is not unfamiliar (Pratt et al., 1994; Hanrahan et al., 1995; Staffa et al., 1995; de Abajo and Rodriguez, 1999; Layton, Key and Shakir, 2003).
INITIAL REGULATORY DELIBERATIONS

Questions arise, inevitably in retrospect, as to whether terodiline should have been approved at all and whether its proarrhythmic potential could have been anticipated. While it may be easy to answer some of these questions in retrospect, the commentary that follows is not based entirely on the benefit of hindsight, because the nature of the problem had become apparent at the regulatory authority immediately on receipt of the first two to three reports of terodiline-induced proarrhythmias.

There is little doubt that urinary incontinence, although relatively benign in terms of morbidity, is a highly prevalent condition that has a serious adverse effect on the quality of life. At the time of the approval of terodiline in 1986, there was no other drug available with a comparable efficacy and favourable risk–benefit ratio. Clinical trials had shown terodiline to be effective and, by all accounts, relatively safe. The efficacy of terodiline had been demonstrated in a number of studies (Fischer-Rasmussen, 1984; Yoshihara et al., 1992; Anon, 1993a; Norton et al., 1994). The majority of adverse reactions reported were anticholinergic in nature and mild in severity. In one randomized, double-blind, two-periods cross-over (3 weeks duration for each period) study in 89 women with motor urge incontinence without other neurological symptoms, no statistically significant difference in incidence of side effects could be demonstrated between 37.5 mg daily of terodiline and placebo (Peters, 1984). The safety of terodiline at a higher dose of 50 mg daily was also evaluated in a 6-month study in 100 women with urgency/urge incontinence (Fischer-Rasmussen, 1984). Ninety-one patients were evaluated after 3 months and 70 after both 3 and 6 months. Adverse reactions, usually those to be expected from the anticholinergic pharmacological effects of the drug, resulted in 12 patients discontinuing the treatment. No significant changes in heart rate or blood pressure occurred except for a small but statistically significant increase (about 2 mmHg) in resting diastolic blood pressure after 6 months. Mean levels of all clinical chemistry variables were well within the normal range. No significant laboratory changes were seen except for a small increase in platelet, serum creatinine and ESR. Unfortunately, ECGs were not recorded in either of these pre-approval studies.

Given the therapeutic options available at the time, there is no question that approval of terodiline was the most appropriate decision in 1986. Even during the few months immediately following its withdrawal, many patients and physicians continued to write to the Agency, testifying to its efficacy and positive impact in transforming the quality of life of many patients, and complaining about the abrupt loss of a clinically useful drug. An option to make the drug available on a named patient basis was under consideration but never followed through. Equally, the withdrawal of terodiline in September 1991 was not a difficult decision, since its risk–benefit was shown conclusively by then to be unfavourable and another equally effective drug, oxybutynin, had already been approved for use in urinary incontinence in January 1991.

SIMILARITIES BETWEEN TERODILINE AND PRENYLAMINE

In the context of the ICH E2E guideline on Pharmacovigilance Planning, some vital pieces of information that might have presaged the potential proarrhythmic risk from terodiline were already known at the time of its re-development. The analogy between terodiline and prenylamine goes well beyond their therapeutic class, and extends into their chemical structures and stereoselective pharmacological and toxicological profiles (Table C.1).

First, it was well known that the use of antianginal drugs (prenylamine and lidoflazine) might be associated with QT interval prolongation and torsade de pointes. Prenylamine was introduced in the United Kingdom in the early 1960s and lidoflazine in 1979. Secondly, both prenylamine and terodiline are highly related in their chemical structures. While terodiline is a diphenyl-propyl derivative of butylamine (Figure C.1), prenylamine is a diphenyl-propyl derivative of phenylethylamine (Figure C.2).

The presence of a chiral centre in each drug gives rise to a pair of enantiomers. It is acknowledged that even a minor modification in the structure of a molecule can dramatically alter the activity of a drug, and indeed this is the basis of metabolic inactivation of most drugs. However, notwithstanding the minor
Table C.1. Similarities between terodiline and prenylamine.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Prenylamine</th>
<th>Terodiline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical structure</td>
<td>Diphenyl-propyl derivative of phenylethylamine</td>
<td>Diphenyl-propyl derivative of butylamine</td>
</tr>
<tr>
<td>Pharmacological class</td>
<td>Calcium channel blocker acting intracellularly</td>
<td>Anticholinergic</td>
</tr>
<tr>
<td>Therapeutic class</td>
<td>Antianginal</td>
<td>Antianginal followed by re-development for the treatment of urinary incontinence</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP2D6 probably metabolizes (+)-(S)-prenylamine</td>
<td>CYP2D6 probably metabolizes (+)-(R)-terodiline</td>
</tr>
<tr>
<td>Half-life</td>
<td>Long and highly variable between individuals</td>
<td>Long and highly variable between individuals</td>
</tr>
<tr>
<td>Stereoselective elimination</td>
<td>Favours (+)-(S)-prenylamine</td>
<td>Favours (+)-(R)-terodiline</td>
</tr>
<tr>
<td>Stereoselective pharmacodynamics</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>IKr or hERG (IC50) of the racemic drug</td>
<td>0.597 μM (for hERG)</td>
<td>0.7 μM (for IKr)</td>
</tr>
<tr>
<td>Stereoselective cardiotoxicity</td>
<td>Yes with (+)-(S)-prenylamine being torsadogenic</td>
<td>Yes with (+)-(R)-terodiline being torsadogenic</td>
</tr>
</tbody>
</table>

Figure C.1. (++)-(R)-terodiline.

Figure C.2. (++)-(S)-prenylamine.

structural differences between terodiline and prenylamine, it is intuitive that terodiline must have some cardiac effects since it was marketed originally as a cardioactive antianginal agent. Not surprisingly, both drugs share a very similar complex pharmacological profile that is discussed later. Thirdly, both prenylamine and terodiline are chirally active and there was already evidence of stereoselectivity in the proarrhythmic potential of prenylamine. Fourthly, there was wide inter-individual variability in the metabolism of terodiline, with aberrant pharmacokinetic behaviour of one of the enantiomers. This is also a feature of the pharmacokinetics of prenylamine. Finally, there was evidence of stereoselectivity in the pharmacodynamic activities of the two enantiomers of terodiline, and therefore the unexpectedly high frequency of anticholinergic effect observed during its use as an antianginal agent should have already suggested an unusual behaviour of one of the enantiomers (the enantiomer with predominantly anticholinergic activity).

To illustrate the regulatory deliberations at the time, frequent references will be made to prenylamine in the commentary that follows. This will highlight...
in detail the striking similarity between these two drugs, and hence the logic that should have supported the re-development of terodiline. Importantly, this comparison emphasizes the strengths of both a scientific synthesis of all the available information when evaluating the significance of even a handful of spontaneous reports of a unique drug reaction, and of formulating the most appropriate regulatory strategies for risk management.

**Prenylamine-Induced Proarrhythmias**

Prenylamine was the first drug to be withdrawn from the market worldwide in 1988 because of its high potential to prolong the QT interval and induce torsade de pointes, often with a fatal outcome (Anon, 1988).

Although prenylamine had been marketed since the 1960s, it was not until 1971 that reports (mostly from France and the United Kingdom) linking prenylamine with prolongation of the QT interval, ventricular tachycardia, ventricular fibrillation and torsade de pointes began to appear (Picard, Auzepy and Chauvin, 1971). Despite changes in dose schedules and warnings, prenylamine-induced proarrhythmias continued to be reported, and by 1988, 158 cases of polymorphic ventricular tachycardia were reported in association with prenylamine, and the drug was withdrawn worldwide soon after its removal from the UK market that year. Approximately 80% of these patients were females. The mean age was 68 ± 11 years and 30 of the 109 patients had received prenylamine as the only medication. The vast majority of the patients were taking prenylamine at the usually recommended daily dose of 180 mg. Hypokalaemia was present in 34 of the 82 patients for whom this information was available.

Strikingly, despite being very potent torsadogens, neither prenylamine nor terodiline had shown any evidence of its proarrhythmic potential during its development. Cardiotoxicity following their routine clinical use did not become fully manifest for about 2–3 years after marketing – a disturbing feature also shared by other torsadogenic drugs removed from the market. A number of prospective studies with prenylamine were conducted to investigate its effect on QT interval, but none could demonstrate a significant change after treatment with the drug. A review of the pre-approval clinical trials data on terodiline proved unhelpful for evaluation of its effect on ECG. However, in one study of 12 asymptomatic patients in sinus rhythm taking stable doses of terodiline (undertaken after its withdrawal from the market), mean QTc interval and QT dispersion were significantly prolonged to 491 and 84 ms during treatment with racemic terodiline compared with measurements of 443 and 42 ms, respectively, made off therapy (Thomas et al., 1995). The mean drug-induced increases were 48 ms for the QTc interval and 42 ms for QT dispersion. In this study, QT interval prolongation was shown to correlate closely with steady-state plasma concentrations of (+)-(R)- and (−)-(S)-terodiline.

Both prenylamine and terodiline further illustrate a more general difficulty in successfully containing a clinical risk by revising the prescribing information. These revisions may include reduced doses, additional contraindications, special warnings and precautions for use, requirements for monitoring patients and details of potentially cardiotoxic drug interactions. Unfortunately, this strategy has proved to be highly disappointing in risk management, as evidenced by the withdrawal of a number of high-profile drugs such as terfenadine, astemizole, cisapride (all associated with proarrhythmias) and troglitazone and bromfenac (both associated with hepatotoxicity) (Shah, 1999). The most recent casualty of inappropriate prescribing (resulting in rhabdomyolysis) was cerivastatin, which continued to be prescribed at high doses at the outset despite a recommendation to start treatment at lower doses, or concurrently with gemfibrozil despite this combination being contraindicated.

**Polymorphic CYP2D6-Mediated Stereoselective Metabolism**

It appears probable that the metabolism of both terodiline and prenylamine may be mediated by the P450 cytochrome CYP2D6, the isoform responsible for debrisoquine hydroxylation. This major drug-metabolizing isozyme is expressed polymorphically in all populations, resulting in two major drug-metabolizing phenotypes – extensive (EM) and poor (PM) metabolizers. The latter are unable to effect the metabolic elimination of CYP2D6 substrates, and
these include antiarrhythmic agents, \( \beta \)-blockers, antihypertensive drugs, neuroleptics and antidepressants. Consequently, PM individuals are exposed to higher concentrations of the parent drug for longer duration.

The pharmacokinetics of prenylamine are enantioselective, favouring the elimination of the \((+)\)-(S)-enantiomer (Gietl et al., 1990; Paar et al., 1990). On multiple dosing, the apparent oral clearance of the \((+)\)-(S)-enantiomer was 4.6-fold and the renal clearance 2.4-fold higher than that of the \((-)\)-(R)-enantiomer. The maximum plasma concentration and AUC (area under curve of plasma concentration vs. time) of the \((+)\)-(S)-enantiomer were 4–5 times lower than those of the \((-)\)-(R)-enantiomer. After a single dose, the mean plasma half-lives of \((-)\)-(R)-prenylamine and \((+)\)-(S)-prenylamine were 8.2 and 24 hours, respectively. On chronic dosing, the mean half-lives for \((-)\)-(R)-prenylamine and \((+)\)-(S)-prenylamine were reported to be 13.7 and 17.4 hours, respectively (Gietl et al., 1990). However, the apparently only slightly higher mean value of the half-life of \((+)\)-(S)-enantiomer following a single dose was mainly a consequence of its extremely long plasma half-lives of 82 and 83 hours in 2 of the 8 volunteers. The remaining 6 subjects showed an average half-life of 11 hours. Although none of these subjects had been phenotyped for their CYP2D6 metabolic capacity, prenylamine fulfils all the structural requirements of a CYP2D6 substrate and it is worth speculating whether these two individuals were PMs of CYP2D6 with an impaired ability to eliminate \((+)\)-(S)-prenylamine. Patients with prenylamine-induced proarrhythmias have not been genotyped or phenotyped for their CYP2D6 metabolizing capacity.

Studies with rat liver microsomes suggest that more than one CYP isoform may be involved in the metabolism of terodiline, with different isoforms mediating the metabolism of the two enantiomers (Lindeke et al., 1987). In studies using human liver microsomes, the metabolism of terodiline at high concentrations has been shown to be stereoselective favouring the \((+)\)-(R)-enantiomer (Noren et al., 1989), although the ratio of concentrations of the two enantiomers at steady-state following administration of clinical doses is close to unity (Hallen et al., 1995).

Although much of the data in man are incomplete, puzzling or often difficult to reconcile, there is fairly persuasive evidence to suggest that the major isozyme involved in the metabolism of \((+)\)-(R)-terodiline is CYP2D6, and therefore the metabolism of \((+)\)-(R)-terodiline is subject to genetic polymorphism. The formation of \(p\)-hydroxy-terodiline from \((+)\)-(R)-terodiline was found to be impaired in one PM of debrisoquine (Hallen et al., 1993). In this study of the pharmacokinetics of a 25 mg oral dose of \((+)\)-(R)-terodiline in healthy volunteers, the mean half-life of this enantiomer in 4 EMs of debrisoquine was 42 (range 35–50) hours and in the only PM in this study, it was 117 hours. In another study (Thomas and Hartigan-Go, 1996) in healthy volunteers, which included 7 EMs and 2 PMs who were administered a single oral dose of 200 mg racemic terodiline, the maximum plasma concentrations and AUC of \((+)\)-(R)-terodiline were significantly higher compared with \((-)\)-(S)-terodiline, although their half-lives were similar. Even at this high dose (which would be expected to conceal the pharmacokinetic difference between the two genotypes), the PM/EM clearance ratios for \((+)\)-(R)-terodiline and \((-)\)-(S)-terodiline were 45% and 56%, respectively. In common with all drugs subject to polymorphic metabolism, the pharmacokinetic difference between the EMs and the PMs are less evident at higher doses because of increasing saturation of metabolism in EMs at higher doses.

It is worth pointing out that the \((+)\)-(R)-enantiomer of tolterodine (a structural analogue of terodiline) with anticholinergic properties is marketed for the treatment of urinary incontinence. Its oxidative hydroxylation has been confirmed in \textit{in vitro} and \textit{in vivo} studies to be mediated principally by CYP2D6 (Brynee et al., 1998; Postlind et al., 1998). CYP3A4-mediated dealkylation provides a major alternative, albeit less effective, route of elimination in those who are PMs of CYP2D6 (Brynee et al., 1999).

The consequence of this stereoselective and (most probably) polymorphic metabolism is that the calcium antagonistic \((-)\)-(S)-terodiline would accumulate in all patients over time, but in addition there will also be an accumulation of the anticholinergic \((+)\)-(R)-terodiline in the poor and intermediate metabolizers of CYP2D6 substrates. Thus, genetically determined accumulation of \((+)\)-(R)-terodiline could constitute another risk factor. While it is true that the doses used in Sweden and Japan were generally lower, this CYP2D6-mediated metabolism of \((+)\)-(R)-terodiline might also explain the striking inter-ethnic differences.
in the incidence of ventricular arrhythmias associated with its use. Whereas 9% of the UK population are PMs, the corresponding figures for Sweden and Japan are only 6.8% and less than 1%, respectively. The higher frequency of PM alleles in the UK population will necessarily result in a higher prevalence of the heterozygous CYP2D6 genotype – a subgroup most at risk of drug–drug interactions – and therefore give rise to a higher potential for drug–drug interactions in the United Kingdom between terodiline and other QT interval-prolonging substrates of CYP2D6, such as neuroleptics, antidepressants and other antiarrhythmic drugs.

Ford, Wood and Daly (2000) investigated the roles of CYP2D6 and CYP2C19 genotypes in eight patients who survived terodiline-induced proarrhythmias (six with torsade de pointes and two with ventricular tachycardia). One of these eight patients had a CYP2D6 PM genotype, and it was observed that CYP2D6 alleles were no more frequent in these eight individuals than in the normal population. This study also found a statistically higher frequency of the mutant CYP2C19∗2 allele in this population. As a result, these investigators suggested that whereas CYP2D6 PM status was not a risk factor for terodiline cardiotoxicity, possession of the CYP2C19∗2 allele might contribute to adverse cardiac reactions to terodiline. This study, however, has serious limitations that the investigators themselves have acknowledged. Only two mutant alleles of CYP2D6 were looked for and there was no ECG evidence confirming the adverse drug response phenotype (i.e. the presence of QT interval prolongation or torsade de pointes). There was a lack of information on co-medications in 2 patients. In another 2 patients, there was co-administration of diuretics that may predispose to hypokalaemia, and therefore to torsade de pointes.

It may be speculated whether any of the 12 patients with terodiline-induced proarrhythmias reported to the CSM, and in whom there were no obvious risk factors may have had a pharmacogenetic defect in their CYP2D6-mediated drug metabolism of (+)-(R)-terodiline. Connolly et al., (1991) and Andrews and Bevan (1991) have also reported one case each of torsade de pointes in patients without any risk factors and in whom plasma terodiline levels were markedly elevated. Information on the genotypes of such patients would have been more helpful in elucidating the role of (pharmacokinetic) genetic susceptibility to terodiline-induced proarrhythmias.

In addition, the susceptibility role of CYP2C19∗2 suggested by Ford, Wood and Daly (2000) does not explain either the absence of terodiline cardiotoxicity among the Japanese (in whom the frequency of the CYP2C19∗2 allele is much higher at 0.29–0.35), or the high frequency of anticholinergic effects mediated by (+)-(R)-terodiline in Scandinavia (where the frequency of the CYP2C19∗2 allele is far lower, at no more than 0.08). There is also the evidence showing that the frequency of this allele is not any higher among the elderly (Yamada et al., 1998), who were the target population for the use of terodiline. Neither can the closely related CYP2C9 isoform be implicated. Terodiline 50 mg daily did not influence the plasma levels of warfarin enantiomers, nor the anticoagulant effect, following continuous daily administration of a mean dose of 5.3 mg warfarin (Hoglund, Paulsen and Bogentoft, 1989).

PHARMACOKINETICS AND RECOMMENDED DOSE SCHEDULES

Both terodiline and prenylamine bear an uncanny resemblance in their pharmacokinetics. Therefore, the dose schedules of the two drugs should be scrutinized in the context of wide inter-individual variability, their long elimination half-lives and the potential to accumulate.

Prenylamine is extensively metabolized in man by ring hydroxylation and further methylation of the subsequent phenolic metabolites – its absolute bioavailability is estimated to be 15% (Paar et al., 1990). This metabolism displays wide inter-individual variation, with a terminal elimination half-life of 14.1 ± 6.9 hours. Generally, the steady-state plasma level was reached after 5–7 days, indicating that the terminal half-lives of both the enantiomers of prenylamine were in the region of 24 hours (Gietl et al., 1990). The time to steady-state concentrations may be much longer in those who cannot eliminate the drug effectively (see later). However, when first marketed, the standard recommended dose of prenylamine for the majority of patients was 60 mg three-times daily, which could be increased to 60 mg four- or five-times
daily in those patients who did not respond within 7 days of starting treatment.

Thus, another area of concern in the re-development of terodiline should have been its metabolic disposition and its impact on dosing recommendations. Terodiline is also extensively (85%) metabolized to a phenol, \( p \)-hydroxy-terodiline, and there is wide inter-individual variation in its metabolism (Karlen et al., 1982; Hallen et al., 1994). Although \( p \)-hydroxy-terodiline has a profile of pharmacological activity similar to that of racemic terodiline, its potency is low. Even at steady state, this metabolite constitutes only 10%–20% (about 0.05 \( \mu \)g/mL) of the terodiline steady-state plasma level in man. These observations indicate that in man the contribution of this metabolite to the anticholinergic effect observed in clinical studies is minor (Hallen et al., 1990).

Following their studies on the pharmacokinetics of terodiline in nine healthy volunteers who were given (i) 12.5 mg intravenously and orally and (ii) 20 mg intravenously and 25 mg orally, on two different occasions, Karlen et al. (1982) had concluded that the long serum half-life of terodiline should permit its once-daily administration. Side effects were often encountered at concentrations exceeding 0.6 \( \mu \)g/mL (Andersson, 1984). The mean half-life of terodiline in the elderly is 131 (range 63–237) hours, in contrast to 57 (range 35–72) hours in young adults (Hallen et al., 1989). Therefore, the corresponding times to steady-state plasma levels would be 7–15 days in young adults but 2–7 weeks in the elderly.

The average steady-state serum concentrations on a 12.5 mg twice-daily dose are 0.238 \( \mu \)g/mL in healthy volunteers, and 0.518 \( \mu \)g/mL in geriatric patients. This concentration in the elderly, the main target population for the use of terodiline, is close to the toxic concentration, and yet the dose recommended for the elderly was 25 mg twice daily.

The similarity to the inappropriate dosing recommendation for prenylamine is self-evident. The dosing recommendations for prenylamine and terodiline have to be seen in the context of their CYP2D6-mediated polymorphic metabolism, and the potential for accumulation in those unable to effectively eliminate the cardiotoxic enantiomers.

When announcing its withdrawal, the marketing authorization holder of terodiline advised prescribers to identify immediately all their patients being treated with it, and to stop the drug as soon as practicable. They also cautioned prescribers to bear in mind the long half-life of terodiline if alternative anticholinergic treatment was considered, and recommended a washout period that on average would be 2–3 weeks (but in some cases as long as 6 weeks).

**PHARMACODYNAMIC SIMILARITY TO PRENYLAMINE**

Terodiline also resembles prenylamine in terms of pharmacodynamic activity. Both have complex pharmacodynamic effects that are stereoselective and are active at multiple channels. Some aspects of this similarity had been pointed out as long ago as 1983 (Fleckenstein, 1983).

Although prenylamine has been described as a calcium antagonist, it is not a true calcium channel blocker since it does not act selectively at the membrane-associated, voltage-dependent calcium channels. However, it is a potent inhibitor of calmodulin-dependent enzymes, relaxes smooth muscle and reduces slow inward current. In addition, it depresses peak sodium conductance (Hashimoto et al., 1978; Bayer, Schwarzmaier and Pernice, 1988). Hashimoto et al. (1978) have also shown that prenylamine increases action potential duration, indicating that the drug may interfere with the late outward repolarizing current mediated by potassium ions. Thus, in addition to its negative inotropic effect, prenylamine most probably has sodium and potassium channel blocking activities. More recently, prenylamine has been shown conclusively to block the potassium channel that is primarily responsible for cardiac repolarization (Katchman et al., 2006).

With regard to stereoselective pharmacodynamic effects, \((+)-(S)\)-prenylamine has a positive inotropic effect in cat papillary muscle preparations that is particularly evident at low concentrations, and at low stimulation rates (Bayer, Schwartzmaier and Pernice, 1988). The maximum velocity of depolarization is somewhat increased by both \((+)-(S)\)-prenylamine and the racemic mixture at low concentrations. \((-)-(R)\)-prenylamine is associated with a negative inotropic effect and a decrease in the maximum velocity of depolarization. As far as cardiac repolarization is concerned, \((+)-(S)\)-prenylamine prolonged the action
Potential duration and induced arrhythmia in 4 of the 12 isolated papillary muscle preparations. In contrast, the (−)-(R)-isomer shortened the action potential duration to a minor extent. This effect was independent of stimulation rates but evident at low concentrations.

Terodiline not only blocks the uptake of calcium, it also blocks the utilization of some intracellular stores of calcium. Pressler et al. (1995) have investigated the in vitro and in vivo electrophysiological effects of terodiline, and have shown that it blocks sodium and calcium channels as well as muscarinic receptors in canine cardiac tissues. Terodiline has been shown to be a non-selective muscarinic receptor antagonist (Noronha-Blob et al., 1991), and therefore its anticholinergic effects on the heart are not altogether surprising. The primary pharmacological activities of terodiline are potent calcium antagonistic and non-selective anticholinergic effects within the same clinical concentration range. Although both activities probably contribute to the therapeutic effect to a variable extent, the anticholinergic effect predominates at low concentrations and the calcium blocking action at high concentrations (Andersson, 1984). In another study in anesthetized dogs, terodiline (10 mg/kg given intravenously) significantly prolonged the QTc interval by 6%–8%, an effect associated with induction of torsade de pointes (Natsukawa et al., 1998). Like prenylamine, terodiline too has been shown to block the potassium channel responsible for cardiac repolarization (Jones et al., 1998).

The pharmacological activities of terodiline are also enantioselective. The effects of racemic terodiline on isolated detrusor preparations from rabbit and man were compared with those of its (+)-(R)- and (−)-(S)-isomers, and with those of its main metabolite, p-hydroxy-terodiline (Andersson, Ekstrom and Mattiasson, 1988). It was concluded that (+)-(R)-terodiline is the main contributor of the detrusor effects of the racemate, and that a component of this activity is anticholinergic in nature. Whereas (+)-(R)-terodiline has been shown to be almost ten times more potent than (−)-(S)-terodiline in its anticholinergic activity, (−)-(S)-terodiline is almost ten times more potent than its antipode as a calcium antagonist (Larsson-Backstrom, Arrhenius and Sagge, 1985; Andersson, Ekstrom and Mattiasson, 1988).

Available data indicate that terodiline in low concentrations has mainly an anticholinergic action arising from the (+)-(R)-enantiomer, and as the concentration rises, additional calcium antagonistic effects from (−)-(S)-terodiline begin to emerge (Husted et al., 1980). Since in vitro data suggest that at high concentrations the metabolism of terodiline is stereoselective favouring the (+)-(R)-enantiomer (Noren et al., 1989), it seems likely that the dominant enantiomer circulating in human plasma at clinical doses of 25 mg is (+)-(R)-terodiline. As discussed below, this has significant implications in terms of the cardiac effects of terodiline.

**STEREOSELECTIVITY IN PROARRHYTHMIC POTENTIAL**

Steroselective interactions at receptors and ion channels are well known in the activities of β-blockers and dihydropyridine calcium channel blockers. Similar stereoselective interactions at potassium channels have also been described with enantiomers of drugs such as (+)-(R)-bupivacaine, (+)-(R)-halofantrine and (−)-(4S,6S)-acetylmethadol (levacetylmethadol). As regards their adverse pharmacodynamic effects on the heart, both prenylamine and terodiline display stereoselectivity (Rodentikchen, Bayer and Mannhold, 1980; Bayer, Schwarzmaier and Pernice, 1988; Hartigan-Go et al., 1996).

Although a number of currents, predominantly mediated by potassium ions, are involved during repolarization, the one almost universally affected by all the drugs (non-cardiovascular and non-antiarrhythmics alike) that prolong the QT interval and induce torsade de pointes is the rapid component of the delayed rectifier potassium channel, known as the I_kr current. At a molecular level, the native I_kr channel is a co-assembly of hERG (human ether-a-go-go related gene) α-subunits and MiRP1 β-subunits. The hERG channel is the target of almost every QT-prolonging drug. Although prenylamine and terodiline have both been shown now to block either the hERG or the I_kr channel (Jones et al., 1998; Katchman et al., 2006), there are no published reports of in vitro studies investigating the activity of individual enantiomers of these drugs on either of these targets. Interestingly, however, tolterodine (a structural analogue of terodiline) is marketed as the (+)-(R)-enantiomer, and has
recently been shown in in vitro studies to block the hERG cardiac ion channel (Kang et al., 2004).

As discussed earlier, the overall data suggest that the proarrhythmic effect of prenylamine in man is most likely mediated by (+)-(S)-prenylamine, as demonstrated by studies on action potential duration (Bayer, Schawrzmaier and Pernice, 1988). This conclusion must be seen in the context of the observations that although the maximum plasma concentration and AUC of the (+)-(S)-enantioomer are normally 4–5 times lower than those of the (−)-(R)-enantioomer, the reverse may be the case in PMs of CYP2D6, since the data suggest that this CYP isoform most probably mediates the metabolic elimination of (+)-(S)-prenylamine. Due to its longer elimination half-life, (+)-(S)-prenylamine would accumulate in the PMs. Not surprisingly, most patients with prenylamine-induced proarrhythmias were also receiving doses in the lower range of the recommended schedule. A number of drugs such as quinidine only induce torsade de pointes at low concentrations because other electrophysiological effects suprime at higher concentrations. As far as the author is aware, there are no published reports of in vitro studies investigating the activity of individual enantiomers of terodiline on action potential duration.

There are no in vivo data on stereoselective cardiac effects of prenylamine, or on the concentrations of the two enantiomers in patients during episodes of prenylamine-induced proarrhythmias. However, in vivo studies in nine healthy volunteers have shown conclusively that the proarrhythmic potential of terodiline resides exclusively in its (+)-(R)-enantioomer (Hartigan-Go et al., 1996). Peak effects occur 8 hours after dosing, when mean increases in the QTc interval from baseline were 3 ms after the placebo, 23 ms after 200 mg racemic terodiline, 19 ms after 100 mg (+)-(R)-terodiline and 0 ms after 100 mg (−)-(S)-terodiline. Although there were differences in the pharmacokinetics of the two enantiomers, these were not sufficient to account for the differences in ECG effects, and at these high doses, their elimination half-lives were similar. In the two genotypic PMs of CYP2D6, the half-lives of (+)-(R)-terodiline ranked 7th and 8th and those of (−)-(S)-terodiline 4th and 9th in order. It will be recalled, however, that at clinical doses, (+)-(R)-terodiline predominates in the plasma and could accumulate further in PMs of CYP2D6.

LESSONS TO BE LEARNT

The important lessons to be learnt from re-development and withdrawal of terodiline are (a) the benefits of drawing on experiences with other drugs of the same class and (b) the perils of exploiting adverse secondary pharmacological effects to re-target a drug. These lessons are highly relevant to the Safety Specification requirements of ICH E2E, and in addressing important potential risks and outstanding safety questions that warrant further investigations in order to refine an understanding of the risk–benefit profile during the post-approval period. A retrospective analysis of the safety issues associated with other drugs of the same chemical, pharmacological or therapeutic class, and the need to explore these, is the cornerstone of strategic development of other new drugs in the same class. This approach, following clinical experiences with prenylamine and lidoflazine (both antianginal drugs associated with QT interval prolongation and torsade de pointes), would have forewarned of the potential cardiac problems associated with terodiline.

Additionally, there should be a more realistic appreciation of the limitations of clinical trials and the weaknesses of even the more formal studies in identifying post-marketing risks. Since QT interval prolongation and/or torsade de pointes are ECG-based diagnoses, the negative findings from PEM and VAMP studies referred to earlier are not surprising. The databases used for these studies (general practice based) were not appropriate for the identification or quantification of risks that require ECG diagnosis, and not sensitive enough to sample hospital-based diagnoses. It is inconceivable that the risk of QT interval prolongation can be characterized when only 0.8% of the cohort under investigation had an ECG investigation (Hall et al., 1993). Inman et al. (1993) acknowledge

In what is likely to be the largest study ever conducted on this drug, we can find no case of cardiovascular collapse which was attributed to the so-called torsade de pointes arrhythmia... It is very unlikely, however, that this abnormality would be encountered in general practice since it would only be identified by ECG.
When torsade de pointes is sustained, its clinical manifestations include dizziness, syncope and convulsions. Following the report by McLeod, Thorogood and Barnett (1991) associating terodiline with torsade de pointes, Veldhuis and Inman (1991) re-examined the PEM database for several possible clinical manifestations of this tachyarrhythmia, and compared their incidences in terodiline-treated patients with corresponding rates in broadly matched nabumetone-treated patients used as controls. Confusion, syncope, cerebrovascular accidents, transient ischaemic attacks and falls and fractures were appreciably more frequent in the terodiline group. Although this post hoc analysis was not considered conclusive, these investigators recommended that an ECG should be performed on patients who develop confusion, syncope or cerebrovascular accidents while taking terodiline. Of course, from a regulatory perspective, such post hoc analyses of non-specific clinical manifestations of a tachyarrhythmia do not confirm the risk of potentially fatal proarrhythmias, and cannot form the basis of any regulatory actions. This point applies especially in this case, because out of all the events reported in the cohort, only 51 were suspected to be adverse reactions causally related to terodiline, and these included only 2 cases of dizziness (a non-specific symptom that may be associated with torsade de pointes).

The problem with the PEM and the VAMP studies was that neither had included a large enough sample of patients with ECG monitoring. Even when a drug is known to prolong the QT interval, it requires large prospectively designed hospital-based studies to uncover the proarrhythmic risk. A particularly good example of such a study is the SWORD study. Although the drug under investigation was (+)-(S)-sotalol, a known potent torsadogen, it required recruitment of as many as 3121 of the planned 6400 patients before it was terminated prematurely (Waldo et al., 1996). The mortality (presumed to be due to arrhythmias) was 5% in the (+)-(S)-sotalol group and 3.1% in the placebo group – an increase of 65% in mortality following the active treatment. Even in this study, the dose of (+)-(S)-sotalol was carefully titrated against QTc interval, and patients were closely monitored during the first few weeks for excessive (and therefore proarrhythmic) prolongation of the QTc interval, and those with duration greater than 560 ms during this period were excluded. Even if the background frequency of torsade de pointes is zero, it would require approximately 15 000 patients to identify a risk of an event with a frequency of 0.03% at the 99% confidence level, despite assuming that the database is sensitive enough in terms of the population and the adverse reaction to be studied. In contrast, the strength of spontaneous reporting systems in identifying a serious clinical risk that requires hospital-based resources has been demonstrated repeatedly, and almost all major regulatory actions in managing the clinical safety of drugs, or averting major risks to public health, have followed ‘signals’ from spontaneous reporting systems (Clarke, Deeks and Shakir, 2006; Olivier and Montastruc, 2006).

WHY THE REGULATORY CONCERNS ON DRUG-INDUCED QT INTERVAL PROLONGATION?

The QT interval on the ECG, measured from the beginning of the Q wave to the end of the T wave, represents the interval from the beginning of depolarization to the end of repolarization of the ventricular myocardium. Prolongation of QT interval is most frequently associated with prolonged repolarization following administration of class III antiarrhythmic drugs. This class of antiarrhythmic drugs is intended to act by blocking the repolarizing current mediated by potassium channels and produce their desired therapeutic effect by a moderate and controlled prolongation of ventricular repolarization, and therefore an increase in the myocardial refractory period.

However, excessive prolongation of ventricular repolarization, and therefore of the QT interval, can be proarrhythmic and degenerate into torsade de pointes, a ventricular tachyarrhythmia with a unique twisting morphology on the ECG. It is usually transient and self-terminating, lasting only a few seconds, and therefore is often asymptomatic. When sustained, however, the clinical manifestations of torsade de pointes include palpitation, syncope, blackouts, dizziness and/or seizures. Torsade de pointes can subsequently degenerate into ventricular fibrillation in about 20% of cases (Salle et al., 1985) and, not uncommonly, cardiac arrest and sudden death may be the outcome. The overall mortality associated with torsade de pointes is of the order of 10–17% (Salle et al., 1985).
et al., 1985; Fung et al., 2000). Clearly, the balance between the therapeutic antiarrhythmic and the potentially fatal proarrrhythmia prolongation of QT interval is a very delicate one, and depends not only on the drug concerned and its plasma concentration, but also on a number of host factors. These include electrolyte imbalance (especially hypokalaemia), bradycardia, cardiac disease and pre-existing prolongation of QT interval. Females are at a greater risk, and the risk is further enhanced during the menstrual period.

Unfortunately, however, a number of non-antiarrhythmic drugs are found to possess this class III electrophysiological activity as part of their secondary (undesirable in this instance) pharmacological properties. The number of drugs with ‘QT-liability’, and by inference a potential to induce torsade de pointes, continues to increase inexorably (Shah, 2002). The clinical and public health concerns on the potential of non-cardiac drugs to prolong QT interval and induce torsade de pointes have been eloquently summarized in an editorial (Priori, 1998). Concerns have legitimately been expressed that:

Almost every week a new agent is added to the list of drugs associated with acquired long QT syndrome (LQTS) and torsades de pointes (TdP). Despite this impressive number of reports, the awareness of this subject is still limited among medical professionals and . . .

It is likely that prevention of drug-induced TdP will never be fully successful, because it is a moving target. A patient may not be at risk when therapy is initiated, and may become at risk 5 days later because

It is intuitive that when two or more agents sharing potassium-channel-blocking activity are simultaneously administered, the risk of excessive prolongation of repolarisation is substantially increased.

The exclusion of potassium-channel-blocking properties might be considered in the future as a requirement before new molecules are approved for marketing, and more strict warnings in the package insert of drugs with known repolarisation prolonging activity could be enforced.

Apart from the number of drug classes implicated, additional concerns arise from the size of the population at risk. The expression of $\text{I}_{\text{Ks}}$ and other potassium channels is under the control of genes that are known to carry mutations responsible for expression of channels with diminished or dysfunctional capacity – the so-called ‘diminished cardiac repolarization reserve’. $\text{I}_{\text{Ks}}$ channels with mutations of the hERG $\alpha$-subunit (encoded by the KCNH2 gene located on chromosome 7) or the MiRP1 $\beta$-subunit (encoded by the KCNE2 gene located on chromosome 21) very frequently conduct a repolarizing current of smaller amplitude, and in consequence the repolarization process is delayed in individuals carrying these mutations (giving rise to congenital long QT syndromes of types 2 and 6 respectively). The most familiar clinical phenotypes of patients with potassium channel mutations are the Romano–Ward or Jervell–Lange-Neilsen syndromes, with ECG evidence of QT interval prolongation, and the propensity to develop potentially fatal cardiac arrhythmias including torsade de pointes.

However, there is now abundant evidence that in view of the low penetration of many of the mutations of potassium channel genes, the size of the population carrying these mutations may be substantially larger than that diagnosed by ECG evidence of a prolonged QT interval. Relatively large numbers of individuals who carry these ‘silent’ mutations of long QT syndrome genes have been identified, and despite a diminished repolarization reserve, they have a normal ECG phenotype (Priori, Napolitano and Schwartz, 1999). Nevertheless, because of the compromised repolarization reserve, they are at a greater risk of cardiac arrhythmias following administration of QT-prolonging drugs, even at doses that are clinically safe in non-carriers (Yang et al., 2002; Paulussen et al., 2004; Shah, 2004). It has been postulated that drug-induced long QT syndrome might represent a ‘forme fruste’ of the long QT syndrome.

It may be speculated whether some of the 12 patients with terodiline-induced proarrrhythmias referred to earlier, and in whom there were no obvious risk factors, might be carriers of potassium channel mutations (clinically silent congenital long QT syndrome with a normal ECG phenotype). Genetic factors may also operate remotely through other mechanisms. For example, cardiac failure is the end result of many genetically (and non-genetically) determined cardiac diseases. Cardiac failure is typically associated with down-regulation of potassium channels (Tomaselli and Zipes, 2004), and this will also increase the susceptibility of these
patients to QT interval prolongation and proarhyth- 
rmias. It is interesting to note that despite 
urinary incontinence, 27 of the 69 patients with 
terodiline-induced proarrhythmias discussed earlier 
were receiving diuretics, and 33 were in receipt 
of other cardioactive medications. Hypokalaemia 
induced by the diuretics, or electrophysiological activ-
ities of the cardioactive medications, further potentiate 
the pharmacodynamic susceptibility of the patients 
concerned. In addition, patients with a wide range 
of non-cardiac diseases have a pre-existing prolonga-
tion of QT interval, and therefore have an increased 
susceptibility to torsade de pointes by QT-prolonging 
drugs. These conditions include those associated with 
autonomic failure (as in diabetes or Parkinson’s dis-
ease), hypoglycaemia, cirrhosis and infection with 
human immunodeficiency virus.

ELECTROPHYSIOLOGICAL BASIS OF 
TORSADE DE POINTES

Prolonged ventricular repolarization and subsequent 
QT interval prolongation result most frequently from 
a reduction in outward repolarizing potassium current. 
However, in rare instances, these could also result 
from enhanced or sustained depolarizing inward 
sodium or calcium currents (Figure C.3).

Two hypotheses have been proposed to explain the electrophysiologic mechanisms underlying the 
induction of torsade de pointes (Surawicz, 1989).

One hypothesis postulates a trigger mechanism, while 
the other has re-entry as its basis. However, it 
now appears that the two hypotheses are not mutually exclusive, but may in fact be complementary 
(Figure C.4) (Antzelevitch, 2004).

Against a background of prolonged QT interval, the 
presence of a slow heart rate gives rise to early after-
depolarizations (EADs), mediated by slow inward 
calcium current during the late phase 2 of the action 
potential. The amplitude of these EADs is cycle 
length dependent, with a strong correlation between 
the preceding RR interval and the amplitude of EAD 
that follows. When these EADs reach a critical thresh-
old, they trigger an ectopic beat that initiates torsade 
de pointes (Figure C.4).

A ventricular cell subtype designated the M-cell, 
which is found in the deep sub-epicardial to mid-
myocardial layers, is very sensitive to the effects 
of I_Kr blockers. These cells, also found in human 
ventricles, have electrophysiological properties that 
are different from those of epicardial or endocardial 
ventricular cells, and intermediate between those of 
the ventricular muscle and the Purkinje fibres. Rela-
tive to the epicardial and endocardial myocytes, these 
M-cells are characterized by (i) the weak presence 
of the slowly activating component of the repolariz-
ing potassium current (I_Ks) and (ii) the presence of 
the more sustained depolarizing slow sodium (I_Na) 
and calcium (I_Ca) currents. Another hallmark of these 
M-cells is the ability of their action potential to 
lengthen markedly with decreasing stimulation rate.

Figure C.3. Cardiac action potential, ion currents and QT interval on surface ECG.
Since the repolarizing \(I_{ks}\) is weak, these M-cells rely almost exclusively on the presence of fully functional \(I_{Kr}\) for repolarization. All these differences render the M-cells more susceptible to the effects of \(I_{Kr}\) block, which thereby respond with a more prolonged action potential and induction of EADs. Not surprisingly, \(I_{Kr}\) blockers have profound effect in these cells, giving rise not only to prolongation of the QT interval on the surface ECG, but also to an increase in transmural dispersion of repolarization (radially) across the myocardial wall at tissue level. An increase in transmural dispersion of repolarization creates an electrophysiological environment, or gradient, for the development of re-entry (Figure C.4). This radial dispersion of repolarization, rather than QT interval prolongation, is now widely regarded as both the proarrhythmic substrate and a more predictive and reliable marker of the proarrhythmic risk (Fenichel et al., 2004; Antzelevitch, 2005).

As a corollary, drugs that block both \(I_{Kr}\) and \(I_{ks}\) (and other relevant ion channels and receptors) may be expected to uniformly prolong the action potential across the entire thickness of the ventricular wall (and therefore, the QT interval), without having any significant effect on transmural dispersion of repolarization. Although these agents (e.g. amiodarone and the recently developed antianginal drug ranolazine) prolong the QT interval, they have not been found to be proarrhythmic.

**DRUG-INDUCED QT INTERVAL PROLONGATION AND REGULATORY GUIDANCE**

In view of the numerous high-profile, non-antiarrhythmic drugs which attracted considerable regulatory attention during the period 1990–96 due to their potential to prolong the QT interval and induce torsade de pointes, the *Committee for Proprietary Medicinal Products* (CPMP) adopted two significant documents in December 1997. One of these was the CPMP document ‘Points to Consider: The Assessment of the Potential for QT Interval Prolongation by Non-cardiovascular Medicinal Products’ (Anon, 1997a). The recommendations contained therein were
not mandatory, but they represented preclinical and clinical strategies that the EU regulators advocated for the investigation of any new chemical entity (NCE) for its capability to prolong the QT interval and induce proarrhythmia. Following the regulatory concerns and the CPMP document, the European Society of Cardiology organized a Policy Conference on drug-induced QT interval prolongation under the auspices of its Committee for Scientific and Clinical Initiatives. This conference endorsed a more rigorous investigation of the preclinical electrophysiologic and clinical electrocardiographic effects of new drugs (Haverkamp et al., 2000). A similar Expert Meeting in the United States, sponsored by the Duke Clinical Research Institute and American Heart Journal, also advocated a proactive approach to identifying this important risk (Anderson et al., 2002).

A number of drugs such as terfenadine, astemizole, pimozide and cisapride were found to induce torsade de pointes and other proarrhythmias following drug interactions. Therefore, the other strategic document adopted by the CPMP was its ‘Note for Guidance on the Investigation of Drug Interactions’ (Anon, 1997b). Such is the regulatory concern on drug-induced QT interval prolongation that there has now evolved two internationally harmonized regulatory guidelines on strategies by which to evaluate new drugs for this liability. In May 2005, the ICH adopted two guidelines that deal with this safety concern – one dealing with preclinical strategy (ICH S7B) and the other dealing with clinical strategy (ICH E14). While the focus of ICH S7B is on detecting delayed ventricular repolarization and QT interval prolongation, ICH E14 focusses on detecting QT/QT interval prolongation.

At the time of writing this chapter, the Committee for Medicinal Products for Human Use (CHMP) of the EU had adopted (Step 5 of ICH) these guidelines (ICH E14 as CHMP/ICH/2/04 and ICH S7B as CHMP/ICH/423/02) during their meeting in May 2005, with an operational implementation date of November 2005 (Anon, 2005a,b). Both the US Food and Drug Administration and the Japanese Ministry of Health, Labour and Welfare will notify later the dates for implementation of these guidelines within their jurisdictions. Both ICH S7B (preclinical) and ICH E14 (clinical) provide state-of-the-art recommendations on strategies for investigating a new drug for its potential to delay ventricular repolarization and induce QT interval prolongation.

Both the CPMP document ‘Points to Consider: The Assessment of the Potential for QT Interval Prolongation by Non-cardiovascular Medicinal Products’ and the ICH guideline S7B provide recommendations on preclinical strategies by which to investigate a drug for its QT-liability. The core studies recommended by the ICH S7B guideline are in vitro $I_{Kr}$ or hERG channel studies, and in vivo investigations in dog or other laboratory animals such as monkey, swine, rabbit, ferret and guinea pig.

Both the CPMP document ‘Points to Consider: The Assessment of the Potential for QT Interval Prolongation by Non-cardiovascular Medicinal Products’ and the ICH guideline E14 also provide recommendations on clinical strategies by which to investigate a drug for its potential to prolong the QT interval. Of special current interest is the call by ICH E14 for a single clinical trial, termed the ‘thorough QT/QTc study’, specifically dedicated to investigating the effect of an NCE on ECG parameters, with a special focus on QT interval (Anon, 2005b). This clinical guideline raises a number of important issues and will present significant challenges during drug development.

The conduct of the ‘thorough QT/QTc study’, typically in healthy volunteers, requires prior knowledge of the full pharmacology of the drug, as well as its potential therapeutic doses in man. Unfortunately, even today, the CYP isoform(s) responsible for the metabolism of terodiline has not been adequately identified, and the role of CYP2D6-mediated genetic factors remains a matter of informed speculation. It is also obvious that the pharmacokinetics and pharmacodynamics of each individual enantiomer of chirally active drugs should be fully investigated. Despite the known stereoselectivity in primary pharmacodynamics of terodiline enantiomers, little was investigated with respect to their cardiac effects, most particularly their electrophysiological effects at ion channels, and yet the techniques were available at the outset. In the absence of these vital data, it is impossible to predict special patient populations at risk, and the hazards from potential drug interactions. It is ironic that terodiline should have been withdrawn from the market in the year in which the CPMP adopted its guideline on ‘Clinical Investigation
of Chiral Active Substances’ (Anon, 1993b; Shah, Midgley and Branch, 1998).

**PRECLINICAL INVESTIGATIONS OF THE ‘QT-LIABILITY’ OF A DRUG**

Since the discovery of the hERG channel in 1994, sponsors conduct *in vitro* studies ( unicellular preparations as well as recombinant hERG channels expressed in heterologous systems) to evaluate all new chemical entities (NCE) for their potential to inhibit the current mediated by the native cardiac I<sub>Kr</sub> channel. Indeed, early use of hERG channel studies as a screening test is now routine. As long as the results are interpreted carefully with regard to safety margins and other properties of the drug, these studies are valuable in identifying drugs with a potential to prolong the QT interval and hence probably induce torsade de pointes (Shah, 2005a). Drugs known to be torsadogenic in man have always been shown to be positive in these assays. False positive hERG studies are relatively frequent. Rarely, a false negative result may arise if the drug concerned prolongs repolarization not by inhibiting hERG, but by interfering with normal trafficking of this channel protein (e.g. arsenic trioxide or pentamidine) (Ficker et al., 2004; Katchman et al., 2006; Kuryshev et al., 2005).

Unicellular recordings of action potentials from ventricular tissues, myocytes or Purkinje fibres are also used to evaluate the effect of drugs on action potential duration and therefore the QT interval. Arising from the qualitative and quantitative distribution of various ion channels, M-cells seem to have a better predictive value than do other tissues. From one set of *in vitro* investigations, it is possible to obtain a broad range of clinically useful information. The species used for these tissue experiments could be guinea pig, rabbit or dog, depending on laboratory skills and database. The relevance of the selected species and tissue to man is perhaps the most important determinant of how useful the information obtained from these studies will be with regard to the risk posed by the drug to humans.

In addition to the above *in vitro* investigations, studies are also performed *in vivo* using dogs or other suitable species, and a number of proarrhythmic models have been developed over the last few years. Preclinical investigations of drugs for their potential to delay ventricular repolarization and prolong the QT interval are now very sophisticated, and have a remarkable predictive value with regard to clinical risk of torsade de pointes (Fenichel et al., 2004; Joshi et al., 2004; Shryock et al., 2004; Recanatini et al., 2005; Sanguinetti and Mitcheson, 2005).

More recent focus of preclinical studies is to document the predictive value of transmural dispersion in repolarization and TRImD (triangulation, reverse use dependency, instability and dispersion), rather than QT interval prolongation alone. HERG blockade still remains the basic mechanism underlying these relatively new markers (Antzelevitch, 2004; Shah and Hondeghem, 2005). Efforts are also underway to evaluate the predictive value of beat-to-beat variations in the morphology and amplitude of T-waves, which may potentially serve as indicators of delayed repolarization and electrophysiological instability.

Of the drugs listed earlier in the Introduction, studies with hERG channels would have successfully predicted the proarrhythmic activities of pimozide, sertindole, astemizole, terfenadine, cisapride, halofantrine, thioridazine, droperidol and levacetylmethadol. Studies using hERG channels have also been used to characterize the relative QT-prolonging potencies of various members of a chemical or pharmacological class, such as quinolone antibacterial agents or gastric prokinetic drugs.

Recent *in vitro* studies have confirmed that terodiline blocks the I<sub>Kr</sub> current – the molecular substrate for prolongation of the QT interval. Whereas the therapeutic concentrations of terodiline are in the range of 1.5 μM, its IC<sub>50</sub> value for I<sub>Kr</sub> block was found to be 0.7 μM (Jones et al., 1998). In guinea pig papillary muscles and ventricular myocytes, clinically relevant concentrations of terodiline lengthened the action potential duration by up to 12%, while higher concentrations shortened the duration in a concentration-dependent manner. Further voltage-clamp studies in guinea pig ventricular preparations indicate that terodiline at much higher concentrations also inhibits two other membrane currents that govern repolarization: (i) an L-type calcium current (IC<sub>50</sub> value of 12 μM) and (ii) a slowly activating, delayed rectifier potassium current (I<sub>Ks</sub>) with an IC<sub>50</sub> value of 26 μM (Shuba et al., 1999). Fossa et al. (2002) tested cisapride and terodiline in conscious
dogs at their clinically relevant free drug concentrations. Using a sophisticated beat-to-beat QT–RR interval assessment, they were able to demonstrate the QT-prolonging effects of both these drugs. The dose-response curve for both was bell-shaped. For terodiline, the greatest mean QT prolongation occurred at a free drug concentration of 0.0329 µM, with concentrations higher than this being less active in this regard. This is interesting in view of the stereoselective concentration-dependent pharmacodynamic properties of terodiline discussed earlier. Fossa et al. (2002) were also able to show that for drugs that affect repolarization through multiple channels, the effect on the mean QT interval may be more difficult to detect, but individual responses to the QT–RR interval relationship increased the sensitivity for more accurate clinical prediction.

PRE-APPROVAL CLINICAL SAFETY DATASET

The extent of the dataset required in terms of ECG monitoring in subsequent clinical studies will depend on a variety of factors, particularly the results from S7B-compliant preclinical studies and the ‘thorough QT/QTc study’ (Shah, 2005b).

The ICH E1A guideline (‘The Extent of Population Exposure to Assess Clinical Safety for Medicines Intended for Long-term Treatment of Non-life Threatening Conditions’) (Anon, 1995) is helpful when considering the clinical safety dataset necessary for regulatory submissions when exploring the potential of an NCE indicated for a long-term treatment of non-life threatening conditions, and for hazards associated with other drugs of the same chemical, pharmacological and/or therapeutic classes. For the most usual case, that is frequent and early onset (these are generally concentration-related) events, this guideline (adopted in 1995) provides for 1500 patients to be studied over 3 months. It is estimated that this database will characterize an adverse event with a cumulative 3-month incidence of about 1% or more. Whereas prolongation of the QT interval may be observed in some patients in the dataset, it is most unlikely that any episodes of torsade de pointes (induced by a non-antiarrhythmic drug) will be identified, since the latter is often transient, requires an ECG machine for diagnosis and usually has a frequency in the order of 1 in 10 000 or much less.

EXCEPTIONAL CIRCUMSTANCES REQUIRING EXTENDED DATABASE

The ICH E1A guideline recognizes that a larger database and/or a longer period of exposure than usual may also be required in some circumstances. To this end, it provides for exceptional circumstances when the harmonized general standards for clinical safety evaluation may not be applicable and an expanded database may be required. These exceptions cover a diverse range of circumstances, and can best be discussed using drug-induced QT interval prolongation/torsade de pointes as an example. The approach is equally applicable to other rare but serious adverse effects, such as clinical hepatotoxicity, gastro-intestinal haemorrhage, neutropenia and so on. Although there are a number of exceptional circumstances specified in the guideline, six are particularly relevant to most NCEs.

CHEMICAL STRUCTURE

Without doubt, any drug that shares a structural similarity with prenylamine is a candidate for an expanded clinical safety dataset, in order to better assess its potential to prolong the QT interval. Not surprisingly, terodiline, terfenadine, cisapride and pimozide all bear an obvious structural similarity to prenylamine, and would have called for an expanded clinical dataset to characterize their potential for QT interval prolongation and torsade de pointes. With regard to QT interval prolongation, many chemical classes have been implicated (Shah 2002; Aptula and Cronin, 2004; Aronov, 2005; Recanatini et al., 2005), and therefore a wide range of NCEs would require an expanded clinical dataset.

PHARMACODYNAMIC/PHARMACOKINETIC PROPERTIES KNOWN TO BE ASSOCIATED WITH SUCH ADVERSE EVENTS

When an investigational drug is found in preclinical studies to block $I_{Kr}$ or hERG channel and/or prolong the action potential, ICH E14 recommends
that the clinical safety dataset focusing on ECG effects needs to be expanded, regardless of a negative ‘thorough QT/QTc study’ if the preclinical/clinical discrepancy cannot be explained. References have already been made to pharmacodynamic and pharmacokinetic similarities between terodiline and prenylamine. In retrospective preclinical studies conducted post-approval, prenylamine, terodiline, terfenadine, astemizole, pimozide, halofantrine, cisapride and levacetylmethadol have all been found to possess QT-prolonging properties, and would have called for an expanded clinical dataset had these studies been conducted prior to their approval. Focussed clinical studies with terodiline, albeit following its removal from the market, and other drugs confirmed that they had the potential to prolong the QT interval in man.

DATA FROM ANIMAL STUDIES

In compliance of the ICH E14 guideline, the clinical safety dataset needs to be expanded if ICH S7B-compliant in vivo studies are strongly positive, regardless of the status of the ‘thorough QT/QTc study’. The requirements for preclinical investigations at the time of developing prenylamine were rudimentary. Information on findings from animal studies with prenylamine was now difficult to obtain. Although original preclinical studies with terodiline showed no effect on the QT interval in conscious dog or rat, ECG effects (including prolongation of the QT interval) were reported in anaesthetized cats. This finding in itself would have warranted further preclinical studies and an extended clinical safety database. Webster et al. (2001) have recently shown that terodiline does induce QT prolongation in dogs and emphasized that for compounds known to be clinical torsadogens (terfenadine, terodiline, cisapride), there is little differentiation between the QT-prolonging and the clinically effective free plasma concentrations in man (<10-fold). This is reflective of their limited safety margins.

OTHER AGENTS OF THE SAME PHARMACOLOGICAL CLASS

A range of ICH guidelines (ICH E1A, ICH E2E, ICH S7B and ICH E14) emphasize the need to take into account the pharmacological activities associated with other members of the same chemical or pharmacological class as the NCE under investigation. Therefore, this particular scenario requires that the safety database be expanded to exclude any class-related risks. Apart from prenylamine and lidoflazine, a number of other antianginal drugs such as bepridil, tedisamil, fendiline and aprindine have all been shown to prolong the QT interval and induce proarrhythmias. Therefore, during their clinical development, terodiline as well as any other antianginal drug would call for an expanded clinical safety database, for routinely evaluating their potential to prolong the QT interval. This is analogous to all non-steroidal anti-inflammatory drugs (NSAIDs) being evaluated for their gastro-intestinal toxicity. With regard to QT interval prolongation, many pharmacological classes have been implicated (Shah, 2002; Aptula and Cronin, 2004; Anson et al., 2005; Aronov, 2005; Recanatini et al., 2005), and therefore, again as stated above, a wide range of NCEs would require an expanded clinical dataset.

When discussing the ‘pharmacological class’ of a drug, the notion of its ‘therapeutic class’ deserves a comment. Following structural modifications of a lead compound or following the approval of a drug, it is often discovered to have more potent activity at a pharmacological target other than that intended originally. Therefore, drugs are often intended for development in one specific therapeutic area but are later developed or used clinically in an entirely different therapeutic area. Thus, drugs frequently cross ‘therapeutic boundaries’ (Shah, 2002). Therefore, lack of a safety concern in drugs of a therapeutic class is not altogether wholly reassuring when developing another drug in the same therapeutic class – what really matters is the chemical or the pharmacological class. Terodiline itself was re-developed for use in a completely different therapeutic area (urinary incontinence) that was not associated with any proarrhythmic risk. Terfenadine is another typical example. It was discovered through a central nervous system programme aimed at synthesizing new antipsychotic agents, but because of its more potent secondary pharmacological effects at the H1-antihistamine receptor, its development was diverted to market it as the first non-sedating H1-antihistamine. However, like other antipsychotic agents, it was sooner or later bound to
attract regulatory attention because of the potential of antipsychotics-related chemical structures to have an effect on the QT interval. As an antihistamine, terfenadine remained a highly successful and popular drug until withdrawn, due to reports of torsade de pointes resulting from drug interactions. Sildenafil, originally intended for development as an antianginal drug, was developed instead for male erectile dysfunction, and it is not surprising that at high concentrations, it too has been shown to prolong cardiac repolarization by blocking the rapid component of the delayed rectifier potassium current (Geelen et al., 2000). At clinical doses, however, a significant effect on QT interval is most unlikely (Morganroth et al., 2004), especially since the drug is used intermittently. However, its further development for use in pulmonary hypertension may present interesting dilemmas (Shah, 2005b).

NEED TO QUANTIFY LOW FREQUENCY EVENTS

Depending on whether a drug is a class III antiarrhythmic drug or not, the frequency of QT interval prolongation and/or torsade de pointes can vary widely. For a number of antianginal or non-cardiac drugs, these are low frequency events associated with their use. It is therefore self-evident that an expanded clinical safety database would be required for a new antianginal drug. The size of the database would be determined by the preclinical data and the anticipated frequency of the event to be detected, as well as the confidence with which the risk is to be excluded. Since the risk of torsade de pointes is often as low as 1 in 10,000 or even lower, requirements for very large databases can be counter-productive to the extent that they delay the introduction of otherwise beneficial medicines to the market.

ALERTS/SIGNALS DURING CLINICAL TRIALS

A dataset that is larger and/or of longer exposure may also be appropriate when a specific serious adverse event that represents an alert is observed unexpectedly in early clinical trials. When the potency of an NCE to delay ventricular repolarization is high, signals are often detected during early clinical trials, frequently pharmacology studies in healthy volunteers or early dose-ranging studies in patients. Pimozide, for example, was found to prolong the QT interval in about 10% of the patients in one study in 1989. Similarly, halofantrine was also found to produce an effect on the QT interval during early clinical trials. This is especially important when an event is a ‘moving target’ depending on the presence of other risk factors, such as drug interactions or other intercurrent events.

As it was, the clinical trials database on terodiline was comparable with those for other contemporary drugs intended for urinary incontinence. In retrospect, however, it was not large enough for a drug with its chemical and pharmacological pedigree. It had included 8 controlled \((n = 229)\) and 6 uncontrolled \((n = 147)\) studies with a total population of 376 patients exposed to terodiline. Of these, 241 had received the drug for up to 1 month, and a further 39 for 2–3 months. Seventy-five patients had been treated for 4–12 months. In the aftermath of its withdrawal, a number of studies investigated the ECG effects of terodiline. Apart from the study by Thomas et al. (1995) referred to earlier, other studies have shown that adequate ECG monitoring of the patients during clinical trials ought to have identified the proarrhythmic risk. In the study by Yoshihara et al. (1992) in 109 Japanese patients receiving 24 mg daily of terodiline for 4 weeks, side effects such as orthostatic hypotension and arrhythmia were observed, and these symptoms disappeared following discontinuation of the treatment. Of note is the prospective study by Stewart et al. (1992) in 8 elderly in-patients treated with terodiline for urinary incontinence. They found that after 7 days of treatment with 12.5 mg twice daily, terodiline significantly increased the QT interval by a mean of 29 ms and the QTc interval by 15 ms and decreased the resting heart rate by a mean of 6.7 beats per minute.

As a result of experiences with some of the established as well as newly introduced drugs, clinical trials programmes now usually include ECG monitoring in at least one or two large studies, particularly those investigating high doses or studying the effect of inhibition of drug elimination (e.g. drug interaction studies). Depending on the ECG findings from these ‘exploratory’ studies, the database may require expansion to address the proarrhythmic risk more fully.
RISK–BENEFIT ASSESSMENT

Despite the fact that QT interval is not a very reliable surrogate of torsade de pointes, it is nevertheless true that drugs that prolong QT interval are considered more likely to cause torsade de pointes in susceptible patients than drugs that do not. Therefore, QT interval prolongation has been used in distinguishing safer drugs from those that are less safe within the same class. Not surprisingly, regulatory authorities are reluctant to approve drugs that prolong the QT interval when the potential benefits are very modest, and especially when alternatives without the QT-liability are already available. For example, ebastine (a non-sedating H1-antihistamine) has not been approved in the United States because of its ability to prolong the QT interval, although there are no documented reports of torsade de pointes associated with its extensive use elsewhere. The reason is almost certainly the availability of alternatives without such a liability. However, it should not be assumed that just because a drug prolongs the QT interval, it might not be approvable.

A number of factors determine whether drugs that prolong the QT interval can be approved, particularly because the QT-liability of a drug does not necessarily translate into a proarrhythmic activity (Shah, 2002; 2004). In contrast to ebastine, drugs such as ziprasidone or arsenic trioxide that prolong the QT interval to a much greater extent have nevertheless been approved, because they were considered to have an acceptable risk–benefit profile. Arsenic trioxide illustrates particularly well how even a drug with very marked potential to prolong the QT interval, and actually induce torsade de pointes, may be approved with specific guidelines associated with its clinical use, if it is shown to fulfill an unmet need. Arsenic trioxide (‘Trisenox’) was approved in September 2000 in the United States and in October 2001 in the EU for its remarkable efficacy in induction of remission and consolidation in patients with a specific form of acute promyelocytic leukaemia who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy. Protease inhibitors are another class of drugs that block hERG, prolong the QT interval and induce torsade de pointes (Anson et al., 2005). However, their clinical benefits far outweigh their very small proarrhythmic risk.

With respect to risk–benefit analysis of a drug that actually induces torsade de pointes and other ventricular tachyarrhythmias, the benefit offered by the new drug merits very careful assessment. Furthermore, the risk of torsade de pointes is not an ‘all-or-none’ effect. Depending on the benefit offered by the drug, an incidence of 1 in 3000 might be unacceptable whereas an incidence of 1 in 500 000 may be considered acceptable with a whole range of risk–benefit in between. As stated earlier, risk–benefit analysis in drug development and the regulatory approval process includes not only the alternatives already available, but also the seriousness of the condition under treatment. For relatively benign indications such as hay fever or gastroparesis, a risk of proarrhythmias even as low as 1 in 100 000 recipients is unlikely to be acceptable.

DEVELOPMENT OF SINGLE ENANTIOMERS OR METABOLITES OF MARKETED RACEMIC DRUGS

The comparison between prenylamine and terodiline described in this chapter shows the strengths of a scientific synthesis of all the available information when evaluating the significance of even a handful of spontaneous reports of an adverse event, and formulating the most appropriate regulatory strategies for risk management. This is especially relevant when another member of the same chemical, pharmacologic or therapeutic class is associated with the same low frequency adverse event.

The marketing authorization holder of terodiline has to be commended for the speed and the willingness with which the drug was withdrawn as soon as it became evident that the risk is unlikely to be immediately manageable. Unfortunately, they did not follow up the recommendation from the regulatory assessor to investigate separately the two enantiomers systematically for their pharmacology, and possibly develop one of these if it can be shown to be devoid of potassium-channel-blocking activity while retaining a beneficial therapeutic effect. In the light of subsequent investigations showing that (−)-(S)-terodiline does not affect the QTc interval (Hartigan-Go et al., 1996) and does indeed have some anticholinergic properties, the possibility that (−)-(S)-terodiline might have
a much superior risk–benefit profile compared to the racemic mixture is a real one. At the time of its withdrawal in 1991, the development of a single enantiomer may have appeared an arduous and potentially unrewarding activity, but paradoxically this has been one of the striking features of new drug development in the period 1994–2002. This trend has resulted in the development of (S)-ketoprofen, (S)-ofloxacin, (S)-omeprazole, (R)-salbutamol, (S)-citalopram and (S)-ketamine among many others that are still in the pipeline (Shah, 2000).

It is interesting that astemizole has two metabolites – desmethylastemizole and norastemizole. Preclinical data show that desmethylastemizole is as cardiotoxic as the parent drug. Since desmethylastemizole has a very long half-life relative to astemizole, plasma levels of desmethylastemizole are generally about 30-fold higher than that of astemizole, and the clinically observed cardiotoxicity appears to be mainly due to desmethylastemizole. In one patient with astemizole-induced torsade de pointes, plasma desmethylastemizole and astemizole concentrations were 7.7–17.3 ng/mL and < 0.5 ng/mL, respectively (Volperian et al., 1996). Not surprisingly, cardiotoxicity of astemizole is the highest following an overdose, or when a high loading dose is administered to quickly achieve the steady-state therapeutic concentrations (Anon, 1987). In both these situations, there is rapid accumulation of desmethylastemizole. Findings such as these not only preclude the development of some metabolites, but also illustrate the strengths of simple observations that should guide the drug development programme and evaluation of post-marketing case reports of adverse drug reactions.

Development of active but safer metabolites which are devoid of the unwanted secondary cardiotoxic pharmacology, or unwanted metabolic profile and drug interaction potential, has been another trend in drug development (Shah, 2005a). Preclinical data have suggested that the risk–benefit ratio might be superior for the metabolite compared to the corresponding parent drug for fexofenadine (a metabolite of terfenadine), norcispamide (a metabolite of cispamide), norastemizole (a metabolite of astemizole), desmethylloratadine (a metabolite of loratadine) or norlevacetylmethadol (a metabolite of levacetylmethadol). These preclinical leads have already been followed up for some of these metabolites, and fexofenadine and desmethylloratadine are now already on the market.

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REFERENCES

Anon (1993b) Clinical investigation of chiral active substances. CPMP Guideline (CPMP/3501/91). In: The Rules Governing Medicinal Products in the


