Pharmacology & Therapeutics 139 (2013) 213–248

Contents lists available at SciVerse ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

The Lambeth Conventions (II): Guidelines for the study of animal and human ventricular and supraventricular arrhythmias

Michael J. Curtis [a,*], Jules C. Hancox [b], András Farkas [c], Cherry L. Wainwright [d], Catherine L. Stables [e], David A. Saint [f], Hugh Clements-Jewery [g], Pier D. Lambiase [h], George E. Billman [i], Michiel J. Janse [j], Michael K. Pugsley [k], G. André Ng [l], Dan M. Roden [m], A. John Camm [n], Michael J.A. Walker [o]

[a] Cardiovascular Division, KCL, Rayne Institute, St. Thomas' Hospital, London, SE17EH, UK
[b] Cardiovascular Research Laboratories, School of Medical Sciences, University Walk, Bristol, BS8 1TD, UK
[c] 2nd Department of Medicine and Cardiology Centre, Faculty of Medicine, University of Szeged, Korányi fasor 6, H-6720, Szeged, Hungary
[d] School of Pharmacy and Life Sciences, Robert Gordon University, Schoolhill, AB10 1FR, Aberdeen, UK
[e] Department of Neurology, University of Michigan, Ann Arbor, MI, 48109, USA
[f] School of Molecular and Biomedical Science, University of Adelaide, Adelaide, SA, 5005, Australia
[g] West Virginia School of Osteopathic Medicine, 400N Lee Street, Lewisburg, WV, 24901, USA
[h] Institute of Cardiovascular Sciences, UCL 16-18 Westmoreland St., London, W1G 8PH, UK
[i] Department of Physiology and Cell Biology, The Ohio State University, 304 Hamilton Hall, 1645 Neil Ave., Columbus, OH 43210-1218, USA
[j] Experimental and Molecular Cardiology Group, Academic Medical Center, University of Amsterdam, Meibergdreef 9, K2-105, 1105, AZ, Amsterdam, The Netherlands
[k] Department of Toxicology/Pathology, Johnson & Johnson PRD OMP 2357, 1000 Route 202 South Raritan, NJ, 08869, USA
[l] Department of Cardiovascular Sciences, University of Leicester, Clinical Sciences Wing, Glenfield General Hospital, Leicester, LE3 9QP, UK
[m] Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, 2215B Garland Avenue, Nashville, TN, 37232-0575, USA
[n] St. George's University of London, Cranmer Terrace, London, SW17 ORE, UK
[o] Department of Anesthesiology, Pharmacology & Therapeutics, University of British Columbia Vancouver, 2176 Health Sciences Mall, Vancouver, V6T 1Z3, BC, Canada

ARTICLE INFO

Keywords:
Antiarrhythmic
Lambeth Conventions
Methods
Supraventricular arrhythmia
Torsades de pointes
Ventricular arrhythmia

ABSTRACT

The 'Lambeth Conventions' is a guidance document, written in 1987 (Walker et al., 1988), intended to be of practical value in the investigation of experimental arrhythmias induced by ischaemia, infarction, and reperfusion. This is an update, expanded to include guidance on the study of supraventricular arrhythmias, drug-induced arrhythmias, heritable arrhythmias, and advances in our knowledge in core areas since 1987. We have updated the guidance on the design and execution of experiments and the definition, classification, quantification, and analysis of all types of arrhythmias. Investigators are encouraged to adopt the conventions and test their validity in the hope that this will improve uniformity and interlaboratory comparisons, aid clinical research, facilitate antiarrhythmic drug discovery and safety assessment, and improve antiarrhythmic drug deployment for different cardiac conditions. We note that there is a gap between some definitions proposed here and their conventional clinical counterparts, and encourage the research necessary to bridge that translational gap. A web link offers the chance to vote and comment on the new conventions (https://bscr.wufoo.com/forms/z7x0x5/).

Abbreviations: AAALAC, Association for Assessment and Accreditation of Laboratory Animal Care, International; AF, atrial fibrillation; AFL, atrial flutter; AHA, American Heart Association; AP, action potential; APB, atrial premature beat; APD, action potential duration; AT, atrial tachycardia; AV, atrioventricular; AVNRT, atrioventricular nodal re-entrant tachycardia; AVRT, atrioventricular re-entrant tachycardia; bpm, beats per minute; ECG, electrocardiogram; FFT, Fast Fourier transform; FIH, First (time a drug is studied) in human; GM, genetically modified; HDO, high definition oscillometry; hERG, human ether-a-go-go related gene; HR, heart rate; ICH, International Conference on Harmonization; IK_r, rapid delayed rectifying potassium current; IK_s, slow delayed rectifying potassium current; I_{Na}, fast inward sodium current; I_{to}, transient outward current; NC3Rs, National Centre for the Replacement Refinement and Reduction of Animals in Research; QA, interval between Q wave and the onset of the aortic blood pressure pulse; readout, the combined data set obtained from an experiment; SVT, supraventricular tachycardia; TDP, torsades de pointes; test article, procedure or drug under investigation; TG, transgenic; T_{peak}–T_{end}, interval between start and end of the T wave; USDA, United States Department of Agriculture; validation, proof of clinical predictive accuracy; VF, ventricular fibrillation; VPB, ventricular premature beats; VT, ventricular tachycardia; WT, wild type.

* Corresponding author.
E-mail addresses: michael.curtis@kcl.ac.uk (M.J. Curtis), jules.hancox@bristol.ac.uk (J.C. Hancox), farkas.andras@med.u-szeged.hu (A. Farkas), c.wainwright@rgu.ac.uk (C.L. Wainwright), cstables@med.umich.edu (C.L. Stables), david.saint@adelaide.edu.au (D.A. Saint), hclementsjewery@osteo.wvsom.edu (H. Clements-Jewery), pier.lambiase@uclh.nhs.uk (P.D. Lambiase), billman.1@osu.edu (G.E. Billman), m.j.janse@amc.uva.nl (M.J. Janse), mkpugsley@yahoo.com (M.K. Pugsley), gan1@le.ac.uk (G.A. Ng), dan.roden@vanderbilt.edu (D.M. Roden), jcamm@sgul.ac.uk (A.J. Camm), mjawalker@yahoo.com (M.J.A. Walker).

0163-7258/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pharmthera.2013.04.008

Contents

1. Introduction

A meeting was held in London in September 2010 to update the guidance for research on arrhythmias that was originally published in 1988: the Lambeth Conventions (Walker et al., 1988). The intention of the meeting was to examine the flaws in the present conventions and to construct a revised set. This document is the outcome. The revised conventions are intended to be of practical value in terms of the design, execution, and analysis of experiments, with emphasis on the definition, classification, and quantification of ventricular premature beats (VPB), ventricular tachycardia (VT), torsades de pointes (TDP), ventricular fibrillation (VF), atrial tachycardia (AT), atrial flutter (AFL) and atrial fibrillation (AF) and rhythms of the atrioventricular (AV) node. We aimed for scientific appropriateness, but acknowledge that some judgments were arbitrary, including the minimum number of consecutive ventricular complexes that constitutes VT. The conventions are intended to apply to preclinical and clinical research. Many of the conventions have been validated by experiment, but further work is necessary to explore whether validity extends between species and circumstances. We invite investigators to state whether or not they have used the conventions in their studies, and to test their validity by experiment. We plan to hold a third meeting to examine the flaws of the current conventions and to construct a revised set, once a sufficient body of new literature has accumulated to justify this.

2. Methods

We took the original Lambeth conventions and restructured them to include advances in the intervening years. A preliminary text was prepared for discussion at a meeting held at Lambeth Palace (Lambeth Palace is the official London residence of the Archbishop of Canterbury in England, see http://www.archbishopofcanterbury.org/pages/about-lambeth-palace.html) in September 2010. After discussion a vote of 80% or more in favour of a convention ensured that it was adopted, otherwise the question was reconsidered later by email correspondence among authors. Some topics were elaborated entirely by email. We struggled to reach agreement over several of the definitions. The following sections examine all aspects of arrhythmia research, each ending with a guidance statement (convention). In the final section of the document we revisit the most contentious issues, and provide some guidance about the further research necessary to resolve uncertainties. This is important because, as we explain, translation from preclinical drug discovery and cardiac safety pharmacology to clinical practice has been suboptimal in the last 20 years, with few new antiarrhythmic drugs emerging with real impact (Curtis & Pugsley, 2012).

3. Results: the Lambeth Conventions

3.1. Performance of pilot studies (convention 1)

Research is built on the foundation of knowledge, but research is necessary and undertaken when knowledge is incomplete (which it always is). This paradox is fundamental to research, and requires the performance of pilot studies to bridge the gap between uncertainty and the initiation of discovery. In antiarrhythmic drug research, the selection of an appropriate drug dose range avoids unnecessary experiments. Thus, to help design and analysis of large, blinded, formal dose-response study, a prior open pilot study may be useful. The community would benefit if pilot studies were published. However pilot study data may detract from the main study, especially if conducted in an 'open' (non-randomised, non-blinded) manner.

3.1.1. Convention 1

Pilot studies may be reported but the data should not be merged with the results obtained from the full study.