Peer reviewed article

Molecular and clinical determinants of drug-induced long QT syndrome: an iatrogenic channelopathy

Hugues Abriel[a, b], *Jürg Schläpfer*[a], *Dagmar I. Keller*[a, c], *Bruno Gavillet*[b], *Thierry Buclin*[d], *Jérôme Biollaz*[d], *Rudolf Stoller*[e], *Lukas Kappenberger*[a]

[a] Service of Cardiology, CHUV, Lausanne, Switzerland
[b] Department of Pharmacology and Toxicology, University of Lausanne, Switzerland
[c] Cardiology Department, University Hospital, Basel, Switzerland
[d] Department of Clinical Pharmacology and Toxicology, CHUV, Lausanne, Switzerland
[e] Centre for Pharmacovigilance, Swissmedic, Swiss Agency for Therapeutic Products, Bern, Switzerland

Summary

More than 70 drugs present on the Swiss market can cause drug-induced long QT syndrome (LQTS), which is associated with torsades de pointes (TdP) arrhythmias, potentially leading to sudden cardiac death. Basic and clinical investigations performed during the last decade have helped a better understanding of the mechanisms and risk factors of this serious public health problem. In their vast majority, QT interval prolonging drugs block the human ERG (hERG) channel involved in the repolarisation phase of the cardiac action potential, and thus lengthen the QT interval. Beside the well-known QT interval prolonging action of class IA, IC and III anti-arrhythmic drugs, many antibiotics, neurotropic, antifungal, and antimalarial drugs are also able to cause drug-induced LQTS. Reviewing the literature indicates that the risk of QT interval prolongation and TdP is increased in females, in patients with organic heart diseases and hypokalaemia. Furthermore in a few cases, genetic factors have also been reported. However thus far, no genetic test is available to detect at-risk patients, and in consequence, drug prescribers are still relying only on the clinical history and findings to perform an evaluation of the risk. Treatment of drug-induced LQTS and TdP includes identifying and withdrawing the culprit drug(s), infusing magnesium and, in resistant cases acceleration of the heart rate. In this review article we provide a list of QT interval prolonging drugs adapted to the pharmaceuticals found on the Swiss market that can be used as a check-list for drug prescribers and at-risk patients.

Key words: long QT syndrome; adverse drug reaction; torsades de pointes; arrhythmias; pharmacogenetics

Introduction

The long QT syndrome (LQTS) is characterised by a prolonged QT interval in the surface ECG, as well as a propensity to developing syncope and sudden cardiac death (SCD). In most documented cases, death was caused by the malignant polymorphic ventricular arrhythmia called torsades de pointes (TdP). Congenital and acquired forms of LQTS are known. Administration of drugs is one of the most frequent causes of acquired LQTS [1–3]. Drug-induced long QT syndrome can, therefore, be defined as an "iatrogenic" form of this potentially lethal condition. Cardiologists are familiar with this adverse drug effect because it has long been a well-known complication of anti-arrhythmic drug treatment [4]. However, since the nineties, it appeared that a large number of non-anti-arrhythmic drugs may prolong the QT interval and consequently predispose exposed patients to TdP and lethal events [5]. Nevertheless, the occurrence of drug-induced TdP is infrequent, and the odds of a given patient on a QT interval prolonging drug developing TdP are fortunately small [6]. However, in terms of public health and safety, due to the large number of patients receiving such drugs, this issue is becoming increasingly important in daily clinical practice.

Figure 1 presents the number of cases of prolonged QT interval and/or TdP voluntarily reported by health professionals to the Centre for Pharmacovigilance of the Swiss agency of therapeutic products (Swissmedic) since 1997. The absolute number of cases is small, and is probably af-

No financial support declared.

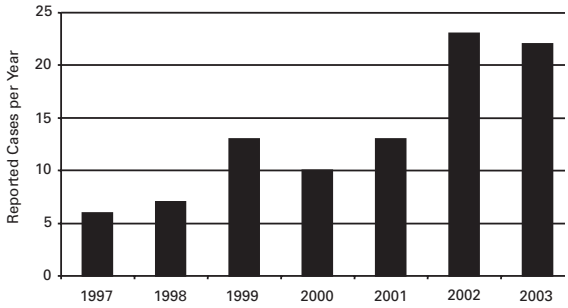


Figure 1

Frequency of drug-induced TdP and prolonged QT interval voluntarily reported to the Centre for Pharmacovigilance of Swissmedic per year.

fected by an underreporting bias. However, a trend toward more cases being reported can be observed, which might be due to a recent increase in awareness of this topic. It is interesting to note that many of the cases reported in 2002 and 2003 were related to the use of methadone [7].

The aim of this review is twofold. First, we present recent findings resulting from basic and clinical investigations, since this field has been very productive in the last 5 years. Indeed, significant progress has been made in our understanding of the molecular mechanisms underlying the delay in cardiac repolarisation, and consequently QT interval prolongation. Second, we also provide a list of drugs known to prolong the QT interval and that is adapted to the Swiss list of registered products. This list may be used as a check-list for drug prescribers and given to patients at-risk of developing TdP, such as congenital LQTS patients.

Ionic and molecular determinants of cardiac ventricular repolarisation

The QT interval of the ECG is predominantly determined by the duration of the action potential (AP) of ventricular cells. Indeed, most cases of QT interval prolongation are caused by factors that prolong the duration of the AP, mainly by delaying the repolarisation phase 3 as schematised in figure 2. A large number of recent studies allowed the dissection of the individual contribution of many different ionic currents, related ion transporters and channels, to the generation of the AP (fig. 3) [8]. Interestingly, the role of specific ion channels in human physiology could only be ascertained by the finding that alterations (ie, mutations) of their genes caused congenital LQTS [9].

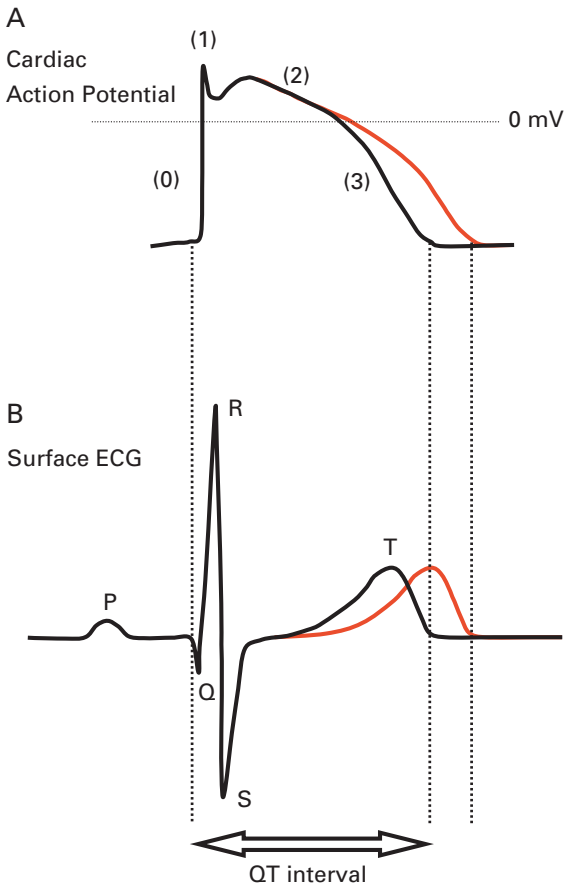


Figure 2

Scheme illustrating the timing and the chronological relationship of the cardiac action potential at the level of the cardiac myocyte (A) and the surface ECG (B). The upstroke depolarisation (0) is rapidly followed by an early repolarisation phase (1). The plateau phase (2) is long in ventricular cells, and is followed by the repolarisation phase (3). Delayed repolarisation (red) may be caused by either increased depolarising currents or decreased repolarising currents. A prolongation of the action potential duration causes a lengthening of the QT interval on the surface ECG (red). See the text for details.

More than 20 currents subdivided into depolarising and repolarising currents are involved in the AP generation of ventricular cells as illustrated in Fig. 3. Depolarising currents are due to an "inward" flux of positive charges (Na^+ and Ca^{2+}) into the cells, and consequently they move the negative resting membrane potential toward more positive voltage values. Repolarisation is achieved by a delayed "outward" flux of positive charges (K^+) out of the cells. The particularity of the cardiac AP, as compared to neuronal AP, is the "plateau" phase 2 which is mainly due to the inward flux of Ca^{2+} significantly prolonging the AP duration (about 200–300 ms). More than 50 years ago the Swiss physiologist S. Weidmann reported that the absolute amount of current flowing through the membrane of cardiac cells during the phase 2 is very small [10]. As a result, small variations of either depolarising or repolarising currents, mainly during phase 2, can significantly alter the AP duration [11]. The class III antiarrhythmic drug sotalol potently blocks one of these outward K^+ currents (called IKr) [12], thus reducing the repolarising current and consequently prolonging both the AP and the QT interval. Sotalol has been found to prolong the QT interval and cause TdP in numerous clinical studies [13].

The congenital forms of the LQTS are caused by mutations mostly located in genes encoding cardiac ion channel subunits [14]. This disorder therefore belongs to the genetic *cardiac channelopathies*. In its classic description, the congenital LQTS includes the Romano-Ward [15, 16] and Jervell and Lange-Nielsen syndromes [17]. The latter syndrome is also clinically characterised by neurosensorial deafness. In the Romano-Ward syndrome, patients have been found to be heterozygous carriers of mutations in the genes *KCNQ1*, *KCNH2*, *SCN5A*, *ANK2*, *KCNE1* and *KCNE2*, defining respectively the LQT1 to LQT6

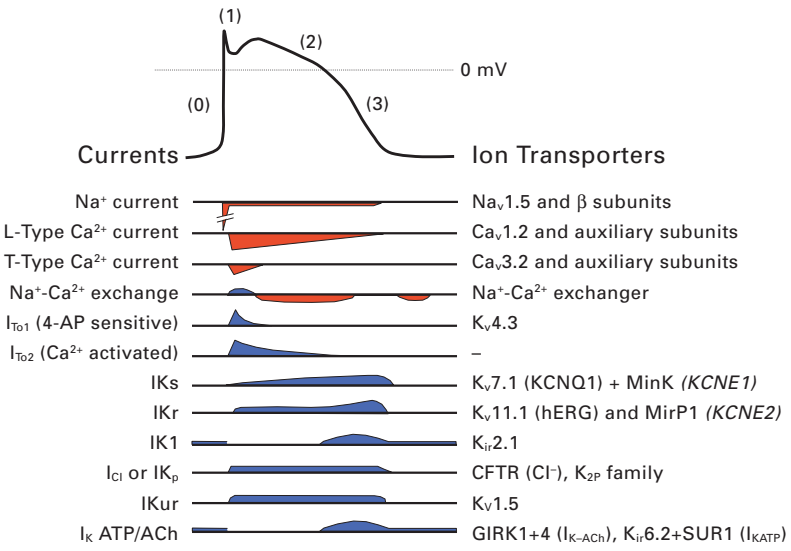


Figure 3

Schematic representation of the ionic currents and ion transporters responsible for the different phases of the cardiac action potential (AP). Red (depolarising) and blue (repolarising) shapes are indicative for relative current amplitude, duration and direction. The shape of the current is aligned with its approximated time of action during the AP. The phase 0 (upstroke depolarisation) is caused by the very rapid activation of voltage-gated sodium channels $Na_v1.5$. These channels will afterwards inactivate rapidly. The first repolarisation phase 1 (notch) is due to the transient outward K^+ current for which two components are recognised, I_{to1} and I_{to2}. The plateau phase 2 is mainly maintained by inward Ca^{2+} current flowing through $Ca_v1.2$ voltage-gated channels that inactivate slowly. Repolarisation (phase 3) is obtained through the concerted action of three types of outward currents called IKs (slow), IKr (rapid) and finally IK1. The main pore forming subunit (alpha subunits) of IKs is called K_vLQT1 or KCNQ1 (new nomenclature $K_v7.1$), of IK_r hERG (new nomenclature $K_v11.1$) and for IK1 $K_{ir}2.1$. These principal alpha subunits are often found in association with so-called ancillary beta-subunits that are not directly involved in the gating machinery of the channels. The currents generated by all other electrogenic transporters (ATPases, exchangers and ion channels) also contribute to shape the AP.

subtypes. For the Jervell and Lange-Nielsen syndrome, the JLN1 and 2 subtypes are caused by mutations of the *KCNQ1* and *KCNE1* genes; the patients are homozygous carriers [18]. The alterations caused by these mutations, in most cases, prolong the AP duration by either increasing inward/depolarising currents or decreasing outward/repolarising currents during the plateau phase. Most mutations found in the gene coding for the cardiac voltage-gated sodium channel $Na_v1.5$, *SCN5A*, result in a small but clinically relevant persistent depolarising current throughout the AP duration. These mutations are referred as to "gain-of-function" alterations causing the LQTS type-3 phenotype. Furthermore, numerous mutations in five different genes encoding channel subunits involved in the IKr, IKs and IK1 currents were also found in congenital LQTS. In almost every case, these mutations, by different mechanisms, reduce the outward repolarising currents ("loss-of-function" mutations), and consequently prolong the AP duration and QT interval. A significant proportion of the mutations causing congenital LQTS is found in the gene *KCNH2* encoding the K^+ channel hERG (human Ether-à-go-go Related Gene). In fact, almost all drugs known to prolong the QT interval block the hERG channel, illustrating that congenital and drug-induced forms of LQTS share similar pathogenic mechanisms [19]. For further information, the website "Inherited Arrhythmias Database" supported by the European Society of Cardiology hosts an updated list of published genes and mutations causing LQTS [20].

In summary, the AP duration of the ventricular cells is a major determinant of the QT interval. Genetic or acquired factors that alter the delicate balance between inward and outward currents during the phase 2 of the AP significantly prolong its duration, and consequently create a substrate for TdP. The mechanism by which a prolonged AP leads to TdP is still a matter of controversy [21, 22], and its discussion is beyond the scope of this review.

Normal values of QT interval

The QT interval is measured from the onset of the QRS complex to the end of the T wave (Fig. 2B). Small physiological U waves should not be included in the QT interval measurements. However, tall U waves that are not separated from the T wave are considered pathological and may be counted as part of the QT interval. The QT interval adapts to the heart rate, the higher the rate, the shorter the QT interval. It is therefore accepted to normalise the QT interval for the heart rate. Despite several limitations, the most frequently used formula to correct the QT interval value (QTc) for the heart rate is the Bazett formula, where $QTc = QT/(RR)^{1/2}$ [23], RR is the preceding RR duration expressed in seconds; this makes QTc equal to QT for a heart rate of 60 bpm. For yet unknown reasons, adult females have on average a QTc interval about 20 ms longer than adult males, and in consequence one has to refer to different normal values for both genders [24]. Table 1 presents QTc values (corrected with the Bazett formula) that are considered normal, borderline and clearly prolonged for both genders [25].

Table 1

Corrected QT interval values according to the Committee for Proprietary Medicinal Products [25]; QTc according to Bazett formula: $QTc = QT/(RR)^{1/2}$ [23].

	Adult Males	Adult Females
Normal	<430 ms	<450 ms
Borderline	431–450	451–470
Prolonged	>450	>470

Cardiac repolarisation reserve

Recently, a novel and important concept has been proposed: every individual seems to have a physiological "cardiac repolarisation reserve". This functional reserve allows to counterbalance any endogenous (genetic defects or cardiac disorders for instance) or exogenous (drugs for example) factors that would either reduce repolarising or increase depolarising currents during the AP [26]. The extent of this cardiac repolarisation reserve is variable, and may be reduced in some individuals. It can therefore be postulated that individuals with a reduced repolarisation reserve are more susceptible to developing significant and manifest QT interval prolongation and TdP when exposed to IKr blocking drugs. As stated above, women tend to have a longer QT interval, most probably because their cardiac cells generate less repolarising current [27]. The reduced repolarisation reserve in women may explain their increased propensity to develop TdP when taking QT interval prolonging drugs [28]. It has also been suggested that the magnitude of this repolarisation reserve is genetically determined [29, 30]. Asymptomatic individuals with normal or "borderline" ECGs at baseline, may harbour genetic variants reducing their cardiac repolarising currents, corresponding to a "forme fruste" of LQTS [31]. Several case reports were recently published clearly supporting this concept [32–34]. In these cases, patients with a normal baseline ECG, but manifest QT interval prolongation when taking an IKr blocking drug, were found to have mutations in the same genes (cardiac ion channel subunits) as in congenital LQTS patients [30].

Acquired forms of long QT syndromes

Beside the congenital forms of LQTS, prolonged QT interval is also observed in many different acquired clinical conditions presented in table 2. The role of drugs in causing LQTS is clearly important and clinically relevant since it can be prevented in many circumstances. Cardiac disorders are also a frequent cause of acquired LQTS. QT interval prolongation has been reported in chronic heart failure [35, 36], acute and chronic ischaemic heart disease [37–39], and cardiomyopathies [40]. Bradycardia due to sinus dysfunction, as well as conduction block, has also been shown to prolong the QT interval [41–43]. Electrolyte imbalance, mainly hypokalaemia, hypomagnesaemia and hypocalcaemia, is also a common cause of prolonged QT interval. Interestingly, it appears that a low plasma/extracellular K^+ concentration prolongs the AP by reducing the hERG mediated IKr currents in experimental settings. The molecular mechanism of this apparent paradoxical phenomenon has been recently unravelled [44]. Here again, the channel hERG plays a central role in this delayed repolarisation disorder. Finally many metabolic, nutritional, neurological and endocrine pathological conditions have been reported to prolong the QT interval (table 2).

Table 2

Congenital and acquired forms of long QT syndromes. Mutations in six different genes have been identified in patients and families with congenital LQTS, allowing the classification of LQT1–LQT6. The Andersen syndrome (AND1 or LQT7) is a rare disorder characterised by neurological and morphological abnormalities in addition to a prolonged QT interval [62]. Three sporadic cases of prolonged QT interval associated with syndactyly have been reported [63]. However, the significance of this finding may be quite low because of its rarity.

Long QT syndromes: congenital forms
Romano-Ward Syndrome: LQT1–LQT6
Jervell and Lange-Nielsen Syndrome: J-LN1 and J-LN2
Associated with the Andersen Syndrome: AND1 or LQT-7
Associated with Syndactyly
Long QT syndromes: acquired forms
Antiarrhythmic drugs (IA, IC and III)
Other drugs (antibiotics, antifungal, psychotropic drugs, …)
Cardiac disorders (chronic heart failure, cardiomyopathies, …)
Electrolyte disorders: hypokalemia, hypocalcemia and hypomagnesemia
Neurological disorders
Nutritional (alcoholism, anorexia, …)
other

Drug-induced long QT syndrome

Molecular and structural aspects of drug-induced long QT syndrome

With only a few exceptions (see [3, 45] for an extensive discussion), all different drugs known to prolong the QT interval were shown either to block the hERG channels or to reduce the IKr current recorded in cardiac myocytes. This observation has been quite puzzling since, unlike other ion channels, the chemical structures of these hERG-blocking drugs are very diverse. However, with class Ic drugs, such as flecainide, the QT interval prolongation is mainly caused by an increase in QRS duration due to a blockade of sodium channels. Inhibition of hERG channels by flecainide [46] is most likely marginal since the JT interval is not significantly increased in humans [47]. Fur-

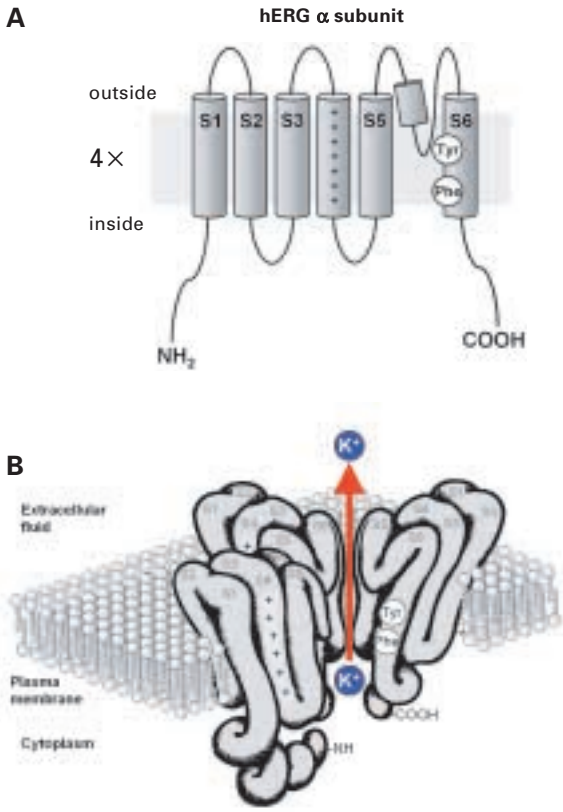


Figure 4

Molecular structure and membrane topology of the hERG (Kv11.1) channel. (A) The molecular architecture of hERG is similar to that of other voltage-gated K^+ channels. Four alpha subunits co-assemble to form the full hERG channel. Each alpha subunit has six transmembrane domains, intracellular N- and C-termini and a pore loop (P loop) linking the S5 and S6 domains. The S4 segment contains positive charges serving as the voltage sensors. In the alpha subunits of the hERG channel, the S6 segment contains two aromatic amino acids (tyrosine-Tyr and phenylalanine-Phe), which participate in the binding site of most of the drugs blocking this channel (see text for details). (B) Three of the four alpha subunits of the hERG channel are schematised in this diagram. The central cavity lined by the four S6 segments is especially wide for this channel because these segments lack a bend found in other K^+ channels. This peculiarity may explain why hERG channels can be blocked by drugs of many different chemical structures.

thermore, flecainide has been recently shown to decrease the QT interval in patients with $Na_v1.5$ gene mutations [48, 49].

The human ERG (kv11.1) channel gene *KCNH2* was cloned in 1994 [50], and not long after was shown to be mutated in patients suffering from the congenital LQTS type-2 [51]. Simultaneously, it was found to be the target of many drugs prolonging the QT interval [52]. These findings clearly underscored the pivotal role of the encoded channel in normal as well abnormal cardiac excitability. The currents mediated by the hERG potassium channel, when studied in expression systems, recapitulate most of the key characteristics of the IKr currents found in human cardiac myocytes, namely a rapidly activating outward voltage-gated potassium current, with strong inward rectification properties [51]. As illustrated in Fig. 4, the native channels are formed by tetramers of four identical subunits (alpha-subunits), each consisting of six transmembrane domains, with the S4 segment serving as the main voltage sensor thanks to its positively charged amino acids.

Recent structural studies provided interesting elements of response to the question of why so many drugs can bind to and block hERG channels [53–55]. Two main features were found to be important. First, most K^+ channels – but not hERG – have two proline residues in the last transmembrane segment (S6) of the alpha-subunit, that produce a sharp bend in the four S6 helices, thus reducing the volume of the cavity inside the channel. Hence, the hERG channel lacks this kink and the larger inner pore volume can accommodate larger chemical structures than in other K^+ channels. Second, two aromatic residues (tyrosine and phenylalanine) face the central cavity of the channel (fig. 4) allowing high affinity Pi-stacking interactions with aromatic moieties found in the blocking drugs. Detailed mutational studies clearly support this structural model [53, 54], and provide a rationale for the development of future drugs that may not interact with hERG channels.

Table 3

Identified risk factors for developing TdP in patients taking drugs that prolong the QT interval. Modified from Viskin S, Justo D, Halkin A, Zeltser D. Long QT syndrome caused by non-cardiac drugs. Progress in Cardiovascular Diseases 2003;45:415–27 [58], with permission from Elsevier.

Risk factors commonly identified
Female gender
Heart disease (cardiac hypertrophy, chronic heart failure, cardiomyopathies)
Hypokalemia, hypocalcemia and hypomagnesemia
High drug levels (impaired metabolism or excessive dosage)
Drug interactions (concomitant use of 2 drugs that prolong the QT interval)
Risk factors less commonly identified
Bradycardia
Diuretic use
History of congenital long QT syndrome
Prolonged baseline QT interval
Genetic variants (polymorphisms or mutations)

Risk factors for developing TdP

The occurrence of TdP in patients taking non-antiarrhythmic drugs is defined as an idiosyncratic reaction. Indeed, it represents an adverse drug reaction that is infrequently encountered (see fig. 1) and not predictable at the present time. However, during the last few years several systematic studies have aimed at better defining the risk factors for developing QT interval prolongation and TdP in patients. These clinical factors were recently analysed in an extensive review of the literature [56] (table 3). In this work, Zeltser et al. identified 249 reported patients with TdP related to the use of non-cardiac drugs [56]. As previously reported [30] and discussed [57], the most commonly identified risk factor was female gender (71% of all patients). Heart diseases and hypokalaemia were respectively reported in 41% and 28% of patients. Importantly, potential drug interactions associated with the administration of two or more drugs prolonging the QT interval were present in 39% of patients. However, only 18% of all patients with drug-induced TdP had a familial history of LQTS, a previous episode of TdP or an obviously prolonged QT interval in the absence of drug [56]. Less commonly identified risk factors were bradycardia and diuretic treatment.

Practical attitudes – prevention

Despite the low prevalence of drug-induced TdP in the general population, the risk can be further reduced by carefully obtaining the patient's medical history. Viskin et al. recently provided practical approaches for risk stratification [58] in patients taking non-antiarrhythmic drugs that can potentially prolong the QT interval. As presented in Table 4, the risk may be classified from "very low" in patients without risk factors (Table 3), to

Table 4

Proposed practical approaches when prescribing non-antiarrhythmic drugs known to prolong the QT interval in patients. Hospitalisation with ECG monitoring is only mandatory in high risk patients who need to be treated with QT interval prolonging drugs. Modified from Viskin S, Justo D, Halkin A, Zeltser D. Long QT syndrome caused by non-cardiac drugs. Progress in Cardiovascular Diseases 2003;45:415–27 [58], with permission from Elsevier.

Risk	Definition	Screening ECG	Follow-Up ECG	Cardiologist Consultation	ECG Monitoring
Very low	No risk factors are present	Not required	Not required	Not required	Not required
Low	Women without risk factors	Not required	Not required	Not required	Not required
Medium	Heart disease	Advisable	Advisable	Advisable	Not required
High	Drug interactions	Required	Required	Required	Questionable
Very high	History of LQTS	Mandatory	Mandatory	Mandatory	Mandatory

"very high" in patients with a history of drug-induced or congenital LQTS. In high-risk patients, administration of any drug known to prolong the QT interval is contraindicated. In low-risk patients, the most important preventive measure is to carefully *avoid administering more than one drug known to prolong the QT interval*. This is important because many clinical situations exist where this could occur: for instance, clarithromycin treatment in a psychiatric patient under risperidone, or, cisapride treatment in a patient treated with sotalol for atrial fibrillation. It is also crucial to be aware of drugs or food, such as grapefruit juice [59], that inhibit the metabolism of drugs prolonging the QT interval. For instance, drugs such as fluoxetine and methadone (table 5) are both metabolised by the CYP34A enzymes that are inhibited by macrolide antibiotics, antifungal drugs and grapefruit juice.

It has to be stated, however, that the recommendations found in table 4 are, thus far, not supported by any kind of clinical trial.

Table 5

List of drugs found on the Swiss market that can prolong the QT interval.
The drugs found on this list have been shown to either block the hERG channel or to prolong the QT interval in humans. This list is adapted from the ACERT list available on the www.QTdrugs.org or www.torsades.org websites. It reflects the last updated version of April 20th 2004, and will be available as an updated version on the www.QTsyndrome.ch website. At-risk patients (see Tables 3 and 4) should be informed that taking these drugs is contraindicated or should only be used in exceptional circumstances such as vital indications, if no safer alternative is available.

Drugs for cardiovascular disorders			
Amiodarone	Cordarone®	Amiodarone-Mepha®	Other
Disopyramide	Norpace®		
Dobutamine	Dobutrex®		
Dopamine	Dopamin B. Braun		
Ephedrine	Ephedrin Streuli	Demo® elixir	Other
Epinephrine	Adrenaline Sintetica	EpiPen®	Other
Flecainide	Tambocor®		
Ibutilide	Corvert®		
Indapamide	Fludapamide®	Fludex® SR	Other
Isradipine	Lomir SRO®		
Midodrine	Gutron®		
Norepinephrine	Scandonest	Xylestesin®	Other
Quinidine	Kinidin-Duriles®		
Sotalol	Sotalex®	Sotalol-Mepha®	
Drugs for neuropsychiatric disorders			
Amitriptyline	Saroten® Retard	Tryptizol®	Limbitrol®
Chloral Hydrate	Chloraldurat®	Medianox®	Nervifene®
Citalopram	Citalopram-Mepha®		Other
Chlorpromazine	Chlorazin®		
Clomipramine	Anafranil®		
Doxepine	Sinquane®		
Droperidol			
Felbamate	Taloxa®		
Fluoxetine	Fluctine®	Fluocin®	Other
Flupentixol	Fluanxol®	Deanxit®	
Galantamine	Reminyl®		
Haloperidol	Haldol®	Sigaperidol®	
Imipramine	Tofranil®		
Levomepromazine	Nozinan®		
Lithium	Priadel®	Neurolithium®	Other
Methadone	Ketalgine®	Methadone Streuli	
Methylphenidate	Ritalin®	Concerta®	

Table 5 cont.

Nortriptyline	Nortrilen®		
Olanzapine	Zyprexa®		
Paroxetine	Deroxat®	Parexat®	
Quetiapine	Seroquel®		
Risperidone	Risperdal®		
Sertindole	Serdolect®		
Sertraline	Zoloft®	Gladem®	
Thioridazine	Melleril®	Mellerettes®	
Tizanidine	Sirdalud®/- MR		
Trimipramine	Surmontil®	Trimin®	
Venlafaxine	Efexor®		
Drugs for gastrointestinal disorders			
Cisapride	Prepulsid®		
Dolasetron	Anzemet®		
Domperidone	Motilium®/-lingual		
Granisetron	Kytril®		
Octreotide	Sandostatine®		
Ondansetron	Zofran®		
Phentermine	Adipex®	Ionamine®	
Sibutramine	Reductil® 10/15		
Drugs for respiratory disorders			
Salbutamol	Ventolin®	Ecovent®	Other
Salmeterol	Serevent®	Seretide®	
Terbutaline	Bricanyl®		
Drugs against bacterial infections			
Azithromycine	Zithromax®		
Ciprofloxacine	Ciproxine®	Ciproflox®	Other
Clarithromycine	Klacid®	Klaciped®	
Erythromycine	Erythrocine®	Karex®	Other
Levofloxacine	Tavanic®		
Moxifloxacine	Avalox®		
Ofloxacine	Tarivid®		
Trimethoprime-Sulfamethoxazole	Bactrim®	Cotrim®	Other
Drugs against viral infections			
Amantadine	Symmetrel®	PK-Merz®	
Foscarnet	Foscavir®		
Drugs against parasitic infections			
Chloroquine	Nivaquine®	Chlorochin®	
Mefloquine	Lariam®	Mephaquine®	Other
Pentamidine	Pentacarinat®		
Drugs against fungal infections			
Fluconazole	Diflucan®		
Itraconazole	Sporanox®		
Ketoconazole	Nizoral®		
Voriconazole	Vfend®		
Other drugs			
Alfuzosin	Xatral®		
Phenylephrine	Phenylephrine 5%	Phenylephrine 5% SDU Faure	Other
Phenylpropanolamine	Kontexin® Retard	Rhinotussal®	Other
Pseudoephedrine	Otrinol®	Benical®	Other
Tacrolimus	Prograf®	Protopic®	
Tamoxifene	Tamoxifen Farmos	Novaldex®	Other
Vardenafil	Levitra®		

Performing serial ECGs in patients receiving one or several drugs known to prolong the QT interval is of questionable usefulness, since clinical evidence is lacking to support definite recommendations in this area. Drug-related ECG alterations are fluctuating, and even in congenital LQTS patients ECG, may fail to show QT interval prolongation. It would be exaggerated to suggest that the prescription of any drug in table 5 imposes an ECG recording to all patients. On the other hand, a new QT interval prolongation above 470 ms in a patient taking such a drug, should lead to a decrease or cessation of the treatment. In patients at risk, eg, those having already presented with QT interval prolongation and who must receive a drug with arrhythmic potential, or those receiving several drugs from table 5 for life-saving indications, ECG monitoring might be considered justified on empirical grounds. But even in such selected cases, the sensitivity and specificity of ECG tracings to detect and prevent life-threatening arrhythmia has not been established. Cardiology patients receiving antiarrhythmic drugs known to prolong the QT interval should have a control ECG 4–6 days after the initiation of the treatment.

Patients who definitely develop significant prolongation of the QT interval (>30 ms as compared to baseline [25]) or TdP after administration of a QT interval prolonging drug should be informed about their risk when re-exposed to similar drugs. We recommend carefully informing such patients and providing them with the list found in table 5 (see below). In addition, in Switzerland suspected or confirmed drug-induced TdP cases have to be reported to the Swissmedic pharmacovigilance office by filling in the form found in the Swiss drug compendium or downloaded from the Swissmedic website (http://www.swissmedic.ch/files/formulare/B3.2.16–d.pdf).

Practical attitudes – treatments

In an acute setting, the management of patients with drug-induced TdP should first aim at identifying and discontinuing the QT interval prolonging drug(s), and maintain a plasma K^+ concentration between 4–4.5 mmol/L. Administration of 1–2 g magnesium sulphate i.v. reduces the occurrence of TdP [60]. Patients who are symptom-free should receive slow injections (1–2 g over 2 min), whereas, in patients with long runs of TdP, 2 g over 30–60 s may be administered. The 2 g dose can be repeated once after 5–15 min, and followed by an i.v. infusion of magnesium at a rate of 2 to 4 mg/min. At higher doses, toxic effects such as hypotension, lethargy and eventually cardiac arrest may occur [1]. In refractory patients, or those with frequent pauses after ventricular premature beats, heart rate acceleration by means of cardiac pacing may be required since bradycardia increases the risk of TdP initiation in the presence of prolonged QT interval.

A special case is represented by patients with tachyarrhythmias in the setting of tricyclic antidepressant intoxication. Because of its concomitant blocking effect of sodium and hERG channels, this class of drug may lead to severe ventricular tachycardias, which are difficult to treat. In patients with acidosis, alkalinisation of the serum (and potentially the urine) using sodium bicarbonate is the treatment of choice [61].

List of QT interval prolonging drugs found on the Swiss market

Patients at risk of developing TdP should obviously avoid QT interval prolonging drugs. However, the list of such drugs is long and in some situations alternative treatments may be difficult to find, for instance tamoxifen treatment in breast cancer patients. Several review articles and textbooks provide such lists, but none is adapted to the drugs found on the Swiss market. We therefore adapted the list maintained by the Arizona Center for Education and Research on Therapeutics (ACERT, www.QTdrugs.org or www.torsades.org, last updated version of April 20th 2004) to the Swiss drugs. To the best of our knowledge, this is the most accurate and updated available list according to new findings from the literature or the Federal Drug Administration of the USA. Drugs not on the Swiss market were removed and drugs not on the US market were added (Table 5). We did not subdivide the list into four classes as on the ACERT site for the sake of simplicity. Interested physicians are encouraged to visit this site for further information. Of note, drugs that are not on this list can not be considered as risk-free, since many old compounds available on the market may not have been investigated for their specific effects on the QT interval or the hERG channels. This document (table 5) may be given to the patients at-risk, informing them that taking drugs found on that list is contraindicated or should only be used in exceptional circumstances such as vital indications, if no safer alternative is available. We plan to keep an updated version of this Swiss list on the www.QTsyndrome.ch website.

Conclusions

Prolongation of the QT interval in congenital or acquired LQTS is associated with an increased risk of TdP and SCD. By far, the most common cause of acquired LQTS is drug-induced, the antiarrhythmic drugs being the pharmaceutical class most commonly implicated. However since the nineties, the regulatory authorities had to remove a significant number of non-cardiac drugs from the

market because of their propensity to prolong the QT interval and cause TdP. Recent basic and clinical studies have allowed a better understanding of the molecular determinants of this phenomenon and its associated risk factors. Nevertheless, a key question which is still awaiting an answer is why the response of individual patients is so variable. Genetic factors modulating the pharmacokinetics and/or pharmacodynamics of these drugs are likely to be involved. However thus far, only scant information supporting this notion is available, and genetic tests for the identification of patients at high risk are not yet available. In most cases, clinicians are therefore relying solely on clinical history and findings in order to asses the risk before prescribing drugs. Furthermore, the list of offending drugs is still growing (vardenafil being the most recently added), and as a result, the risk of drug-induced TdP will probably remain a significant issue in the future. In order to minimise the risk of this serious pro-arrhythmic effect, all health professionals prescribing and/or dispensing drugs, as well as the patients taking these drugs, have to be informed about these risks and educated accordingly.

Note added in proof: Congenital LQTS associated with syndactyly (table 2) has been recently shown to be caused by mutations in the gene encoding the Cav1.2 calcium channel. Reference: Splawski I, Timothy KW, Sharpe LM, Decher N, Kumar P, et al. Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. Cell 2004;119:19–31.

Acknowledgments

This work has been supported in part by grants from the Swiss National Science Foundation to H.A. (SNF-Professorship #632–66149.01) and the Fondation Vaudoise de Cardiologie. We are grateful to Drs. J. Diezi and T. Gibbs for their useful comments on this manuscript. We would like to thank the anonymous reviewers for their useful suggestions.

Correspondence:
H. Abriel, MD PhD, SNF-Professor
Department of Pharmacology and Toxicology
University of Lausanne
Bugnon, 27
CH-1005 Lausanne
Switzerland
E-Mail: Hugues.Abriel@unil.ch

References

1 Viskin S. Long QT syndromes and torsade de pointes. Lancet 1999;354:1625–33.
2 Roden DM. Drug-Induced Prolongation of the QT Interval. N Engl J Med 2004;350:1013–22.
3 Fenichel RR, et al. Drug-Induced Torsades de Pointes and Implications for Drug Development. J Cardiovascular Electrophysiol 2004;15:475–95.
4 Tartini R, Kappenberger L, Steinbrunn W, Meyer UA. Dangerous interaction between amiodarone and quinidine. Lancet 1982;1:1327–9.
5 Woosley RL. Cardiac actions of antihistamines. Ann Rev Pharmacol Toxicol 1996;36:233–52.
6 Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. Pharmacotherapy 2001;21:1468–72.
7 Violand C, Piguet V. Methadon – dosisabhängiges Risiko von Torsade de pointes/Kammertachykardien und QT-Verlängerung. Swissmedic Journal 2004;3:17–8.
8 Roden DM, Balser JR, George AL Jr, Anderson ME. Cardiac ion channels. Ann Rev Physiol 2002;64:431–75.
9 Keating MT, Sanguinetti MC. Molecular and cellular mechanisms of cardiac arrhythmias. Cell 2001;104:569–80.
10 Weidmann S. Effect of current flow on the membrane potential of cardiac muscle. J Physiol 1951;115:227–36.
11 Kass RS. (Genetically induced reduction in small currents has major impact. Circulation 1997;96:1720–1.
12 Numaguchi H, et al. Probing the interaction between inactivation gating and Dd-sotalol block of HERG. Circ Res 2000; 87:1012–8.
13 MacNeil DJ. The side effect profile of class III antiarrhythmic drugs: focus on d,l-sotalol. Am J Cardiol 1997;80:90G–98G.
14 Splawski I, et al. Spectrum of mutations in long-QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. Circulation 2000;102:1178–85.
15 Romano C, Gemme G, Pongiglione & R. Aritmie cardiache rare dell'età pediatrica. Clin pediat 1963;45:656–83.
16 Ward OC. A new familial cardiac syndrome in children. J Irish Med Assoc 1964;54:103–6.
17 Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the QT interval, and sudden death. Am Heart J 1957;54:59–68.
18 Schwartz PJ, Priori SG, Napolitano C. The Long QT Syndrome. In: Cardiac Electrophysiology: From Cell to Bedside (Zipes DP, JalifeJ, eds.), 2000 pp. 597–615. W.B. Saunders Company, Philadelphia.
19 Clancy CE, Kurokawa J, Tateyama M, Wehrens XH, Kass RS. K^+ channel structure-activity relationships and mechanisms of drug-induced QT prolongation. Annu Rev Pharmacol Toxicol 2003;43:441–61.
20 Study group on molecular basis of arrhythmias. Inherited Arrhythmias Database. 2004. http://pc4.fsm.it:81/cardmoc/, accessed September 7, 2004.
21 Volders PG, et al. Progress in the understanding of cardiac early afterdepolarizations and torsades de pointes: time to revise current concepts. Cardiovasc Res 2000;46:376–92.
22 Vos MA, van Opstal JM, Leunissen JD, Verduyn SC. Electrophysiologic parameters and predisposing factors in the generation of drug-induced Torsade de Pointes arrhythmias. Pharmacol Ther 2001;92:109–22.
23 Bazett HC. An analysis of the time relations of the electrocardiograms. Heart 1920;7:353–70.
24 Stramba-Badiale M, Locati EH, Martinelli A, Courville J, Schwartz PJ. Gender and the relationship between ventricular repolarization and cardiac cycle length during 24-h Holter recordings. Eur Heart J 1997;18:1000–6.
25 Committee for Proprietary Medicinal Products. Points to consider: The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. The European Agency for the Evaluation of Medicinal Products. 1997. http://www.emea.eu.int/pdfs/human/swp/098696en.pdf, accessed September 7, 2004.
26 Roden DM. Pharmacogenetics and drug-induced arrhythmias. Cardiovasc Res 2001;50:224–31.
27 Drici MD, Burklow TR, Haridasse V, Glazer RI, Woosley RL. Sex hormones prolong the QT interval and downregulate potassium channel expression in the rabbit heart. Circulation 1996;94:1471–4.
28 Drici MD, Clement N. Is gender a risk factor for adverse drug reactions? The example of drug-induced long QT syndrome. Drug Saf 2001;24:575–85.
29 Schulze-Bahr E, Haverkamp W, Eckardt L, Kirchhof P, Wedekind H, Breithardt G. Genetic aspects in acquired long QT syndrome – a piece in the puzzle. Eur Heart J Supplements 2001;Supplement K:K48–K52.

30 Yang P, et al. Allelic variants in long-QT disease genes in patients with drug- associated torsades de pointes. Circulation 2002;105:1943–8.
31 Donger C, et al. KVLQT1 C-Terminal Missense Mutation Causes a Forme Fruste Long-QT Syndrome. Circulation 1997; 96:2778–81.
32 Piippo K, et al. Effect of the antimalarial drug halofantrine in the long QT syndrome due to a mutation of the cardiac sodium channel gene SCN5A. Am J Cardiol 2001;87:909–11.
33 Makita N, et al. Drug-induced long-QT syndrome associated with a subclinical SCN5A mutation. Circulation 2002;106: 1269–74.
34 Napolitano C, et al. Evidence for a cardiac ion channel mutation underlying drug-induced QT prolongation and life-threatening arrhythmias. J Cardiovasc Electrophysiol 2000;11:691–6.
35 Marban E. Cardiac channelopathies. Nature 2002;415:213–8.
36 Davey PP, Barlow C, Hart G. Prolongation of the QT interval in heart failure occurs at low but not at high heart rates. Clin Sci (Colch.) 2000;98:603–10.
37 Schwartz PJ, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction Circulation 1978;57:1074–7.
38 Dekker JM, Crow RS, Hannan PJ, Schouten EG, Folsom AR. Heart rate-corrected QT interval prolongation predicts risk of coronary heart disease in black and white middle-aged men and women: the ARIC study. J Am Coll Cardiol 2004;43:565–71.
39 Glancy JM, Garratt CJ, Woods KL, de Bono DP. QT dispersion and mortality after myocardial infarction. Lancet 1995; 345:945–8.
40 Maron BJ, et al. Assessment of QT dispersion as a prognostic marker for sudden death in a regional nonreferred hypertrophic cardiomyopathy cohort. Am J Cardiol 2001;87:114–5, A9.
41 Kurita T, et al. Bradycardia-induced abnormal QT prolongation in patients with complete atrioventricular block with torsades de pointes. Am J Cardiol 1992;69:628–33.
42 Strasberg B, et al. Polymorphous ventricular tachycardia and atrioventricular block. Pacing Clin. Electrophysiol 1986;9: 522–6.
43 Ishida S, Takahashi N, Nakagawa M, Fujino T, Saikawa T, Ito M. Relation between QT and RR intervals in patients with bradyarrhythmias. Br Heart J 1995;74:159–62.
44 Numaguchi H, Johnson JP Jr, Petersen CI, Balser JR. A sensitive mechanism for cation modulation of potassium current. Nat Neurosci 2000;3:429–30.
45 Fenichel RR. Development of drugs that alter ventricular repolarization. Am J Ther 2002;9:127–39.
46 Paul AA, Witchel HJ, Hancox JC. Inhibition of the current of heterologously expressed HERG potassium channels by flecainide and comparison with quinidine, propafenone and lignocaine. Br J Pharmacol 2002;136:717–29.
47 Sarubbi B, Ducceschi V, Briglia N, Mayer MS, Santangelo L, Iacono A. Compared effects of sotalol, flecainide and propafenone on ventricular repolarization in patients free of underlying structural heart disease. Int J Cardiol 1998;66:157–64.
48 Benhorin J, et al. Effects of flecainide in patients with new SCN5A mutation: mutation-specific therapy for long-QT syndrome? Circulation 2000;101:1698–706.
49 Abriel H, Wehrens XHT, Benhorin J, Kerem B, Kass RS. Molecular pharmacology of the sodium channel mutation D1790G linked to the long QT syndrome. Circulation 2000:102:921–5.
50 Warmke JW, Ganetzky B. A family of potassium channel genes related to eag in Drosophila and mammals. Proc Natl Acad Sci USA 1994;91:3438–42.
51 Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED, Keating MT. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. Cell 1995;80:795–803.
52 Sanguinetti MC, Jiang C, Curran ME, Keating MT. A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the IKr potassium channel. Cell 1995;81: 299–307.
53 Chen J, Seebohm G, Sanguinetti MC. Position of aromatic residues in the S6 domain, not inactivation, dictates cisapride sensitivity of HERG and eag potassium channels. Proc Natl Acad Sci USA 2002:99:12461–6.
54 Sanchez-Chapula JA, Navarro-Polanco RA, Culberson C, Chen J, Sanguinetti MC. Molecular determinants of voltage-dependent human ether-a-go-go related gene (HERG) K^+ channel block. J Biol Chem 2002;277:23587–95.
55 Mitcheson JS, Chen J, Lin M, Culberson C, Sanguinetti MC. A structural basis for drug-induced long QT syndrome. Proc Natl Acad Sci USA 2000;97:12329–33.
56 Zeltser D, Justo D, Halkin A, Prokhorov V, Heller K, Viskin S. Torsade de pointes due to noncardiac drugs: most patients have easily identifiable risk factors. Medicine (Baltimore) 2003;82: 282–90.
57 Haverkamp W, et al. The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications. Report on a policy conference of the European Society of Cardiology. Eur Heart J 2000;21:1216–31.
58 Viskin S, Justo D, Halkin A, Zeltser D. Long QT syndrome caused by noncardiac drugs. Progress in Cardiovascular Diseases 2003;45:415–27.
59 Bailey DG, Malcolm J, Arnold O, Spence JD. Grapefruit juice-drug interactions. Br J Clin Pharmacol 1998;46:101–10.
60 Tzivoni D, et al. Treatment of torsade de pointes with magnesium sulfate. Circulation 1988;77:392–7.
61 Kerr GW, McGuffie AC, Wilkie S. Tricyclic antidepressant overdose: a review. Emerg Med J 2001;18:236–41.
62 Plaster NM, et al. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. Cell 2001;105:511–9.
63 Marks ML, Whisler SL, Clericuzio C, Keating MT. A new form of long QT syndrome associated with syndactyly. J Am Coll Cardiol 1995;25:59–64.

Swiss
Medical Weekly

Official journal of
the Swiss Society of Infectious disease
the Swiss Society of Internal Medicine
the Swiss Respiratory Society

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)

- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses

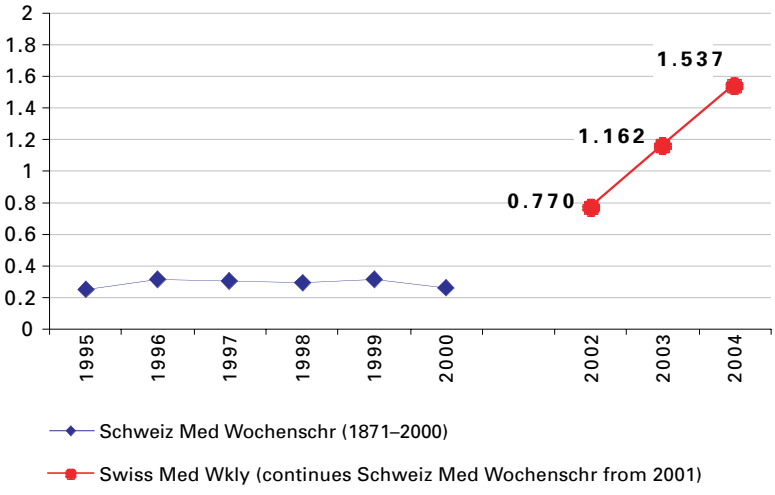
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly



EMH FMH Schwabe
Editores Medicorum Helveticorum

All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnsburgerstrasse 8
CH-4132 Muttenz

Manuscripts: submission@smw.ch
Letters to the editor: letters@smw.ch
Editorial Board: red@smw.ch
Internet: http://www.smw.ch