

Original article

Age-dependent effects on cisapride-induced QTc prolongation in the isolated guinea pig heart

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Abstract

Introduction: The isolated guinea pig heart preparation has been suggested as a suitable small animal model for investigating potential for QTc prolongation. The purpose of this study was to investigate the effect of age on electrophysiological parameters measured in the isolated guinea pig heart preparation. In addition, the effect of a compound known to prolong the QT interval (cisapride) was investigated in both young and adult guinea pigs. **Methods:** Male guinea pigs were divided into 2 groups ($n=6$). One group of guinea pigs was between 3 and 4 weeks old (young) and the other group was between 16 and 17 weeks old (adult). Concentrations (0, 1, 5, and 50 ng/mL; 2, 11, and 110 nM) of cisapride were perfused for 15 min from low to high concentration. Measurements of PR, QRS, RR and QT intervals were typically made on 5 consecutive electrocardiogram complexes during the last minute of each concentration. The QT interval was corrected for changes in heart rate using the cube root formula of Fridericia (QTc_F). **Results:** Adult guinea pigs had significantly longer RR and QTc_F intervals when compared to young animals. Cisapride prolonged QTc_F in both young and adult animals at the same concentrations (5 ng/mL and 50 ng/mL). The maximal change in QTc_F at 50 ng/mL was similar in young (44 ± 3 ms) and adult animals (40 ± 1 ms). **Discussion:** In summary, the present study demonstrated that there was an increase in the RR and QTc_F intervals with age in isolated guinea pig hearts. However, this age difference does not appear to impact the sensitivity of the assay to drug-induced QTc_F prolongation.

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Keywords: Ageing; Cisapride; Guinea pig; Isolated heart; Langendorff; QTc; Methods

1. Introduction

Prolongation of the cardiac action potential duration (APD), reflected in the electrocardiogram (ECG) as QT interval prolongation has been associated with arrhythmias, including torsades de pointes (TDP) (Bass, Tomaselli, Bullingham, & Kinter, 2005; De Ponti, Poluzzi, & Montanaro, 2001; Moss, 1999; Thomas, 1994). A growing number of drugs have been shown to increase the QT interval, having a major influence on drug safety assessment and drug development (Bass et al., 2005; Bass, Kinter, & Williams, 2004; Redfern et al., 2003). Recently, the isolated guinea pig heart preparation has been suggested as a suitable small animal model for investigating the potential for

QTc prolongation (Hamlin et al., 2004). However, there is little background data investigating the effects of animal age on the results from this assay.

Age has been shown to affect a wide variety of electrophysiological parameters including RR and QT interval across a variety of species. For example, the literature supports that the RR

Table 1
RR, QT and QTc_F intervals in young and adult guinea pigs

Concentration (ng/mL)	Young guinea pigs			Adult guinea pigs		
	RR± S.E.M. (ms)	QT± S.E.M. (ms)	QTc _F ± S.E.M.	RR± S.E.M. (ms)	QT± S.E.M. (ms)	QTc _F ± S.E.M.
0	278±7	147±3	226±3	440±30	192±4	253±5
1	279±8	148±3	227±3	449±35	195±3	256±5
5	296±9	160±4*	239±4*	459±34	211±3*	275±6*
50	347±20*	187±4*	266±3*	519±25*	238±3*	297±3*

*Significantly different ($p<0.05$) than vehicle.

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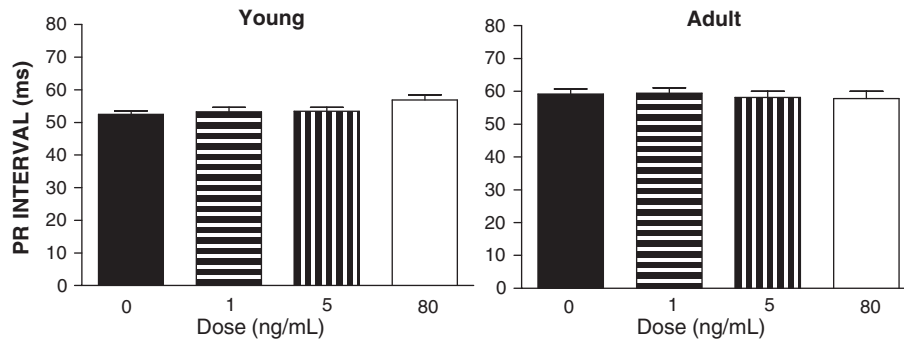


Fig. 1. Effect of cisapride on PR interval in the isolated guinea pig heart. Plots of mean \pm S.E.M. ($n=6$) measurements for incremental concentrations. Measurements were made 15 min after initiation of perfusion of each concentration.

interval is lengthened with age in guinea pigs (Horton, Kaufman, White, & Mahony, 1993; Jones, Lancaster, & Boyett, 2004), humans (Mangoni, Kinirons, Swift, & Jackson, 2003; Taneja, Mahnert, Passman, Goldberger, & Kadish, 2001), rabbits (Wu, Su, & Sun, 2003), and dogs (Obreztkhikova et al., 2003). In humans, the literature suggests that there is an increase in QTc with age (Mangoni et al., 2003; Taneja et al., 2001). In contrast, there is no change in dogs when comparing young to adult animals (Obreztkhikova et al., 2003). Despite the potential effects of age on baseline electrophysiology, a wide variety of ages (approximately 4–15 weeks) have been used in the literature to investigate the effects of drugs on electrophysiology in the guinea pig isolated heart preparation (Pinney, Koller, Franz, & Woosley, 1995; Roche, Kijawornrat, Hamlin, & Hamlin, 2005).

The purpose of this study was to investigate the effect of age on electrophysiological parameters measured in the isolated guinea pig heart preparation. In addition, the effect of a compound known to prolong the QT interval (cisapride) was investigated in both young and adult guinea pigs.

2. Methods

2.1. Approvals

The study was approved by the Institutional Animal Care and Use Committee and conformed with the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institute of Health (NIH Publication No. 85-23, revised 1996).

2.2. Drugs

Cisapride was purchased from Sigma Chemical Co. The stock drug concentration was 50 μ g/mL dissolved in 100% DMSO. The stock solution was then diluted with modified Krebs–Henseleit solution to 1, 5, and 50 ng/mL in 0.1% DMSO.

2.3. Experimental protocol

Male guinea pigs (Charles River, NY) were divided into 2 groups. One group of guinea pigs was between 3 and 4 weeks old and considered to be young (Jones et al., 2004). The second group of guinea pigs was between 16 and 17 weeks old and considered to be adults (Jones et al., 2004).

On the day of the experiment, guinea pigs were anesthetized with approximately 2% isoflurane (Baxter Healthcare, IL) and 100% oxygen. Animals were intubated and ventilated at a frequency of approximately 26 breaths/min (Engler, FL). Hearts were exposed through a median sternotomy. The hearts were removed quickly (30–90 s) and were suspended on a Langendorff perfusion apparatus (Hamlin et al., 2004; Pinney et al., 1995; Roche et al., 2005). Modified Krebs–Henseleit solution, gassed with 95% oxygen and 5% carbon dioxide, with pH of approximately 7.4, temperature of approximately 37 $^{\circ}$ C, and at a perfusion pressure of 84 mm Hg was used as perfusate. The Krebs–Henseleit solution contained (in mM) 118 NaCl, 4.7 KCl, 17 glucose, 25 NaHCO₃, 1.2 MgSO₄, 3.4 CaCl₂, 1.2 KH₂PO₄, and 1 mM tetrasodium EDTA. Two electrodes (Hugo Sachs

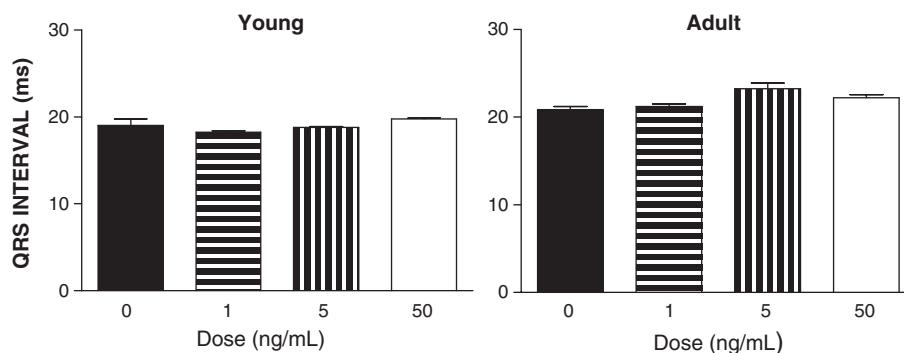


Fig. 2. Effect of cisapride on QRS interval in the isolated guinea pig heart. Plots of mean \pm S.E.M. ($n=6$) measurements for incremental concentrations. Measurements were made 15 min after initiation of perfusion of each concentration.

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