行政院國家科學委員會專題研究計畫成果報告

Preparation of NSC Project Reports

計畫編號：NSC 90-2314-B-002-161
執行期限：90 年 8 月 1 日至 91 年 7 月 31 日

主持人：吳美環　台大醫學院小兒科
共同主持人：蘇銘嘉　台大醫學院藥理所

一、中文摘要

Cisapride 是相當有效的胃腸蠕動促進劑，但 cisapride 的使用有可能導致 QT 間距延長及 torsade de pointes 心室頻脈。而在兒童也有 AV block 的個案報告。本研究利用 Langendorff 灌流之兔子心臟模型探討 cisapride 對心臟傳道系統的影響，並進而測定是否有年齡性之差異。我們發現在臨床之劑量濃度（0.03 μM），cisapride 可延緩 His-Purkinje 系統之恢復。在 0.1 μM 時，His-Purkinje 系統的不反應期與傳導時間皆變長，QT 間距與心室不反應期也延長。在新生兔這些變化顯著比在成兔來的多。此外，新生兔甚至加入 cisapride 後會變成 infranodal AV block。因此我們推論，cisapride 對心臟傳導系統，尤其是 His-Purkinje 系統有抑制其興奮性的作用。未成熟之心臟對 cisapride 之敏感度可能更高，因此在幼兒使用 cisapride 應採用較窄之治療範圍濃度。

關鍵詞：cisapride、心律不整、QT 間距延長

Abstract

Cisapride is widely used to treat the gastrointestinal motility disorders. However, it has been associated with QT prolongation, torsades de pointes, and cardiac arrest. Only in children, has atrioventrciular block after cisapride also been described. This study uses Langendorff- perfusion to define the direct effects of cisapride (0.03, 0.1, 0.3 and 1 μM) on conduction properties of neonatal (< 7 days) and adult (> 3 months) rabbit hearts. At a clinically relevant dose (0.03 μM), cisapride slowed the recovery of the His-Purkinje system. At 0.1 μM, the refractoriness of His-Purkinje system and the conduction through this system were prolonged. Corrected QT intervals and ventricular refractory period were also lengthened. These parameters were significantly more prolonged in the neonate than in the adult. The level of atrioventricular block at rapid atrial pacing shifted from the AV node to the His-Purkinje system, with an ED_{50} of 0.06 and 0.52 μM in the neonate and the adult, respectively. In the neonate, cisapride even resulted in infranodal atrioventricular block rhythm (ED50 = 0.12 μM), but not in the adult. Polymorphic ventricular tachycardia after cisapride was induced in one of seven adults (14%, 0.03 μM) and one of seven neonates (14%, 0.1 μM). In conclusion, cisapride may affect the refractoriness of cardiac tissue and the His-Purkinje system appears to be the most sensitive. In neonatal hearts, this modification may progress to infranodal atrioventricular block. Such susceptibility to cisapride indicates that the therapeutic safety range used in the young heart should be narrower.

Keywords: Cisapride, cardiac conduction system, torsades depointes, QT prolongation

二、緣由與目的

Cisapride, a widely used gastrointestinal prokinetic agent, has been associated with the development of prolonged QT interval, malignant ventricular arrhythmias and sudden death. Cisapride is a gastrointestinal prokinetic agent that facilitates gastrointestinal motility by significantly increasing lower esophageal sphincter pressure and improving gastric emptying.

The gastrointestinal mechanism of action is thought to be attributable to enhancement of the release of acetylcholine at the mesenteric plexus as well as a direct suppression of human ether-a-go-go-related gene (HERG)-like K^+ currents in esophageal smooth muscle. As to the mechanisms underlying the adverse cardiac effects, a direct inhibition of the repolarizing K^+ current and subsequent prolongation of the action potential were suggested. In rabbit Purkinje fibers, cisapride (0.1 –10 μM) lengthened the action potential duration in a concentration-dependent and reverse rate-dependent manner, and early after-depolarizations with subsequently triggered activity were observed at abruptly slowed pacing rates. In isolated rabbit myocytes, the rapid component of delayed rectifying K^+ current (I_{Kr}) was blocked by cisapride with an IC_{50} of 9 nM.

In immature heart, the presence of age-related differences of the K^+ repolarizing currents has been well documented. Whether these differences make immature hearts more vulnerable to cisapride remains undetermined. According to the report to the US Food and Drug Administration Medwatch program, 7 out of 57 arrhythmias associated with cisapride treatment were seen in children. In a cohort of 35 children, 31% of the patients developed a prolongation ofThe QT interval beyond the normal range (≥450 ms) after cisapride. In adults, the adverse cardiac effects were attributed to prolonged QT intervals that lead to a malignant form of ventricular tachycardia. Only in children, the development of 2:1 atrioventricular (AV) block had also been reported. We therefore conducted this study to define the changes in cardiac electrophysiology after cisapride in isolated Langendorff-perfused hearts. This experimental design enables determination of the direct cisapride effects on cardiac conduction as well as the age-related differences in these effects.

三、結果與討論

Anesthesia (sodium pentobarbital, 30 mg/Kg) and heparin (300 units/Kg) were administered i.p. to neonatal (< 7 days) and i.v. to adult (> 3 months) New Zealand white rabbits.

Our methods have been described elsewhere. In brief, the heart was excised via thoracotomy and the aorta was retrogradely perfused. The high right atrial electrode was placed near the junction of the superior vena cava and right atrium to pace the atria. A bipolar electrode consisting of a tungsten wire soldered silver-wire was placed on an area near the apex of the triangle of Koch to record the His bundle electrogram. The ventricular recording electrodes were then placed on the epicardium of the right ventricular apex to obtain an easily recognizable T wave. The ventricular pacing electrode was placed on the pericardium near the right ventricular apex. A programmable stimulator (Bloom Ltd, DTU 215) was used in the pacing studies. A pacing stimulus of 1 millisecond in duration and three times the diastolic threshold voltage was applied to the preparation. The signal was continuously monitored on an oscilloscope (Hewlett Packard, 54503A), and pertinent data were recorded on a two-channel physiological recorder (Gould, RS 3200) with a paper speed of 100 mm s^{-1}.

.

RESULTS

Changes of the electrophysiological parameters after cisapride were assessed in seven adult and seven neonatal rabbit hearts. Intracardiac recording detected the atrial activities, His potential, ventricular activities and its repolarization (T wave). The representative electrograms are shown in Figs. 1 (adult rabbits) and 2 (neonatal rabbits). The changes of the electrophysiological parameters after cisapride are summarized in Table 1. We found that the electrophysiological parameters in adult rabbit hearts exposed to cisapride could not be completely restored to baseline levels after washing with the Tyrode's solution for 1 h. This situation existed to a lesser extent in the neonatal rabbits. Therefore, the time control of the present experiment model was examined in another two adult rabbits to determine the effects (if any) of perfusing

with Tyrode's solution over time. Using the present experimental setting, each parameter did not change significantly for 3 hours (data not shown). In addition, the changes of the electrophysiological parameters with time after washout of cisapride (1 μM) were assessed in two adult rabbits. The changes persisted even after washing with normal Tyrode's solution for 2 h. Based on these controls, the changes after cisapride in adult rabbits were deemed as partially irreversible effects caused by cisapride.

RESULTS

Rhythm disturbances

Cisapride (0.1 μM) resulted in infranodal AV block (2:1 blocked below the His potential) in 3 of 7 neonatal rabbits. At 0.3 μM, all the neonatal hearts developed AV block. The AV block varied from 4:3 to 2:1, and the AV block was observed below the His potential in all but one. In the presence of AV block, the AH interval remained minimally prolonged but the HV interval progressively lengthened and lead to AV conduction block. The AV block could be converted by wash out of the cisapride in all neonatal rabbit hearts along with a recovery of the QT interval prolongation. The ED_{50} for the development of infranodal AV block rhythm by cisapride in the neonate rabbit heart was 0.12 μM. In contrast, none of the adult rabbit hearts developed AV block. Elevation of the extracellular (perfusate) K^+ level to 6 mM failed to prevent the development of AV block after cisapride.

Polymorphous ventricular tachycardia was induced by programmed ventricular extra-stimulation in one adult (1/7, 14%) with cisapride 0.03 μM, and in one neonatal rabbit (1/7, 14%) with cisapride 0.1 μM.

Spontaneous cycle length

Spontaneous sinus or atrial cycle length, without the development of AV block, was not significantly changed by cisapride.

QT interval and ventricular electrophysiological function

Cisapride at the clinically relevant dose (0.1 μM) prolonged the QT intervals in the neonate and adult. Higher concentrations of cisapride might induce infranodal block. Since in the presence of AV block, the corrected QT interval would not be a good index of ventricular repolarization, only the QT interval measured during 1:1 conduction was analyzed. QT prolongation was significantly more in the neonates than in the adults.

The QT intervals measured during incremental atrial pacing rates determined the degree of shortening of QT intervals at faster heart rates. At faster pacing rates, when the phenomenon of T wave alternans developed or the Q wave was fused with the next ventricular activation wave, the QT interval was not measured. We found that the QT interval can be progressively shortened as the pacing atrial cycle length shortens. This relationship persisted for neonates and adults given cisapride (Fig.4). Because the QT interval may change with cycle length, the cisapride-induced changes in QT intervals were compared at the same atrial pacing cycle length of 300 ms at incremental atrial pacing (Fig. 5). We found under these conditions the QT interval was still significantly more prolonged in the neonate.

The ventricular refractory period was significantly increased at the clinically relevant concentration (0.1 μM) in both the adult and neonate. However, the degree of the lengthening of the ventricular refractory period was significantly more in the neonates.

His-Purkinje function

The effective refractory period of the His-Purkinje system increased at clinically relevant concentrations dose-dependently in the neonate and the adult. Although the period was more prolonged in the neonate, no statistical significance was shown. This may be related to the missing data after the development of infranodal AV block in the neonate at the concentration of 0.3 μM. The conduction through the His-Purkinje system was prolonged by cisapride and significantly more prolonged in the neonate. The recovery curves of His-Purkinje system (H_2V_2 *vs* V_1H_2 relation) were shifted to the right dose-dependently in the neonate and the adult. (Fig. 6) In the neonate, AV conduction was blocked at the His-Purkinje system (below the His potential) by higher concentrations of

cisapride.

AV nodal function

Although the conduction through the AV node was not significantly modified by cisapride, the refractory period could be prolonged in the neonate and the adult at higher concentrations of cisapride. The AV nodal recovery curves (A_2H_2 *vs* H_1A_2 relation) were also shifted to the right after cisapride in both the adult and neonate, but to a much smaller degree than the shift of the His-Purkinje recovery curves. The Wenckebach AV block during incremental rapid atrial pacing occurred initially above the level of AV node (above the His bundle activation) in all control adult and neonatal rabbit hearts. But, it shifted to the level of His-Purkinje system (below the His bundle activation, infranodally) after cisapride.

Atrial electrophysiological function

Cisapride did not significantly alter the conduction through the atrial tissue (SA interval) or the refractoriness of the atrial tissue (atrial effective refractory period) in both the adult and the neonate.

五、參考文獻

1. Wysowski KD, and Bacsanyi J 1996 Cisapride and fatal arrhythmia. N Engl J Med 335:290-91
2. Ahmad SR, and Wolfe SM 1995 Cisapride and torsades de pointes. Lancet 345:508.
3. Vandenplas Y, Belli DC, Benatar A, Cadranel S, Cucchiara S, Dupont C. 1999 The role of cisapride in the treatment of pediatric gastroesophageal reflux. J Pediatr Gastroenterol Nutr 28:518-28
4. Akbarali HI, Thatte H, He XD, Giles WR, Goyal RK 1999 Role of HERG-like K (+) currents in opossum esophageal circular smooth muscle. Am J Physiol 277:C1284-90
5. Chen HT, Goh MH, Pan S 1993 The effect and mechanism of the prokinetic action of cisapride on gastrointestinal smooth muscle. Gastroenterol Jpn 28:218-23
6. Puisieux FL, Adamantidis MM, Dumotier BM, Dupuis AB 1996 Cisapride-induced prolongation of cardiac action potential and early afterdepolarizations in rabbit Purkinje fibers. Br J Pharmacol 117:1377-79
7. Carlsson L, Amos GJ, Andersson B, Drews L, Duker G, Wadstedt G 1997 Electrophysiological characterization of the prokinetic agents cisapride and mosapride in vivo and in vitro: Implications for proarrhythmic potential? J Pharmacol Exp Ther 282:220-7
8. Wu MH, Su MJ, Lue HC 1994 Age-related quinidine effects on ionic currents of rabbit cardiac myocytes. J Mol Cell Cardiol 26:1167-77
9. Kilbon MJ, Fedida D. 1990 A study of the developmental changes in outward currents of rat ventricular myocytes. J Physiol 430:37-60.
10. Hill SL, Evangelista JK, Pizzi AM, Mobassaleh M, Fulton R, Berul CI 1998 Proarrhythmia associated with cisapride in children. Pediatrics 101:1053-56
11. Lewin MB, Bryant RM, Fenrich AL, Grifka RG 1996 Cisapride-induced long QT interval. J Pediatr 128:279-81
12. Wu MH, Su MJ, Lee SS, Young ML 1994 The electrophysiological effects of antiarrhythmic potential of a secoaporphine, N-allylsecoboldine. Br J Pharmacol 113:221-7
13. Wiseman LR, Faulds D 1994 Cisapride. An updated review of its pharmacology and therapeutic efficacy as a prokinetic agent in gastrointestinal motility disorders. Drugs 47:116-52.
14. Stevens J 1996 Repeated measures analysis. In: Applied multivariate statistics for the social sciences. 3rd Ed. Hillsdale NJ: Lawrence Erlbaum associates, Publishers, New Jersey. pp.450-78
15. Rampe D, Roy ML, Dennis A, Brown AM 1997 A mechanism for the proarrhythmic effects of cisapride (propulsid): high affinity blockade of the human cardiac potassium channel HERG. FEBS Letters 417:28-32
16. Preechagoon Y, Charles B, Piotrovskij V, Donovan T, Van Peer A 1999 Population pharmacokinetics of enterally administered cisapride in young infants

with gastro-oesophageal reflux. Br J Clin Parmacol 48:688-93
17. Drolet B. Khalifa M. Daleau P. Hamelin BA. Turgeon J 1998 Block of the rapid component of the delayed rectifier potassium current by the prokinetic agent cisapride underlies drug-related lengthening of the QT interval. Circulation 97:204-10
18. Walker BD, Singleton CB, Bursill JA, Wyse KR, Valenzuela SM, Qiu MR, Breit SN, Campbell TJ 1999 Inhibition of the human ether-a-go-go-related gene (HERG) potassium channel by cisapride: affinity for open and inactivated states. Br J Pharmacol 128:444-50
19. Carmeliet E 1992 Voltage and time-dependent block of the delayed K^+ current in cardiac myocytes by dofetilide. J Pharmacol Exp Ther 262:809-17
20. Scamps F, Carmeliet E 1989 Delayed K^+ current and external K^+ in single cardiac Purkinje cells. Am J Physiol 257:C1086-92
21. Nattel S 1999 The molecular and ionic specificity of antiarrhythmic drug actions. J Cardiovasc Electrophysiol 10:272-82
22. Reder RF, Miura DS, Danilo P, Rosen MR 1981 The electrophysiological properties of normal neonatal and adult cardiac Purkinje fibers. Circ Res 48:658-68
23. Wang L, Swirp S, Duff H 2000 Age-dependent response of the elctrocardiogram to K(+) channel blockers in mice. Am J Physiol 278:C73-80
24. Wu MH, Su MJ, Lue HC 1993 Postnatal maturation of inwardly rectifying potassium current in isolated ventricular myocytes. J Formos Med Assoc 92:15-9
25. Carlsson L, Abrahamsson C, Andersson B, Duker G, Schiller-Linhardt G 1993 Proarrhythmic effects of the class III antiarrhythmic agent almokalant: importance of infusion rate, QT dispersion and early afterdepolarizations. Cardiovasc Res 27:2186-93
26. Giles WR, Imaizumi Y 1988 Comparison of potassium currents in rabbit atrial and ventricular cells. J Physiol (Lond) 405:123-45
27. Garson A Jr. Sudden death in a pediatric cardiology population, 1958-1983. In: Morganroth J, Horowitz LN, eds. Sudden cardiac death. New York: Grune & Stratton, 1985:47-56.

行政院國家科學委員會補助專題研究計畫成果報告

※※※※※※※※※※※※※※※※※※※※※※※※※※
※　Cisapride 於成長心臟造成直接電生理特性之改變　※
※　※
※※※※※※※※※※※※※※※※※※※※※※※※※※

計畫類別：□個別型計畫　□整合型計畫
計畫編號：NSC 90－2314－B－002－161
執行期間：90　年 8 月 1 日至　91 年 7 月 31 日

計畫主持人：吳美環 教授
共同主持人：蘇銘嘉 教授
計畫參與人員：

執行單位：台大醫學院小兒科

中　華　民　國　91　年 10　月　31　日