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Use of 24 h ambulatory ECG recordings in the assessment of new chemical entities in healthy volunteers

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1 Ambulatory (24 h) cardiac monitoring (ACM) is frequently used to screen healthy volunteers before inclusion in trials of new chemical entities in man. We analysed 156 consecutive ACM recordings in 'healthy' volunteers (on no medication).
2 Only 20 (13%) of the recordings showed normal sinus rhythm throughout.
3 Supraventricular ectopics were the commonest abnormality (83%). Ventricular ectopics occurred in 11%; ventricular tachycardia (unsustained) in 2% and sinus pauses in 6.5%. One volunteer was found to be in atrial fibrillation throughout.
4 The data indicate that when ACM recordings are performed in the assessment of the effects of experimental drugs, guidelines are needed to assess 'normality' to suggest when cardiological investigation is needed and to assign causality of the arrhythmia to the new chemical entity.
5 Proposed guidelines are presented.

Keywords ambulatory 24 h ECG healthy volunteers new chemical entities

Introduction

Many drugs alter ionic fluxes across membranes and thus influence the electrical behaviour of the myocardium [1]. This has obvious therapeutic implications for drugs designed to affect the cardiovascular system, but many 'non-cardiovascular' drugs also alter the electrophysiology of cardiac function [1]. The ECG is a simple, inexpensive method of assessing changes in cardiac electrophysiology, some of which can be life threatening. However, little published information is available on the use of ECG recordings to assess the safety of new chemical entities (NCE) given to man. When an NCE is administered to humans for the first time, it is common practice to obtain intermittent 12 lead ECG recordings for variable periods of time after administration of the drug. Additionally, a real time ECG display is often monitored for a short period immediately after dosing. However, as has been found in clinical practice, this approach may fail to detect significant cardiac rhythm disturbances.

Twenty-four hour ambulatory cardiac monitor (ACM) recording is increasingly used in the assessment of safety of experimental drugs. For this purpose the range of findings in the normal healthy population must be defined. However, there have been few studies on this population [2–4], in contrast to the extensive use of this technique in patients. Consequently, when an 'abnormality' is found during an ACM recording on a healthy volunteer there are no clear guidelines on the appropriate investigation required to assess the cardiac status of the volunteer and, when an isolated arrhythmia occurs in a study with an NCE, the causality may be difficult to assign.

Zeneca Pharmaceuticals routinely use 24 h ACM as part of the safety assessment of NCEs during Phase I testing of all drugs given to man. This is to help us to discover if the new chemical entity (NCE) has any arrhythmogenic potential. Preclinical, and indeed even full clinical trial programmes, do not always identify cardiac 'risk'. For example in 1993, flosequinan was withdrawn when its arrhythmogenic potential at standard therapeutic dose was identified shortly after its introduction to clinical practice [5–7]. It is important to document that an NCE has no cardiac effects as early as possible to ensure its safe development.

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Prior to inclusion in a trial with an NCE, we use ACM recordings to screen apparently healthy volunteers for any latent arrhythmias which might jeopardise their safety since the effects of NCEs on human cardiac electrophysiology is unknown. At Zeneca we have observed a number of 'abnormalities' during these ACM recordings on healthy volunteers. These observations prompted a review of all ACM recordings made during a 12 month period as part of the routine health checks made on volunteers in our Unit. Based on our results, and review of the literature, we propose guidelines for the use of ACM in assessing the cardiac safety profile of NCEs in healthy volunteers, and we suggest appropriate cardiological investigation to exclude underlying organic heart disease as a cause of arrhythmias detected during either health screening or when testing an NCE. We also suggest certain absolute criteria for exclusion of volunteers from a study with an NCE (or experimental drug), based on ACM criteria.

Methods

The Clinical Pharmacology Unit (CPU) at Zeneca Pharmaceuticals maintains a healthy volunteer panel from which subjects are recruited for clinical trials. Before entering a study with an NCE, all volunteers undergo a thorough medical history and examination including assessment of blood pressure and pulmonary function. The volunteer must have no history or signs of any active disease and all objective markers of health (including extensive haematology, biochemistry, thyroid function tests and urinalysis) must be normal before a volunteer may be enrolled. Volunteers with an immediate family history (first degree relative) of hypertrophic obstructive cardiomyopathy or any other similar heart condition are not included in our healthy volunteer panel. Both 12-lead and 24 h ambulatory ECG recordings are obtained routinely.

In this survey 156 consecutive ACM recordings were reviewed by one of us (JP). These recordings were obtained from 152 volunteers. All had ACM recordings taken at pre-trial medical examinations and three had further recordings made (two subjects one further recording, one subject two further recordings) after recognition of an 'abnormal' rhythm. At the time of the ACM recordings surveyed, all volunteers were symptom free and were members of the healthy volunteer panel. None was taking medication (prescribed or as part of a trial) and all were going about their normal daily activities.

Equipment

The ambulatory ECGs were recorded using a Schiller Microvit MT3 recorder (Baar, Switzerland) which was attached by five electrodes (one under each clavicular head, one at the right sternal edge at 7th rib, one in the anterior axillary line above the right hypochondrium and one over the 5th rib in the left anterior axillary line). The recordings were printed using a Schiller CS6/12 system which automatically displays all ectopic and patient events (recorded by means of a button on the recorder) from two pairs of electrode positions. For this study all recordings were reviewed and the arrhythmias confirmed and recorded.

Definitions of arrhythmias

1 Supraventricular ectopic beats were defined as QRS complexes with identical morphology to the normal sinus beat (duration < 120 ms) but occurring early—before 80% of the prevailing R-R interval (over 10 previous sinus beats) whether or not associated with a P wave.
2 Junctional beats were defined as having morphology of the QRS complex identical to sinus beats (duration < 120 ms), but having an absent, inverted or retrograde P wave.
3 Supraventricular tachycardia (excluding sinus tachycardia) was defined as 3 or more beats at a ventricular rate of at least 120 beats min^{-1} with P waves either not clearly defined or inverted, and narrow QRS complexes (< 120 ms) of the same morphology as the sinus beats.
4 Ventricular ectopics were defined as being of different QRS morphology to the sinus beats with no preceding P wave and having duration of > 120 ms.
5 Ventricular tachycardia was defined as being three or more successive ventricular ectopic beats at a rate of at least 120 beats min^{-1}.
6 Sinus pauses were defined as an absence of electrical activity lasting more than 2 s.
7 First degree heartblock PR internal > 0.22 s
Second degree heartblock
   (i) Wenckebach—progressive lengthening of PR interval until one QRS complex is dropped.
   (ii) Mobitz type II—simple pattern of dropped beats but without change in PR interval.
Third degree heartblock—no correlation between P waves and QRS complexes.

Results

The 156 recordings examined were made in 152 volunteers, mean age 33 ± 9.25 (s.d.) years; 144 were male (age range 18–59 years) mean 32.3 ± 9.0 years and eight (5%) were females (age range 38–56 years) mean 48.7 ± 3.85 years. The females were all involved in one trial and were post-menopausal, thus explaining the higher mean age of that population. No attempt has been made to correlate the ECG data with sex, age, smoking history, alcohol consumption or family history of heart disease.

The prevalence of arrhythmias recorded is shown in Table 1. Only 20 (13%) of the recordings showed normal sinus rhythm throughout. All events described were asymptomatic.

Supraventricular ectopics occurred in 83% of recordings; the most detected in any one subject was 55.

Table 1 Prevalence of arrhythmias in 156 single 24 h ambulatory ECG recordings made on 152 healthy volunteers

Arrhythmias (defined in text)	*Number of ACM recordings showing dysrhythmias (%)*	
Atrial fibrillation	1	(1)
Supraventricular ectopics	129	(83)
Junctional ectopics/rhythm*	24	(15)
Supraventricular tachycardia	4	(2.5)
Ventricular ectopics	17	(11)
Supraventricular + ventricular ectopics**	15	(10)
Ventricular bigeminy	5	(3)
Ventricular couplet	4	(2.5)
Ventricular tachycardia	3	(2)
Sinus pauses	10	(6.5)
Second degree heart block type I	2	(1)
Second degree heart block type II	10	(6.5)
None	20	(13)

*Data not included in supraventricular ectopics summaries.
**Data included in both supraventricular and ventricular ectopics summaries.

Twenty-four recordings showed junctional beats. Sixteen of the 24 recordings with junctional activity showed single ectopics (15 of these 16 also had at least one supraventricular ectopic on the recording). Five of the 24 subjects showed pairs of junctional beats and three subjects had runs of junctional rhythm—one subject regularly had runs of junctional rhythm throughout the recording (more frequently at night); one had a 4 beat run of junctional tachycardia while awake (rate 120 beats min^{-1}); and also had five runs of junctional rhythm each of 5–10 beats in length, again occurring at night. This subject had had an ambulatory ECG 12 months earlier which showed no 'abnormality'.

All runs of supraventricular tachycardia detected were short (6 beats longest) and occurred independent of exercise or time of day.

One volunteer was in atrial fibrillation throughout the ACM. This volunteer had shown sinus rhythm in previous ECGs and ACM recordings and had a regular pulse at his medical. He was referred for cardiological investigation. Idiopathic atrial fibrillation was diagnosed; he was electively cardioverted and has since remained well and in sinus rhythm, but has been withdrawn from our volunteer panel.

Two volunteers had several hundred ventricular ectopics throughout the 24 h recording. One of these had multifocal ventricular ectopics which occurred in couplets on occasion. This volunteer was subsequently investigated in a cardiology centre and no abnormality was found.

Four episodes of monomorphic non-sustained ventricular tachycardia were noted in three volunteers (two male). Three of the episodes occurred during sleep; one at the time of an alarm clock ringing.

One volunteer, who had two episodes of ventricular tachycardia, had one run of 5 beats and one of 15 beats whilst asleep. This volunteer had been noted to have a short run of non-sustained ventricular tachycardia in a previous recording. He had, apart from these two ambulatory recordings, two other 24 h ACM recordings, both of which were entirely normal. He was offered but declined cardiological investigation. The remaining two episodes of ventricular tachycardia (in two other volunteers) were both of three beats' duration.

All sinus pauses (greater than 2 s) and episodes of second degree heart block Type I (Wenckebach) occurred during the hours of sleep as did all but one episode of second degree heart block—Type II/Mobitz II. The largest number of sinus pauses in any recording was 12 and the longest pause was 2.8 s.

One subject had eight sinus pauses and 10 episodes of Type I second degree heart block in a single recording. The largest number of episodes of Type II second degree heart block was 20 in one subject, the next largest number of episodes was 5 in one subject. None of the recorded arrythymias was symptomatic.

Discussion

Much of the published literature has focused upon the detection and prognostic implication of ventricular ectopic activity in normal hearts. Table 2 summarises some of these most recent data (the empty cells reflect the lack of recorded or reported non-ventricular rhythm disturbances).

Our data for the prevalence of ventricular dysrhythmias in healthy subjects is in agreement with other studies [14–18; see Table 2]. We detected less ectopic actvity than some other studies of healthy subjects undergoing ACM—but the subjects in these populations were somewhat older than ours and there is a well documented relationship of increasing ectopic frequency with increasing age [14–16].

Our findings are also consistent with the published report that supraventricular ectopic beats occur in almost every person and they increase with age [19]. They are almost physiological when occurring during sinus bradycardia. Multifocal or frequent atrial ectopics, however, may indicate organic heart disease. Supraventricular tachycardia is often innocuous but warrants investigation as certain forms require therapy. Atrial fibrillation merits investigation to exclude mitral valve disease, thyrotoxicosis, ischaemic heart disease, hypertensive heart disease etc [8].

Some ventricular arrhythmias have a bad prognosis. Ventricular tachycardia and fibrillation are obvious examples [9]. Sustained ventricular tachycardia (lasting more than 30 s) merits a comprehensive evaluation [10], as various specific therapeutic options may be indicated. Two to three repetitive ventricular beats, in the absence of symptoms and with an otherwise normal ECG, do not need investigation or therapy [10], although one study showed an association between frequent ventricular ectopic beats (> 100 per hour) and adverse prognosis in otherwise normal patients [11].

Expert opinion varies regarding the need to investigate non-sustained ventricular tachycardia, indeed its definition remains in debate. Some authorities define it as 3 or more consecutive beats [4] which is the criterion used by the Schiller Microvit MT3 recorder used in this study, and some define it as more than 5 consecutive ventricular ectopic beats but less than 30 s

Table 2 Summary of data from other surveys of 24 h ambulatory ECG recordings made on healthy subjects (Refs 8–15 inclusive). Figures are arrhythmias expressed as a percentage of total recordings made

Arrhythmia	*Reference 12 and 15*	*13*	*14*	*2*	*16*	*17*	*18*
Supraventricular ectopics	87		75	19		56	64
Nodal beats					9	22	4
Supraventricular tachycardia	22			4	5	2	2
Ventricular ectopics	69	24	46	17	73	50	54
Ventricular bigeminy	2	2			3		
Ventricular couplets	8	5	0.7	2		2	0
Ventricular tachycardia	2	2	0.7	0	2	2	2
Pauses						4	
Second degree heart block Type I					2	6	4
Second degree heart block Type II					1	4	0
Nil	7						
Age range of subjects (years)	40–79	18–70	15–66	20–79	16–65	23–27	22–28
Mean age (years)	54.5	42	44				

Empty space = data not recorded or not available from reference.

duration [9, 12]. In the presence of impaired left ventricular function non-sustained ventricular tachycardia indicates a poorer prognosis [13]. The arrhythmia is (relatively) uncommon in apparently normal individuals and to date there has been no authoritative long term review of subjects with this arrhythmia. Prognosis is probably determined by whether or not there is underlying structural cardiac disease.

Second degree heart block is uncommon, but does occur in healthy volunteers [10, 17, 18]. It is usually of the Type I or Wenckebach type, but there are reports [3, 17] of Type II/Mobitz II second degree heart block in apparently healthy subjects. Episodes of second degree heart block reported elsewhere and in our series are commoner during sleep, and may be related to increase in vagal tone. Similarly sinus pauses are commoner during sleep—the longest reported in a healthy volunteer prior to our series was 2.5 s [20].

Our data and proposed guidelines relate to healthy subjects with no evidence of cardiac disease on history, physical examination and resting 12-lead ECG. These data could also be extrapolated to a patient with non-cardiac disease.

The prognostic significance of the arrhythmias we have detected in apparently normal hearts is not clear. Subtle changes in left ventricular function have been demonstrated at angiography in subjects with frequent ventricular ectopic activity [21] but the existence of coronary artery disease does not correlate well with the ectopic activity. However, 25% of asymptomatic patients with ventricular ectopics had significant coronary artery disease [22]. In our opinion, it is important that in the instances described above ($\geq$ 100 ventricular ectopic beats h^{-1} or ventricular tachycardia) that echocardiography be performed to investigate possible underlying cardiac disease such as hypertrophic cardiomyopathy, mitral valve prolapse or viral myocarditis. The prognosis of these conditions is known to be worse in the presence of ventricular tachycardia and management should be individualized for each patient. Several authors have suggested that there is no prognostic significance of ventricular tachycardia on ACM in a normal heart [14, 15, 20, 22].

Our study indicates that a subject with ventricular tachycardia on one ACM recording can have (at least) one other completely 'normal' ACM recording on a different occasion. Thus the prevalence of all arrhythmias must be higher than recognised. In this study the less frequent arrhythmias found were supraventricular tachycardia, ventricular bigeminy, ventricular couplets, sustained ventricular tachycardia and Type I second degree heart block. Longitudinal studies of a healthy population such as this, are few and follow up has been short making prognostic interpretation difficult. What little data there are suggest that even complex ventricular arrhythmias (including ventricular tachycardia) in a 'healthy' heart are not necessarily an adverse finding [14, 15, 20, 23]. Our volunteer panel will be followed regularly for a number of years with ACM and 12-lead ECGs and we plan, from this cross-sectional survey, to collect follow-up data on all the individuals screened here.

There is no information available on whether subjects with asymptomatic abnormalities on ACM are at increased risk from NCEs nor, at the time of the first human exposure, whether any human subject is at risk from the NCE. In these circumstances most clinical researchers would avoid administering an NCE to a subject with a known abnormality on ECG or ACM, since proving that there is a risk might endanger the life of the subject. Although all concerned with early trials of NCEs in man attempt to

maximise safety this can never be absolutely guaranteed in a 'first time in man' study. It is the authors' opinion that ACM recording is straightforward and readily available, and that the use of ACM in NCE studies to detect any arrhythmogenic potential is just as important in the early assessment of NCEs, as screening and measurement of tests for asymptomatic abnormalities of clinical chemistry, haematology and urinalysis. Ultimately, however, the screening and safety monitoring undertaken in any particular NCE assessment is a decision of the clinical researcher and of the pharmaceutical company undertaking the study. When a decision is made to use the ACM our guidelines are intended to aid the clinical management of the volunteer and in the interpretation of the results obtained.

We suggest that pre-study ACM recordings should be analysed before inclusion in a study. An argument may be made that ACM recordings during a first time in man trial should be interpreted within 24 h of drug dosing before more volunteers are exposed to the NCE (as for any other safety assessment in a first time in man study). Our guideline 2 aims to ensure that an arrhythmia detected on ACM is interpreted with the 12 lead ECG. Our guidelines relate to isolated arrhythmias found in ACM recordings in the presence of normal 12 lead ECGs. If ACM is to be used for assessing arrhythmia potential (rather than safety screening) then data from ACM could be interpreted at the end of the study and analysed statistically against placebo and historical incidence data.

These proposed guidelines are intended to protect volunteers, to obviate inappropriate investigation of volunteers (which will induce anxiety and possible 'cardiac neurosis') and to protect a new drug in sensitive, difficult, early safety assessments.

Proposed guidelines for management of ACM recording abnormalities detected in otherwise healthy volunteers

Guideline 1 Management of ACM abnormalities detected in medical screening of healthy volunteers with a normal 12 lead ECG

1(A) Do not enrol into a study with an experimental drug if ACM shows:

(i) More than 200 ventricular ectopics in 24 h [10].
(ii) Ventricular tachycardia [10].
(iii) Second degree heart block.
(iv) Sustained cardiac arrhythmias (atrial fibrillation, SVT, complete heart block).
(v) Any symptomatic arrhythmia (except isolated extra systoles) [11, 25].

1(B) Refer for cardiac investigation if ACM shows:

(i) More than 100 ventricular ectopics per hour [10].
(ii) Ventricular tachycardia with rate > 180 beats min^{-1} [9].
(iii) Ventricular tachycardia > 10 beats [9].
(iv) Ventricular tachycardia with < 10 beats *and* rate > 180 beats min^{-1}.
(v) Any symptomatic arrhythmia (except isolated extra systole).
(vi) Atrial fibrillation, SVT, secondary or complete heartblock.
(vii) Sinus pauses > 3 s.

Suggested initial cardiac investigation is echocardiography.

Guideline 2 Suggested use of ACM, 12 lead ECG and real time continuous cardiac monitoring in NCE studies

2. Suggested guidelines for use of ACM and ECG safety assessments of NCEs:

(i) *Prior to study day*

12 lead ECG and ACM – which should be reviewed before commencement of study.

(ii) *Study day*

12 lead intermittently (pre-dose, hourly for 8 h and at 10, 12 and 24 h after dosing). May be longer for NCE of long half-life. Real time monitor (usually for approximately 4 h after dosing).

ACM for 24 h after dosing.

(iii) *Post study*

12 lead ECG.

(ACM if arrhythmia detected on study day and causality unclear).

Guideline 3 Procedure for assessment of isolated cardiac rhythm disturbance found on ACM in studies with NCEs

(i) Care of volunteer

Withdraw volunteer from the study if any arrhythmia in Guideline 1(A) or (B) occurs. Proceed with study of the other volunteers and assess ACM reading at conclusion of the study comparing incidence of arrhythmia on drug with placebo and historical incidence data.

(ii) Causality

Causality can be considered by comparing incidence of ACM abnormality in volunteers taking the NCE with that of volunteers on placebo and with historical control data. If the incidence of abnormalities in volunteers taking the trial drug is similar to, or less than that on placebo, or that found in historical controls and literature values, then it is less likely that the experimental drug/new chemical entity is the cause of the arrhythmia.

(iii) Refer to cardiologist if ACM shows any of the abnormalities in Guideline 1(B) above since the arrhythmia may have occurred *de novo*. This should always be performed with the GP's consent or indeed via the GP unless in an emergency.

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