Withdrawal of prenylamine: perspectives on pharmacological, clinical and regulatory outcomes following the first QT-related casualty

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Abstract: Prenylamine, an antianginal agent marketed since early 1960, became the first casualty of QT interval related proarrhythmias in 1988 when it was withdrawn from the market. The period of its synthesis and marketing is of particular interest since it antedated, first, any serious clinical safety concern regarding drug-induced prolongation of the QT interval which was, in fact, believed to be an efficient antiarrhythmic mechanism; second, the first description of torsade de pointes as a unique proarrhythmia, typically associated with prolonged QT interval; and third, the discovery and recognition of calcium antagonism as an important cardiovascular therapeutic strategy. This review, 30 years almost to the day following its withdrawal, provides interesting perspectives on clinical, pharmacological and regulatory outcomes that followed. Prenylamine underscored torsadogenic potential of other early antianginal drugs on the market at that time and identified QT-related proarrhythmias as a much wider major public health issue of clinical and regulatory concern. This resulted in various guidelines for early identification of this potentially fatal risk. Application of these guidelines would have readily identified its proarrhythmic potential. Prenylamine also emphasized differences in drug responses between men and women which subsequently galvanized extensive research into sex-related differences in pharmacology. More importantly, however, investigations into the mechanisms of its action paved the way to developing modern safe and effective calcium antagonists that are so widely used today in cardiovascular pharmacotherapy.

Keywords: amiodarone, bepridil, calcium antagonists, drug regulation, lidoflazine, prenylamine, QT interval, terodiline, torsade de pointes

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Introduction

Prenylamine, an antianginal agent sold under a variety of brand names including Segontin and Synadrin, was among the earliest in a novel class of drugs, introduced to the European and non-US market in early 1960, by Hoechst AG, Frankfurt, Germany. Unfortunately, it is also the first drug to be withdrawn from the market, in 1988, because of its propensity to induce serious proarrhythmias associated with QT interval prolongation. While the proarrhythmic risks of prenylamine have been well documented in the literature, less well appreciated

are some of the important outcomes that followed as well as the period of its synthesis and marketing which was characterized by the lack of a regulatory legal framework for marketing human medicinal products, the presence of other QT-prolonging antianginal drugs in the market, and subsequent impact on various aspects of pharmacology and regulation and development of new drugs. This review is a historical perspective on some pharmacological, clinical and regulatory outcomes that followed the withdrawal of prenylamine, the first marketed drug ever to be a QT-related casualty.

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Chemistry, pharmacology and electrophysiology

Chemically, prenylamine is a diphenyl-propyl derivative of phenylalkylamine [3,3-diphenyl-N-(1-phenylpropan-2-yl)propan-1-amine] with a molecular weight of 329.49. The drug is optically active with one stereogenic centre, giving rise to two enantiomers (Figure 1). The product marketed was the racemic mixture.

Prenylamine has two principal molecular targets, calmodulin and myosin light-chain kinase 2 found in skeletal and cardiac muscle. Pharmacologically, it decreases sympathetic stimulation of the cardiac muscle predominantly by depletion of transmitter substance from adrenergic nerve endings by competitive inhibition of reuptake by storage granules.^{1,2} Prenylamine also reduces myocardial metabolism by blocking magnesium-dependent calcium transport ATPase. It inhibits calcium current albeit with much weaker potency than other calcium channel blocking drugs such as verapamil and nifedipine.³ While prenylamine slows the heart rate, available evidence suggests that it lacks any β -blocking activity. Prenylamine has also been shown to inhibit competitively contractions of the detrusor strips from bladder. Although, by 1969, the drug had been on the market for well over 5 years, the pharmacological mechanism underpinning its antianginal activity was not sufficiently understood.^{4,5}

Prenylamine is rapidly and completely absorbed after oral administration, with peak plasma concentration being approximately 1.0 $\mu\text{g/ml}$ after an oral dose of 120 mg. It is more than 95% protein bound and is extensively metabolized in humans, primarily by ring hydroxylation to p-hydroxy-prenylamine, and less than 0.1% of the dose is excreted unchanged. Its metabolism displays wide interindividual variation and is enantioselective, favouring the elimination of the (+)-(S)-enantiomer.^{6,7} Gietl and colleagues studied the pharmacokinetics of S-(+)- and R-(-)-prenylamine in eight healthy volunteers given single and repeated oral doses of the racemic drug. In two of the eight volunteers, plasma half lives for the (+)-(S)-enantiomer following a single dose were exceptionally long (82 h and 83 h compared with a mean half life of 11 h in the other six subjects).⁷ None of these eight participants were genotyped or phenotyped for their metabolic status of any of the known genetic polymorphisms of major drug metabolizing enzymes, but these high values raise the possibility that prenylamine hydroxylation may

Figure 1. Chemical structures of prenylamine and terodiline.

be polymorphic, probably mediated by CYP2D6 enzyme, since the drug meets the criteria of a CYP2D6 substrate.

A number of investigators had studied the electrophysiological properties of prenylamine.⁸⁻¹² In order to explore further its bradycardic, negative inotropic and torsadogenic effects, de Bonfioli Cavalcabò and colleagues¹² studied its electrophysiological activities in great detail and reported that prenylamine was able to abolish early after depolarizations (EADs) which can trigger arrhythmias such as torsade de pointes (TdP). They concluded that prenylamine had an intriguing *in vitro* electrophysiological profile, making it difficult to extrapolate these *in vitro* findings to its *in vivo* pharmacology. In another study in cat papillary muscle preparations, (+)-(S)-enantiomer was found to have positive inotropic action and prolong action potential duration at low concentrations and preferentially at low stimulation rates while (-)-(R)-prenylamine had a negative inotropic effect and shortened the action potential duration but only at high stimulation rates and only to a minor extent.¹¹ (+)-(S)-prenylamine also caused dysrhythmias in 4 of the 12 isolated

papillary muscle preparations. Therefore, overall, the data suggest that the proarrhythmic effect of prenylamine may have been mediated by (+)-(*S*)-prenylamine which, at low concentrations, prolongs action potential plateau and duration. Studies undertaken much later after its withdrawal, reported in 2006, revealed that prenylamine blocks the cardiac hERG (human ether-a-go-go) channel¹³ responsible for ventricular repolarization (QT interval) and, at higher concentrations, also the sodium channel¹⁴ that affects depolarization (QRS complex). Thus, prenylamine resembled quinidine¹⁵ which, at low concentrations, also induces QT prolongation without widening the QRS complex.^{16–18}

Clinical trials with prenylamine

Prenylamine was introduced to the European, Canadian and many other markets (except the US market) and was widely used as testified by the number of countries reporting proarrhythmias associated with its use (see section 'Withdrawal of prenylamine from the market'). It is worth recalling that when drugs such as prenylamine were first introduced in the early 1960s, there was no regulatory or legal framework for drug approval in most countries of the world, including Europe. In the US, the Food, Drug, and Cosmetic Act, enacted in 1938, allowed drugs to be marketed as long as they were shown to be safe but without the requirement to demonstrate efficacy in the labelled indication. Furthermore, by current standards, clinical trials at that time were rudimentary with small sample sizes, generally lacking in statistical rigour and principally focusing on efficacy.

Prenylamine was investigated for its antianginal efficacy in a number of clinical studies of small sample sizes, which generally found it to be effective and well tolerated. Prenylamine reduced resting heart rate as well as post-exercise tachycardia in man. With a therapeutic dose of 60 mg, administered two to four times a day, it was effective in reducing the number of anginal attacks and the frequency of glyceryl trinitrate consumption and increasing exercise tolerance, without significantly affecting blood pressure, in patients with ischaemic heart disease.^{19–27} Even following long-term administration of prenylamine (daily dose range 120–240 mg) to 12 patients, there were no side effects or any serious complications, or any undesirable effect on routine laboratory variables attributable to the drug.²⁶ However, one report of

a series of clinical trials published in 1987, comparing nine calcium antagonists and propranolol against placebo, concluded that all the drugs except prenylamine increased the exercise tolerance significantly.²⁸

Although electrocardiograms (ECGs) were recorded during most of the clinical trials investigating its antianginal activity, the electrocardiographic endpoints of interest were the effect of the drug on ST segment (an indicator of myocardial ischaemia) and PR interval (an indicator of atrio-ventricular conduction) of the ECG, with none reporting its effect on QT interval.

Following the introduction of legislation and regulatory control over marketing of medicinal products in the UK in 1971,²⁹ some 30,000 medicinal products already on the market, prenylamine included, were given Product Licences of Right (PLRs) to enable their continued marketing, conditional upon review of their safety, quality and efficacy in due course by a special advisory body, the Committee on the Review of Medicines, to be established specifically for this purpose.²⁹ This legal requirement for review of PLRs is equivalent to the contract of the US Food and Drug Administration with the National Academy of Sciences/National Research Council in 1966 to evaluate the effectiveness of some 4000 different drug formulations which were approved on the basis of safety without evidence of effectiveness between 1938 when the Federal Food, Drug, and Cosmetic Act was enacted, and 1962 which was the year of the Kefauver–Harris Amendment requiring new drugs to be effective for their labelled indications, as well as safe.³⁰ This review process in the US became known as the Drug Efficacy Study Implementation (DESI) review.

Reports of prenylamine-induced proarrhythmias

Initial publication of a case report of an adverse drug reaction (ADR) has not infrequently heralded an avalanche of other reports of the ADR, exposing the presence of a major drug-related risk to the public, and typically culminating in either the restrictions on the use of a medicinal product or its withdrawal from the market.³¹ Often, these reports have also served to advance pharmacology and therapeutics.³¹ Although a number of other drugs have illustrated this important role of published case reports, prenylamine illustrates this

further and quite vividly in the context of drug-induced torsadogenesis.

Picard and colleagues^{32,33} appear to be the first to report repeated syncope and ECG changes during prolonged treatment with prenylamine. Among other earliest reports were cases published by Fazzini and colleagues³⁴ and Bens and colleagues,³⁵ which described prolonged QT interval, ventricular tachycardia and syncope in association with the use of prenylamine. These early reports were later followed by a number of similar reports associating prenylamine with syncope, QT interval prolongation, ventricular tachycardia and TdP.^{36–50}

Interestingly, in the aftermath of this increasing number of reports of prenylamine-induced QT prolongation and proarrhythmias, Oakley and colleagues⁵¹ investigated the effect of 180 mg daily dose of prenylamine on QTc interval in 29 patients with angina pectoris. Data from 26 evaluable patients revealed 14 patients in whom there was an increase in the QT interval of more than 40 ms when taking prenylamine, four with lesser degree of prolongation and eight in whom there was shortening or no change. The interval to onset of a significant prolongation of QT interval was 1 week of treatment. The effect persisted for the duration of treatment (up to 6 months) and dissipated within 2 weeks following the withdrawal of prenylamine. There were no instances of ventricular tachycardia and none complained of palpitations or syncope. Of the three patients in whom ECGs were monitored for 24 h before withdrawal of therapy, two had occasional ventricular extrasystoles and the third displayed frequent ventricular extrasystoles, occasionally occurring as couplets.

Increasingly since its introduction, the efficacy of prenylamine was being questioned by some clinicians whereas the evidence of its undeniable proarrhythmic risk was gradually accumulating, impacting negatively on its benefit/risk balance. Indeed, reporting a 55-year-old woman with prenylamine-induced TdP 2 weeks after starting a dose of 60 mg three times daily and discussing its torsadogenic propensity, Fraser and Ikram⁵² questioned whether clinicians still needed prenylamine in their antianginal armamentarium. In July 1987, a general review of the efficacy and safety of prenylamine reported that at least 55 case reports of dangerous ventricular arrhythmias had been published, among them 12 patients who required resuscitation from cardiac arrest.⁵³ The same review noted that the UK regulatory

authority had received 22 reports of arrhythmias or ECG abnormality, including one death, and concluded that the drug should be withdrawn.

Withdrawal of prenylamine from the market

Since prenylamine was granted a PLR in the UK in March 1973, subject to a review of efficacy and safety, it was scheduled for review by the UK Committee on the Review of Medicines. An application for a reviewed product licence (equivalent to a full marketing authorization) was made in August 1986 and its safety and efficacy were considered by the Committee in March 1987.

During the period 1975–1986, the sponsor had received 90 reports of cardiovascular ADRs, which included 42 reports of TdP (20 from France, eight from Argentina, six from the UK, four from India, three from Spain and one from Belgium), in addition to other cardiac ADRs from Germany, Japan and Sweden. This illustrates the limitations of spontaneous reporting of ADRs since the literature already included case reports of TdP that could have originated from Germany⁴⁵ and Italy.^{39,41} The available worldwide proarrhythmic safety data, comprising 158 cases reviewed by the Committee, are summarized in Table 1. There were eight deaths among these cases but in many instances, it was difficult to determine the causal relationship of death to prenylamine. Figure 2 shows the decrease in QT interval duration on discontinuation of prenylamine in 36 patients in whom the information on QT interval on and off prenylamine was available. The mean values in these 36 patients were 634 ms on prenylamine and 408 ms off prenylamine. One of the patients with an on-drug QT interval of 840 ms had an off-drug value of 600 ms, suggesting possibly either impaired elimination of prenylamine or pre-existing (congenital) long QT syndrome. Although the details of correction (if any) of the measured QT interval for heart rate in these 36 patients were unknown, the values are comparable to those in eight patients reported by Grenadier and colleagues⁴³ in whom the measured QT intervals were corrected by Bazett's formula (see Table 2).

The Committee provisionally concluded that on grounds relating to safety (reports of cardiac arrhythmias, particularly TdP) and insufficient efficacy in relation to safety, a reviewed product licence could not be granted. During an appeal heard in July 1987, the earlier findings and conclusions were upheld; in particular, it was

Table 1. Prenylamine-induced proarrhythmias.

Total cases of VT/VF/TdP = 158 [§]		
	N	Mean $\pm$ SD or number
Age (years)	114	68 $\pm$ 11 (range 30–88)
Sex	110	87F (79%) / 23M (21%)
Concomitant therapy	109	30 on no other treatment
Serum potassium (mmol/liter)	82	3.6 $\pm$ 0.8 <3.5 (34 patients) >5.4 (none)
Duration of therapy with prenylamine (months)	69	20 $\pm$ 34 <1 week (6 patients) <1 month (10 patients)
Heart rate (bpm)	74	60 $\pm$ 11
QT interval on prenylamine (ms)*	89	630 $\pm$ 107 >500 (80 patients)
QT interval off prenylamine (ms)*	36	408 $\pm$ 52

*There was no consistency in measurement technique and the value reported was uncorrected in some cases and corrected for heart rate in others.
[§]Cases of syncope without electrocardiogram documented arrhythmia *not* included.
 F, female; M, male; N, number of patients with data available; TdP, Torsade de pointes; VF, ventricular fibrillation; VT, Ventricular tachycardia.

Figure 2. QT/QTc intervals on and off prenylamine in 36 patients with prenylamine-induced ventricular tachyarrhythmias.

determined that the risk of cardiac arrhythmias could not be predicted by any known risk factors or

mitigated by regular monitoring of patients for their potassium levels and QT interval, there were safer

Table 2. Summary of eight published cases of torsade de pointes (adapted from Grenadier *et al.*⁴³)

Age	Sex	K ⁺ (mmol/liter)	QTc interval (ms)*	
			On prenylamine	Off prenylamine
76	F	4.9	610	370
62	F	4.0	780	420
82	M	4.0	640	320
72	F	5.3	570	360
67	F	4.6	660	410
64	M	5.1	560	420
74	F	4.7	500	390
84	F	3.9	700	430
Mean		4.6	628	390
*Measured QT interval corrected using Bazett's formula. F, female; M, male.				

alternatives, and no subgroup of patients who could benefit from prenylamine could be identified.

As provided for in the legislation, the sponsor subsequently appealed to the Medicines Commission, a statutory body established to advise the Licensing Authority of the UK. In January 1988, following careful consideration of the safety and efficacy data, the Commission advised the Licensing Authority not to grant a reviewed product licence on the grounds that the serious concerns about the safety of prenylamine outweighed its benefits when there were safer drugs on the market for its indication. Therefore, the PLR for prenylamine lapsed in June 1988 and its marketing ceased.^{54,55} The UK authority was thus at the forefront in addressing a drug safety issue that was later to emerge as a major and much wider drug safety concern. During the period 1990–2006, drug-induced TdP and proarrhythmias accounted for 10 (26%) of the 38 drugs withdrawn from the market, being the second leading cause after hepatotoxicity.^{56,57}

Perspectives on the impact of prenylamine

Apart from the introduction of prenylamine to the market in the early 1960s when there was no formal regulatory or legal framework for the approval of drugs and adequate monitoring of their safety, the period of its synthesis and marketing is of particular interest since it antedated, first, any serious

clinical safety concern regarding drug-induced prolongation of the QT interval which was, in fact, believed to be an efficient antiarrhythmic mechanism; second, the first description of TdP as a unique proarrhythmia,⁵⁸ typically associated with prolonged QT interval; and third, the discovery and recognition of calcium antagonism as an important cardiovascular therapeutic strategy. Before the 1960s, the only QT-prolonging drugs on the market appear to be quinidine (an antiarrhythmic agent in wide use since the early 1920s) and thioridazine (a neuroleptic agent introduced in 1958).⁵⁹ That period is also notable for the synthesis of a number of other antianginal agents such as papaverine, terodiline, bepridil, lidoflazine, amiodarone and perhexiline, all classified as coronary vasodilators, which (as discussed in the next subsection) were later found to be calcium antagonists and associated with varying degree of torsadogenic risk. Search for agents with greater tissue specificity and improved safety ultimately led to the development of modern, more effective and safer calcium antagonists, all devoid of a torsadogenic potential.

Prenylamine underscored torsadogenic potential of other early antianginal drugs

Particularly noteworthy is the coexistence of prenylamine with terodiline, also a phenylalkylamine derivative marketed initially in 1965 as an

antianginal agent (marketed as Bicor by Kabi Group, Stockholm, Sweden) in Scandinavia.⁶⁰ Given its propensity to induce urinary retention, terodiline was later redeveloped for the treatment of urinary frequency, urgency and incontinence, and first introduced in the UK for this new indication in July 1986.⁶¹

Terodiline has potent calcium antagonist and anti-muscarinic activities. Since prenylamine and terodiline are structurally closely related (Figure 1), it is not surprising that the pharmacological effects of terodiline are not only concentration dependent but also enantioselective with calcium antagonist activity residing predominantly in (-)-(S)-terodiline, while the anticholinergic activity resides in (+)-(R)-terodiline.^{62,63} Reports of terodiline-induced QT interval prolongation and TdP began to appear in 1987, and by July 1991, there was a total of 21 reports of ventricular tachyarrhythmias (including 13 of TdP).⁶¹ Retrospective reporting of cases increased this number to 69 by September 1991 and the drug was removed from the market later that month.⁶¹ As with prenylamine,⁵¹ a prospective study in eight elderly inpatients with urinary incontinence, treated with 12.5 mg twice daily of terodiline for 7 days, reported a significant increase in QT interval (mean of 29 ms) and QTc interval (mean 15 ms) and a decrease in resting heart rate (mean 6.7 bpm).⁶⁴ A subsequent study also revealed terodiline-induced prolongation of the QT interval to be mediated exclusively by its (+)-(R)-enantiomer.⁶⁵

Other antianginal drugs that coexisted with prenylamine were lidoflazine and bepridil, both of which were also being investigated for use as antiarrhythmic agents. These agents were also being reported to induce QT interval prolongation and TdP.⁶⁶⁻⁷¹ Indeed, the frequency of TdP associated with these two drugs was sufficiently high that this adverse effect was reported even in small-scale clinical trials. For example, in a study of 28 patients with angina treated with lidoflazine, the increase in QT interval was so pronounced in one patient that severe rhythm disturbances occurred and the patient was withdrawn from the study.⁷² In another study of 24 patients with angina who received propranolol, lidoflazine or their combination, five patients developed ventricular tachycardia when receiving lidoflazine or lidoflazine and propranolol in combination; one of these patients died.⁶⁸ In this study, lidoflazine was associated with a significant prolongation of the QT interval. Hill and Pepine⁷³ evaluated the ECG

effects of bepridil in 13 men with exertional angina and reported it to prolong the QTc interval and produce T-wave changes in each patient. An evaluation of single daily doses of 200, 300 and 400 mg of bepridil and placebo in 178 patients with chronic stable angina reported small reductions in heart rate (mean 3.7 bpm) and prolongation of QT and QTc intervals (~30–40 ms) associated with bepridil treatment.⁷⁴ In France, bepridil had been available since 1981 for treatment of angina and a task force assembled to evaluate its safety and use noted that from 1981 to 1989, there were 108 validated episodes of TdP in patients treated with bepridil.⁷⁵ Data from US clinical trials of bepridil in 840 patients, of whom 820 had chronic stable angina, showed that at a median dose of 300 mg/day, it lengthened the QTc interval in most patients, the mean increase being 7.7% of the baseline duration. TdP occurred in seven patients, an incidence of approximately 1%.⁷⁶ Lidoflazine, although approved in a number of European countries (but not in the US), was never marketed and soon after the withdrawal of prenylamine in 1988, its availability was withdrawn in 1989 due to its QT-related proarrhythmic toxicity. In most countries, bepridil is no longer available for use in angina but its use as an antiarrhythmic agent continues to be investigated.^{77,78}

Although not widely appreciated, amiodarone too was originally marketed in 1962 as a coronary vasodilator for the treatment of angina pectoris.⁷⁹⁻⁸¹ Only much later did its potent antiarrhythmic properties draw clinical attention.^{82,83} While caution is required in equating QT prolongation with torsadogenic propensity, it is interesting that Debbas and colleagues⁸⁴ reported that amiodarone caused a significant lengthening of the QTc interval, there being a good correlation between its plasma and myocardial concentrations, and both correlating well with the percentage increase in the QTc interval. Amiodarone is often said to have a low torsadogenic potential relative to its QT-prolonging effect. However, there is a sufficient number of reports of TdP to question a perception of low frequency.⁸⁵⁻⁹⁰ Poluzzi *et al.*⁸⁹ identified 113 cases of amiodarone-associated reports of TdP over the 4-year period from January 2004 to December 2007 in the public version of the FDA Adverse Event Reporting System. As of April 2018, the European Medicines Agency's EudraVigilance database of ADRs included 657 reports of QT prolongation (16 fatal) and 523 of TdP (35 fatal) from healthcare professionals in association with amiodarone; although

not all these spontaneous reports are fully evaluated for validity or causality. A number of these cases may also include other risk factors,^{91,92} a feature not uncommon with most other well known torsadogens. Furthermore, QT interval prolongation has often persisted despite correction of risk factors such as hypokalaemia; only the discontinuation of the culpable drug restores normal repolarization.^{51,52,86} One meta-analysis of 2878 patients treated with amiodarone reported proarrhythmic events in 57 (2%) patients while exposed to the drug. TdP was observed in one third of these patients (an overall incidence of 0.7%).⁸⁷ In a study of 3906 elderly patients (aged 65 years and older), prescribed at least one drug at admission, amiodarone was the most prescribed QT-prolonging drug with a definite risk of TdP.⁹³ In the recently published report from the DARE study which carefully scrutinized 124 proarrhythmia cases referred by cardiologists, amiodarone topped the list of the culpable drugs⁹⁴; however, the possible bias in this study arising from the referring specialty cannot be ruled out since amiodarone is more likely to be used by cardiologists.

Angina patients and their sensitivity to torsadogenesis

It is now accepted that cardiac disease, bradycardia and hypokalaemia are the more common risk factors that may potentiate the torsadogenic potential of a QT-prolonging drug. Patients with ischaemic heart disease frequently have hypertension and may be in receipt of potassium-depleting diuretics. They may also be on β blockers that reduce the heart rate. The task force on the use and proarrhythmic safety of bepridil, referred to earlier, found that the risk of TdP was indeed increased in elderly patients, especially women greater than 70 years old, as well as in those taking diuretics which can precipitate hypokalaemia.⁷⁵

Against this background of pre-existing risk factors, it is worth recalling that the development of these antianginal drugs predated the discovery of the hERG channel in 1994.⁹⁵ Inhibition of this channel is the principal mechanism underpinning prolongation of action potential duration, QT interval and drug-induced torsadogenesis. Table 3 summarizes the hERG/IKr channel blocking activities of a number of these drugs. Katchman and colleagues¹³ have identified four general categories of hERG blocking potencies; high-potency blockers with IC₅₀ values less than 100 nM, moderate-potency blockers with IC₅₀ values between

100 and <1000 nM, low-potency blockers with IC₅₀ values greater than 1000 nM and ineffective blockers. Accordingly, lidoflazine and bepridil are high-potency hERG blockers whereas prenylamine and terodiline are moderate-potency blockers. These hERG-blocking potencies generally correlate well with their QT-prolonging, but not always with torsadogenic, potentials since other ancillary and ion channel effects modulate the risk of torsadogenesis. For example, there are no cases of TdP associated with verapamil or only isolated cases with papaverine⁹⁶ and perhexiline.⁹⁷ As discussed above, amiodarone is torsadogenic although the frequency of TdP following its use may not be high relative to its QT-prolonging potency. It is evident that a hERG channel assay, as advocated by the current guidelines for new drugs (see section 'Prenylamine heralded QT-related proarrhythmias as a major safety issue'), would have signalled the potential of these coronary vasodilators to induce TdP. Since the risk of QT-related TdP is modulated by other ancillary properties of a drug,⁹⁸ it is also the case that during early drug development, excessive reliance on hERG channel activity as a marker of proarrhythmogenesis may result in valuable compounds such as verapamil being discarded.

Prenylamine emphasized gender differences in pharmacology and drug responses

Abinader and Shahar⁴⁸ published an important analysis that reported episodes of ventricular tachycardia of the TdP type provoked by prenylamine in seven patients with angina who had all received prenylamine in doses of 120–180 mg daily. Syncope or syncopal equivalents occurred in all seven patients and their QT intervals ranged from 520 to 640 ms. Importantly, however, they reported that five (71%) of the seven patients were women, a finding supported by overall data on prenylamine (Table 1) and earlier observations on TdP generally.^{111,112} Almost a decade later, Makkar and colleagues¹¹³ reported an analysis of 332 patients with QTc interval prolongation, using prospectively defined criteria, in which women made up 70% of the TdP cases associated with cardiovascular drugs. Yet another study highlighted how the risk of QT prolongation varied with different phases of the menstrual cycle.¹¹⁴ Maximum (mean $\pm$ SD) increase in QTc after ibutilide infusion was greater in women during the menses (63 ± 13 ms) and the ovulatory phase (59 ± 17 ms) compared with women during the luteal phase (53 ± 14 ms) and compared with men (46

Table 3. hERG/IKr channel blocking activity of early antianginal agents.*

Drug	IC ₅₀ (nM)		Reference
	hERG	IKr	
Prenylamine	590		Katchman <i>et al.</i> ¹³
Terodiline	375		Martin <i>et al.</i> ⁹⁹
		700	Jones <i>et al.</i> ¹⁰⁰
Lidoflazine	37		Katchman <i>et al.</i> ¹³
	16		Ridley <i>et al.</i> ¹⁰¹
Bepridil	73.8		Obejero-Paz <i>et al.</i> ¹⁰²
Amiodarone	9800		Kiehn <i>et al.</i> ¹⁰³
		2800	Kamiya <i>et al.</i> ¹⁰⁴
	70		Ridley <i>et al.</i> ¹⁰⁵
	45		Zhang <i>et al.</i> ¹⁰⁶
Perhexiline	7800		Walker <i>et al.</i> ¹⁰⁷
	5900		Perrin <i>et al.</i> ¹⁰⁸
Papaverine	71,030		Kim <i>et al.</i> ¹⁰⁹
	580		Kim <i>et al.</i> ¹¹⁰
Verapamil	831		Obejero-Paz <i>et al.</i> ¹⁰²

*Data not strictly comparable because the studies were carried out under different experimental conditions and each drug displays different blocking kinetics. The reader is invited to check well established databases such as Tox-Database at <http://tox-portal.net/database/> and hERGAPDBase at <http://www.grt.kyushu-u.ac.jp/hergapdbase/> for further details on electrophysiological effects of drugs.

± 16 ms).¹¹⁴ These important sex-related differences in QT susceptibility and proarrhythmias,¹¹⁵ together with other known pharmacokinetic differences, stimulated extensive research into the effect of sex hormones on cardiac electrophysiology, particularly ventricular repolarization.^{116–123} The issue of differences between men and women has now become important in pharmacology and therapeutics such as pharmacokinetics and clinical outcomes in terms of drug safety and efficacy.^{124–133} Indeed, regulatory authorities now require submission of analysis of data subgrouped by various demographic features of the target population, such as age, sex and ethnicity.¹³⁴

Prenylamine heralded QT-related proarrhythmias as a major safety issue

Withdrawal of prenylamine in 1988, followed by lidoflazine in 1989 and terodiline in 1991, led to

what might be described as a regulatory crisis.⁵⁷ Regulatory concerns on drug-induced QT interval prolongation and TdP intensified during the period 1989–1996 as a result of further reports of TdP (some fatal) associated with pimozone, terfenadine and astemizole. Two new drugs belonging to completely different therapeutic classes were also implicated; namely, halofantrine (an antimalarial drug) and cisapride (a gastric prokinetic drug). All these drugs attracted severe prescribing restrictions on their use. Early results from the Cardiac Arrhythmia Suppression Trial (CAST) in 1989 with flecainide and encainide (class IC antiarrhythmic drugs) and the Survival with Oral d-Sotalol (SWORD) study in 1994 with d-sotalol (QT-prolonging stereoisomer of sotalol) warranted their premature terminations due to increased mortality on the active drugs^{135,136} and this further aggravated the crisis. Soon, widely used drugs such as terfenadine, astemizole

and cisapride were also withdrawn from the market.^{57,59} Over the period since the late 1980s, the list of drugs prolonging QT interval with potential to induce TdP has increased greatly, as has the range of therapeutic classes involved,^{137,138} with drugs that are in widespread use. For example, in the study of 3906 elderly patients prescribed at least one drug at admission and referred to earlier, 2156 (55.2 %) were taking at least one QT-prolonging drug.⁹³

In response to this crisis, the European Union's Committee for Proprietary Medicinal Products was the first to issue, in 1997, a guidance ('Points to Consider') on preapproval characterization of the QT-prolonging potential of new drugs.⁵⁹ This guidance recommended a strategy of preclinical *in vitro* studies and clinical studies in order to better characterize the risk. The essential elements of this European guidance ultimately evolved into two internationally harmonized guidelines (ICH S7B and ICH E14), adopted in 2005. ICH S7B requires an *in vitro* IKr/hERG channel assay and an *in vivo* study in a suitable animal species. ICH E14 requires the sponsor to conduct a clinical study, referred to as the thorough QT (TQT) study, specifically designed to investigate this adverse cardiac electrophysiological activity.^{57,59} Data reported by Katchman and colleagues,¹³ Bayer and colleagues¹¹ and Oakley and colleagues⁵¹ demonstrate that ICH-compliant studies would have identified prenylamine as potentially a high-risk torsadogen. Finding an adverse effect on QT interval in these ICH-compliant investigations has not prevented approval of drugs with QT liability but the information therefrom has led to better risk mitigation and management strategies during their clinical use.^{139,140}

However, with increasing experience over time, the two ICH guidelines have attracted dissatisfaction since they disregard the important role of ion channels other than hERG in modulating proarrhythmogenesis. The TQT study has been shown to be cost ineffective¹⁴¹ and disregards the less than perfect relationship between the extent of drug-induced increase in QTc interval and the frequency of resulting proarrhythmias.^{140,142} Additionally, the outcomes of ICH-compliant studies have sometimes led the sponsor to terminate drugs from further development because of uncertainties surrounding regulatory evaluation of such drugs.^{57,143}

Consequently, a new paradigm, referred to as the 'Comprehensive *in vitro* Proarrhythmia Assay'

(CiPA), is at an advanced stage of consideration for more efficient characterization of the proarrhythmic potential of a drug, as opposed to its QT liability.¹⁴⁴ The details of studies required under this paradigm, including *in silico* modelling of the torsadogenic risk, have been described elsewhere.^{144–148}

Prenylamine and the current concept of safety margin

Following the implementation of regulatory guidelines on drug-induced QT interval prolongation, Redfern and colleagues¹⁴⁹ scrutinized the relative value of preclinical cardiac electrophysiology data (*in vitro* and *in vivo*) for predicting risk of TdP in clinical use. An analysis of data on 52 drugs of varying torsadogenic potential (including those withdrawn from the market) led these investigators to confirm that most drugs associated with TdP in humans are also associated with hERG channel inhibition at concentrations close to, or superimposed upon, their free plasma concentrations found in clinical use and that a 30-fold margin between C_{max} and hERG IC_{50} may be sufficient to mitigate the risk but should be increased for future drug discovery programmes, particularly for drugs aimed at nondebilitating diseases.

The recommended therapeutic dose of prenylamine used clinically was 60 mg thrice daily. Given that the peak plasma concentration of prenylamine after an oral dose of 120 mg is approximately 1.0 µg/ml (3.035 µM), its protein binding is more than 95% and the IC_{50} value for hERG inhibition is 590 nM, the safety margin of prenylamine between antianginal activity and potentially proarrhythmic hERG blockade was only of the order of 4, even if one discounted those patients who might have impaired drug elimination or greater sensitivity to QT prolongation.

Repurposing calcium antagonists for novel indications

Many of the drugs developed during the 1960s for use in the relief of angina pectoris have also proved useful for the treatment of cardiac arrhythmias and hypertension, for example, β -adrenoceptor blocking drugs. Novel indications for older drugs is not uncommon and has been reported with a number of other drugs.¹³⁷ Development of single enantiomers of a previously marketed racemic drug is another feature of modern drug development, often leading to

unexpected hazards since interactions of drugs with their pharmacological targets, including those that prolong the QT interval, are also stereospecific.^{137,150,151}

Although prenylamine was not developed for any other indication, terodiline illustrates well the potential hazards of redeveloping (now often referred to as ‘repurposing’) drugs for novel indications unrelated to the previous one. As stated earlier, terodiline was initially marketed in 1965 as an antianginal agent that was repurposed for use in urinary incontinence due to high frequency of urinary retention associated with its antianginal use. However, its previously uncharacterized and unanticipated electrophysiological effects struck back, resulting in reports of TdP in patients with urinary incontinence.⁶¹ In the context of repurposing antianginal drugs as antiarrhythmic agents, lidoflazine and bepridil provide further grounds for caution. A pilot study as early as 1969 had evaluated the use of lidoflazine as an antiarrhythmic drug in seven patients with atrial fibrillation and reported its potential proarrhythmic effects.¹⁵² Subsequently, lidoflazine was shown to increase the duration of the action potential in various cardiac tissues.¹⁵³ Later, in 1977, a study comparing the efficacy of quinidine *versus* lidoflazine therapy in a group of 35 patients had to be stopped after one of these patients with paroxysmal supraventricular tachycardia developed runs of ventricular tachycardia soon after starting lidoflazine and four patients died while receiving lidoflazine, with the suspicion that their deaths may have been related to drug-induced arrhythmias.¹⁵⁴ The antiarrhythmic efficacy of bepridil was investigated and compared with amiodarone in a study of 14 patients with established atrial fibrillation. Although bepridil seemed to be slightly more effective than amiodarone in converting atrial fibrillation to sinus rhythm, it was associated with the development of ventricular arrhythmias in 8 of 14 patients; two of these patients had TdP of which one degenerated into fatal ventricular fibrillation.¹⁵⁵ No ventricular arrhythmias were seen during amiodarone treatment. A study evaluating the adverse effects of bepridil in 459 patients with atrial flutter/fibrillation reported prolongation of QT interval greater than 550 ms in 13 patients, of whom 4 (0.9% of 459) experienced TdP and 6 developed bradycardias with heart rates less than 40 bpm.¹⁵⁶ It is unclear whether the proarrhythmic effect of amiodarone in the two indications (angina and atrial fibrillation) differs.

Prenylamine paved the way to developing modern calcium antagonists

The term ‘calcium antagonist’ was introduced by Fleckenstein in 1969 to describe the actions of compounds which had both coronary vasodilator and negative inotropic properties.¹⁵⁷ The prototype of this new family of drugs was verapamil (also a phenylalkylamine derivative) but prenylamine had much to do with the discovery of this important pharmacological class of drugs. As explained by Fleckenstein,⁵

‘The discovery of Ca^{++} antagonism occurred by chance. It happened in November 1963, that I was asked by two German pharmaceutical companies (Knoll and Hoechst) to have a look on two newly synthesized coronary vasodilators with unexplained cardiodepressant side effects. One of these compounds was prenylamine. The other compound had not yet a name, but was later called Isoptin, Iproveratril, or by the generic name verapamil’.

Further observations by his group led them to postulate that the common action of verapamil and prenylamine might consist of an interference with the mediator function of Ca^{++} in excitation–contraction coupling of heart muscle. Fleckenstein⁵ designated drugs such as prenylamine, terodiline and perhexiline as group B calcium antagonists and drugs such as verapamil, nifedipine and diltiazem as group A calcium antagonists, the principal difference between the two groups being their potency and tissue specificity as well as their torsadogenic potential. Nifedipine was the next group A calcium antagonist to be introduced in mid 1970s and since then the number of calcium ion antagonists increased rapidly because they were shown to be effective in the control of arrhythmias, cardiomyopathies, hypertension and unstable and stable angina pectoris.^{158–160} These drugs belong to highly heterogeneous chemical structural classes; namely benzothiazepines, phenylalkylamines, dihydropyridines and others.^{159,161} The introduction of group A calcium antagonists for the treatment of cardiovascular disorders has been one of the most significant advances in cardiovascular pharmacotherapy since the introduction of β -adrenoreceptor blocking agents.

Conclusions

Prenylamine went some way to fulfilling an unmet need at the time of its introduction to the market. In the early 1960s, the mainstay of antianginal therapy was nitrates such as pentaerythritol tetranitrate.¹⁶² As observed by Phear in 1963,¹⁶³

‘An effective method for the prolonged relief of severe angina pectoris is badly needed. Glyceryl trinitrate (trinitrin) relieves angina rapidly but its action is short-lived. And none of the many drugs claimed to produce prolonged relief have proved active when tested by acceptable methods of double-blind trial ... Frequent disappointments in the past indicate that the spate of new drugs introduced for angina require formal testing before acceptance. At present we have no drug of proved value’.

Although the therapeutic effect of prenylamine was not confirmed consistently across all the studies or in all the patients, it benefitted a substantial proportion of patients in terms of their angina-free exercise tolerance and reduction of pain-relieving sublingual glyceryl trinitrate. What benefit prenylamine had, however, was soon to be offset by its proarrhythmic activity. Given that a number of alternatives such as β blockers and newer and potent calcium antagonists were available by late 1970s, the decision to withdraw prenylamine from the market in 1988 was probably overdue.

Nevertheless, much has been learnt and gained from the prenylamine experience. The ever-increasing number of published reports of ventricular tachyarrhythmias illustrates how published case reports play a key role in uncovering an unrecognized public health hazard. This has also been observed with a number of other drugs.³¹ These reports corroborated the susceptibility of female sex to the adverse effects of drugs and not only did this spurn much research into sex-related differences in basic pharmacology but also resulted, ultimately, in regulatory requirements for subgroup analysis of clinical trials data by demographic characteristics.^{31,134} More importantly, prenylamine drew attention to the proarrhythmic risks of drugs, the scale of which unfolded after its withdrawal, and this resulted in regulatory requirements to characterize drugs for their cardiac safety. Perhaps the most significant benefit accrued following investigations into the mechanism of action of prenylamine, which opened up a new pharmacotherapeutic class of drugs and paved the way for synthesis and marketing of modern, more effective and safer calcium antagonists extensively used today in a wide range of cardiovascular diseases. More recently, calcium antagonists are also emerging as potential candidates for investigating their therapeutic activity in a number of serious infections such as trypanosomiasis,¹⁶⁴ leishmaniasis,¹⁶⁵

Ebola virus,^{166,167} Japanese encephalitis¹⁶⁸ and cytomegalovirus.¹⁶⁹

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