Original Article

Assessment of Efficacy of Pharmacotherapy for Ventricular Tachycardia

Mark J. Cooper, PhD, FRACP*

Westmead Hospital, Westmead, NSW 2145, Australia

The presence and sinister prognosis of sustained ventricular tachycardia was recognised early in the twentieth century in patients with serious cardiac disease. Treatment was difficult and evolved slowly. The development of antiarrhythmic drug therapy was frequently based on chance clinical observations and on the assessment of drug effects in animal models of arrhythmia that bore little resemblance to the actual clinical scenarios in which the drugs were to be employed. Even early reports of antiarrhythmic drug use were tempered by awareness of serious adverse side effects. Many drugs were brought into wide-spread clinical use without the background of large randomised trials of efficacy.

Assessment of drug efficacy for ventricular tachycardia was frequently based on the effects of an administered drug on inducibility of tachycardia with invasive electrophysiologic techniques. Suppression of inducibility was suggested to be a marker of drug efficacy. Similarly, suppression of spontaneously occurring ventricular ectopic beats was also used as a predictor of drug effect. However, both predictive techniques were hindered by inherent baseline variability. It was subsequently demonstrated that mode of induction of ventricular tachycardia could vary widely at repeat inductions. Antiarrhythmic drugs rarely suppressed inducibility of VT but could alter mode of induction. Techniques were developed to estimate true drug effects by quantitating and allowing for random variability in mode of tachycardia induction. In particular, reproducibility of tachycardia induction was enhanced when baseline and drug studies were performed at short intervals.

Even with these techniques, prediction of long-term drug efficacy in individual patients remained difficult and acute drug testing served principally to demonstrate the fact that drug therapy was more likely to facilitate induction of tachycardia than to suppress it (pro-arrhythmic effect). Large clinical trials also demonstrated the potent pro-arrhythmic effects of drug therapy especially when sodium-channel blocking drugs were used. By the end of the twentieth century, antiarrhythmic drugs were used primarily as adjuncts to device therapy for patients at risk of life-threatening ventricular arrhythmias.

(Heart, Lung and Circulation 2007;16:170–175)

Keywords. Ventricular tachycardia; Arrhythmia; Antiarrhythmic drug therapy

"A point which requires emphasis . . . is the fact that a wide gap exists between the development of a potent chemical product and the discovery of the uses to which it can be put in clinical therapeutics. If one takes an historical view of the matter, one finds that this gap is often filled with vague and inconclusive clinical impressions."

Dr. Harry Gold, 1940[1]

The recent complications associated with the use of Vioxx suggest that the above opinion is not entirely irrelevant even in the current era of large randomised clinical trials. Certainly this opinion is extremely relevant to the manner in which antiarrhythmic drugs were used in the treatment of ventricular arrhythmias in the twentieth century.

The first electrocardiographic representation of ventricular tachycardia (VT) was published in a case report by Lewis in 1909.[2] The possibility of successive ventricular ectopic beats giving rise to tachycardia had been proposed previously by Mackenzie in 1902[3] and Wenckebach in 1904,[4] but the documentation of such an arrhythmia required the use of the then newly developed electrocardiograph. The first electrocardiogram of ventricular fibrillation (VF) was published shortly afterwards by Robinson in 1912.[5]

At that time, effective therapy for either of these tachyarrhythmias did not exist. Lewis, in his article, described multiple episodes of symptomatic non-sustained VT occurring in his patient over a period of three years but does not allude to any specific therapy. In 1917, Robinson and Bredeck[6] reported an unusual case of 'ventricular fibrillation in man with cardiac recovery'. In this report, the authors stated that 'when the human ventricles pass into a state of fibrillation, death is an almost immediate and invariable consequence'.

Available online 24 April 2007

* Correspondence address: 16/1A Ashley Lane, Westmead, NSW 2145, Australia. Tel.: +61 2 9633 2244; fax: +61 2 9891 5742.
E-mail address: vascoo@bigpond.net.au.

1443-9506/04/$30.00
doi:10.1016/j.hlc.2007.03.006

During the following five decades, therapy for VT remained inadequate. Paroxysmal VT was regarded as a rare manifestation of cardiac disease usually occurring in patients with underlying coronary artery atherosclerosis, and frequently associated with acute myocardial infarction.[7–10] The prognosis was almost universally poor.[8] Wolferth and McMillan[11] reviewed the outcome in the 22 cases of ventricular tachycardia that had been published up to 1923. In 50% of cases, the patients died within several days of the first recorded arrhythmia episode.

It was noted in the 1940s that prognosis in patients with ventricular arrhythmias was closely related to the degree of underlying left ventricular dysfunction.[8] The prognosis remained poor in reviews published up to 1951.[10] In most cases, death occurred because there was no effective means of terminating acute episodes of tachycardia or fibrillation. Patients frequently remained in tachycardia for hours to days, with the longest recorded episode of VT persisting continuously for 77 days prior to the death of the patient.[12]

Use of Quinidine as An Antiarrhythmic Drug

The only widely used therapy for acute and recurrent VT in the first 50 years of the last century was quinidine sulphate. The intentional use of quinidine as an antiarrhythmic treatment for atrial fibrillation was first described by Frey in 1918.[13] Wenckebach had previously suggested to his associate Frey that quinine or one of its salts may be an effective antiarrhythmic drug. This idea originated from a patient who frequently travelled to the 'tropics' and who had noted that the antimalarial drug quinine could terminate his atrial fibrillation.[14,15] Frey reported that quinidine sulphate (the dextro-isomer of quinine) was the most effective of the various cinchona derivatives that he compared in the treatment of atrial fibrillation. Based on early case reports of its efficacy, quinidine came to be widely used in the treatment of recurrent atrial fibrillation and in 1921, Scott used orally administered quinidine to control recurrent VT.[16] Quinidine, via either oral or intravenous routes of administration, subsequently became first line therapy for VT.[1,9,10,17]

However, the early use of quinidine for both ventricular and supraventricular tachycardia was tempered by reports of associated syncope and sudden death.[18–22] In some cases, sudden death occurring in patients receiving quinidine appeared to be related to new ventricular tachyarrhythmias. Even by 1943, 25 years after its introduction into clinical practice, Williams and Ellis concluded that 'in general it is difficult to prove the usefulness of this drug by statistical evidence'.[8] Despite the awareness of its pro-arrhythmic effects, quinidine remained the major drug used in the management of VT until the 1950s, largely because of the absence of any other useful therapy. Hence, the first antiarrhythmic drug mirrored the use of subsequent agents; the drug was developed from a chance observation with little scientific understanding of its mode of action. It produced harm and was eventually relegated from common clinical use by randomised trials and statistical data. The use of quinidine faded at the end of the twentieth century with the advent of a meta-analysis which highlighted the risk of sudden death when the drug was used to treat atrial fibrillation.[23]

Development of New Antiarrhythmic Drugs

During the 1950s and 1960s, a wider range of antiarrhythmic drugs became available for use. It had been noted previously that when procaine was applied directly to the myocardium (in animal models), an increased stimulation current was required in order to provoke ventricular ectopic beats.[24,25] Diethylamino-ethanol (a hydrolysate of procaine) was used intravenously to control cardiac arrhythmias occurring under general anaesthesia during the Second World War.[26,27] In 1950, Mark et al. used intravenous procaine amide to control ventricular arrhythmias occurring in an animal model.[28] Lidocaine hydrochloride was also reported to be effective in reducing the occurrence of ventricular ectopic beats in animal models.[29,30]

Recognition of the antiarrhythmic properties of these local anaesthetic agents stimulated research into the development of new drugs with similar electrophysiological actions. The potential usefulness of new agents was initially assessed in various animal models such as by noting a reduced incidence of spontaneous VF following acute coronary artery ligation in dogs, or a reduction in the percentage of ectopic beats after administration of chloroform and adrenaline to cats.[31] Promising agents were then tested in humans for their ability to suppress spontaneously occurring premature ventricular ectopic beats. From this, use of the drug was then generalised to the treatment of potentially lethal arrhythmias where the drug was frequently required to terminate tachycardia as well as prevent recurrence of arrhythmias. In retrospect, it is quite likely that there could be a disparity between the effects of a drug on spontaneously occurring ventricular ectopic beats and on a reentrant circuit.[32]

The development of coronary care units in the 1960s lead to a recognition that ventricular arrhythmias were not as rare as initially thought and that in fact they occurred commonly in patients hospitalised with chest pain.[33–37] The advent of effective methods of terminating arrhythmias such as cardioversion[38] and drug therapy, then led to attempts to prevent the arrhythmia recurring.

Identification of High Risk Patients

High risk patients were identified as those who had survived a cardiac arrest or a sustained episode of VT, particularly when these arrhythmic events did not occur in the context of an acute myocardial infarction.[39–42] This group of patients was considered to have the highest risk of subsequent sudden death[43] and was the focus of drug therapy and clinical trials. However, the chief difficulty in applying drug therapy lay in assessing whether a drug would be effective in these high risk patients. Empirical therapy was not acceptable. Some predictive model was