# INTERACTIONS OF METOCLOPRAMIDE AND CIPROFLOXACIN ON ELECTROCARDIOGRAPHIC INDICES IN ANESTHETIZED NORMAL AND HYPERTHERMIC RATS

**Mohamad-Hesham Y. Daba*, Abdel-Motaal M. Fouda and Gamal M. Dahab**

إن إعطاء دواء ميتوكلوبرامايد ودواء سيبروفلوكساسين مترافقين معاً غير مستبعد في الممارسة الإكلينيكية حيث أن القيئ والغثيان قد يحدثان أثناء الأمراض المصحوبة بارتفاع الحرارة. وقد ربطت بعض الأبحاث المنشورة هذين الدوائين بآثار جانبية قلبية خطيرة بما في ذلك إطالة الفترة الكهربية QT (المسافة بين Q و T في تخطيط القلب الكهربائي) وتوقف القلب. وتعني هذه الدراسة بفحص تأثير هذا الترافق على مؤشرات مخطط القلب الكهربائي وعلى مستوى البوتاسيوم في المصل في الجرذان ذات الحرارة الطبيعية، والجرذان ذات الحرارة المرتفعة.

الطريقة: أعطى دواء ميتوكلوبرامايد (0.2مغ/كغ) و/أو دواء سيبروفلوكساسين (20مغ/كغ) وريدياً في الجرذان المخدرة بمادة ثيوبنتال وذلك بعد استحداث ارتفاع في درجة حرارتها وذلك بحقن مادة بروستاجلاندين $E_2$ داخل بطين المخ (0.4 مكغ/كغ). وقد أجرى تخطيط القلب الكهربائي كل عشر دقائق خلال فترة مقدارها 95 دقيقة. وتم قياس تركيز البوتاسيوم في البلازما بعد صفر، و20، و40، و60، و80 دقيقة.

النتائج: لقد غيرت جرعات صغيرة من كل من ميتوكلوبرامايد وسيبروفلوكساسين من مؤشرات تخطيط القلب الكهربائي بطريقة معنوية عند درجة الحرارة الطبيعية وعند درجة الحرارة المرتفعة للجسم. وقد أحدث دواء ميتوكلوبرامايد بطؤاً في ضربات القلب وإطالة في الفترة PR (المسافة بين P و R في تخطيط القلب الكهربائي) رغم أنها غير ظاهرة أثناء ارتفاع الحرارة ربما بسبب الدفق العصبي السمبتاوي. كما أنها أحدثت زيادة طفيفة في فترة QT (~ 4 ms) في حالة الحرارة الطبيعية والحرارة المرتفعة ومن ناحية أخرى، تسبب دواء سيبروفلوكساسين بتأثيرات غير معنوية على معدل ضربات القلب، وسرعة الحث، ولكنه أطال فترة QT بحوالي 4.3 ms أثناء الحرارة الطبيعية والحرارة المرتفعة. وقد وجد أن ترافق الدوائين لم يؤثر على التأثير المنفرد لدواء ميتوكلوبراميد على معدل ضربات القلب أو سرعة الحث بينما بالغ في التأثير المنفرد لكل منهما على إطالة الفترة QTc, QT . ولم يتأثر هذا التداخل بارتفاع الحرارة.

الاستنتاج: يجب تلافي اعطاء دواء ميتوكلوبرامايد ودواء سيبروفلوكساسين معاً لأن ذلك يؤدي إلى الإطالة الخطيرة لفترة QT بينما لا يعتبر ارتفاع الحرارة تهديداً خطيراً كنتيجة لهذا التداخل.

BACKGROUND: The combination of metoclopramide (MCP) and ciprofloxacin (CPX) is not uncommon in clinical practice, as nausea and vomiting are well known during febrile illness. Some reports in the literature have linked both MCP and CPX to serious cardiac adverse effects including QT prolongation and cardiac arrests. In this study we examined the effect of the combination between MCP and CPX on the ECG parameters and serum potassium in normothermic and hyperthermic rats.

METHODS: Thiopental-anesthetized rats were injected i.v. with MCP (0.2 mg/kg) and/or CPX (20 mg/kg) after induction of hyperthermia by intracerebroventricular administration of $PGE_2$ (0.4 µg/kg). ECG recordings were done every 10 min during 90-min duration. Plasma potassium was measured at 0, 20, 40, 60, and 80-min. RESULTS: small doses of MCP and CPX changed ECG indices in statistically significant manner at normal and elevated body temperatures. MCP produced early bradycardia and prolongation of PR interval although it was less pronounced during hyperthermia possibly due to increased sympathetic nerve discharge. It also produced slight increase in QT interval (~4 ms) in normo- and hyperthermia. On the other hand, CPX

Department of Clinical Pharmacology, Faculty of Medicine, Mansoura University, Egypt.
*Present address: Department of Clinical Pharmacy, College of Pharmacy, KSU, Riyadh, Saudi Arabia
*To whom correspondence should be addressed.
E-mail: mhdaba@hotmail.com

caused non-significant effects on HR and conduction velocity but prolonged the QT interval by ~4.3 ms during normo- and hyperthermia. Combination of MCP and CPX did not affect the influence of MCP alone on the HR or conduction velocity while it exaggerated their individual effects on the QT and QTc prolongation. This interaction was not affected by hyperthermia. CONCLUSION: the combination of MCP and CPX should be avoided as it may lead to serious QT prolongation while hyperthermia is not considered a dangerous threat for this interaction.

***Key words:*** Ciprofloxacin, ECG indices, hyperthermia, metoclopramide, QT interval.

## Introduction

Prolongation of the QT interval is associated with an increased risk of life-threatening polymorphic ventricular tachycardia known as *torsade de pointes* (TdP) (1). By far, the most common cause of acquired QT interval prolongation is drug-induced (2). However since the nineties, the regulatory authorities had to remove a significant number of non-cardiac drugs from the market because of their propensity to prolong the QT interval and cause TdP (3).

Metoclopramide (MCP) and ciprofloxacin (CPX) belong to entirely distinct classes of drugs. MCP is a dopamine receptor antagonist with prokinetic and anti-emetic properties (4). Ciprofloxacin is a fluoroquinolone antibiotic with wide range of antibacterial activity (5). In the last few years, some reports have linked between the use of MCP and occurrence of serious cardiac adverse effects including QT interval prolongation, TdP (6) and even cardiac arrests (7,8), being the same reasons that led to withdrawal of cisapride, a closely related prokinetic agent, from the world market during the last few years (9). Similarly, some members of quinolone antibiotics have been recently withdrawn because of their "QT liability" and torsadogenic potential (10, 11). Although CPX is reported to be the most widely prescribed fluoroquinolone and the least torsadogenic (10), yet it has been recently linked also to some cases of serious QT interval lengthening and TdP (12,13). The FDA has now revised the precaution section of the product labeling to indicate the rare possibility of TdP associating the use of the drug under different circumstances (11).

The combination of MCP and CPX is not unusual in daily clinical practice, as nausea and vomiting are well known during the course of febrile illness. On the other hand, the change of body temperature is a well-known factor that can modulate the orchestration of cardiac electrophysiology and ion channel activities (14,15). To our knowledge, no studies, have investigated the effects of this combination on the ECG indices, either in humans, or in laboratory animals. So the purpose of this study is to investigate the interactions between MCP and CPX, given in single i.v. doses, on electrocardiographic parameters in anesthetized rats during 90-min duration, with special concern to the QT interval prolongation and torsadogenic potential. Moreover, because serious cardiac adverse effects after MCP or CPX are very rare, when they happen it is reasonable to think there must be some predisposing or contributing factors involved. In this study we investigated hyperthermia as might be a predisposing factor for any drug-induced ECG changes, and because we know also that fever may modulate plasma potassium levels, an essential player in the orchestra of cardiac myocyte electrophysiology, we measured plasma potassium at different intervals during the 90-min duration of the experiment.

## Materials and Methods

*1. Animals:*

Male adult Sprague-Dawley rats (200-230 gm body wt.) were obtained from the animal house of Mansoura Faculty of Medicine. Experiments were performed in accordance with the *Guide to the Care and Use of Laboratory Animals* (16).

*2. Surgical procedure for intracerebroventricular (i.c.v.) injection:*

Rats were anaesthetized with i.p. sodium thiopental (Biochemie GmbH, Vienna, Austria) 40 mg/kg and mounted on a stereotaxic apparatus (Stoelting, Stoelting Co., IL, USA) with the head fixed according to the stereotaxic atlas of Paxinos and Watson (17). The guide cannula (0.70 mm outer diameter) was placed at the position of 1.5 mm lateral and 0.8 mm posterior from Bregma and to the depth of 3.0 mm below the outer surface of the skull and fixed in place with dental cement (Dentam, Scitem limited, UK). The injection cannula (0.35 mm outer diameter) was adjusted to protrude 1.0 mm beyond the tip of the guide cannula. The animals were permitted to recover from surgery for 5 days before experiments. After the experiments, 3.0 µl of 1% trypan blue (Sigma Chemical, St. Louis, MO, USA) were injected and the site of injection was

confirmed histologically.

*3. Rectal temperature (RT) and drug administration:*

Thiopental anaesthetized rats were placed in the ambient room temperature (25.0 °C ± 0.1 °C). A thermistor probe (Takara Thermistor, Yokohama, Japan) was introduced approximately 4 cm into the rectum. After the rectal temperature had stabilized after the initial insertion, 0.4 µg/kg of prostaglandin $E_2$ ($PGE_2$) (Sigma Chemical, St. Louis, MO, USA) dissolved in 3.0 µl of 154 mM NaCl, or the same volume of vehicle alone, was injected i.c.v. over 1 min (18). After 2 min, 0.2 mg/kg of MCP and/or 20 mg/kg of CPX were injected through the cannulated tail vein. RT was measured at 5-min intervals after drug injections.

*4. Electrocardiographic (ECG) recording and computer analysis:*

The system used consisted of a strip-chart ECG recorder and a PC connected to an optical scanner (VuegoScan 640P, Acer Peripheral Inc, Taiwan) and a 17 inch RGB high resolution monitor (ViewSonic; ViewSonic Corporation, Tokyo, Japan). Image processing and computer operations were performed on Adobe Photoshop version 6.0 (Adobe Systems Corporation, San Jose, CA, USA) in a MS-Windows 98 environment (Microsoft Corporation, Redmond, Washington, USA). The surface lead II ECG was obtained from the limb electrodes at a paper speed of 50 mm/s. After obtaining stable RR interval, ECG measurements were carried out to obtain the pretreatment values. Thereafter, vehicle or drugs were injected as described above. ECG signals for 10–15 sec at each point were recorded at 10-min intervals for 90 minutes. Segments equals 10 seconds were scanned on an optical resolution of 600 dpi-RGB. A window containing the first cardiac cycle is maximized on screen to its actual pixels. With the aid of "Measure Tool", the X and Y measurements of all cardiac cycles in 10 sec duration were done in milliseconds (ms) (horizontal), and millivolts (mV) (vertical). The PR interval was from the onset of P waves to the onset of Q waves, QRS duration was from the onset of Q waves to the end of S waves, QT interval was from the onset of Q waves to the end of T waves. T wave morphology and end was carefully determined according to the principles described in reference (19). The QTc interval was calculated according to Bazzett formula: $QTc = QT/\sqrt{RR}$ (20).

*5. Measurement of plasma potassium:*

Heparinized blood samples (100 µL each) were withdrawn from the tail vein at 0, 20, 40, 60, and 80-min. Plasma potassium was measured using ion-selective electrode (AVL9180, Roche Diagnostics Ltd., Basel, Switzerland).

*6. Statistical analyses:*

All statistical calculations and graphic representations of the data were performed with SPSS version 10.0 for Windows (SPSS Inc, Chicago, IL, USA). Data were presented as means ± SE. Statistical analyses were performed using the unpaired student's *t* test and Dunnett's multiple range test. P-values of 0.05 or less were considered significant. Pearson correlation coefficient (*r*) was used to assess the correlation between bivariate parameters. *r*-values between 0.5 and 1 were considered good positive.

## Results

*1. Effect of i.c.v. injection of $PGE_2$ on RT and ECG indices:*

Under thiopental anesthesia, the rectal temperature of the experimental animals was 35.9±0.2°C, which was about 0.2°C lower than that of conscious rats. Control animals injected with the vehicle only did not have any significant changes in rectal temperature, ECG parameters, or plasma potassium during 90-min interval. The i.c.v. administration of $PGE_2$ immediately caused an increase of rectal temperature at a rate of 0.073°C/min, reached the ΔRT max value of 2.9±0.09°C at 40 min ($P<0.01$), and then started to decline at a rate of 0.017°C/min (fig 1). During the period of increase in rectal temperature, an increase in heart rate (HR) ($P<0.01$), decrease in the PR interval ($P<0.05$), and decrease in the QRS duration ($P<0.05$) were found (fig 4). As compared with the control values, the ΔHR max value was 57.4±8 beats/min (20.7%) at 10 min. the ΔPR max value was -5.6±1.0 ms (-9.4%) at 10 min. the ΔQRS max value was –1.0±0.2 ms (-2.8%) at 10 min (fig.4). There was nonspecific ST and T wave changes. All parameters returned to the level of vehicle injection 20±5 min after the rectal temperature reached its peak.

*2. Effect of drugs on ECG indices at normal RT:*

As shown in fig 3, injection of MCP (0.2 mg/kg i.v.) caused a significant decrease in HR ($P<0.01$), prolongation of the PR interval ($P<0.01$), and increase in the QT ($P=0.054$) and QTc intervals. There was no significant change in the QRS duration. As compared with the control values, the ΔHR max value was –19.3±3.0 beats/min (-6.8%) at 10 min, the ΔPR max value was 5.4±1.0 ms (9.3%) at 10 min, the ΔQT max value was 4.0±1.0 ms (3.3%) at 30 min, and the ΔQTc max value was 5.5±1.0 ms (2.1%) at 50 min. There was poor correlation between ΔQT and ΔQTc intervals ($r$ = 0.3) in this group. Injection of CPX (20 mg/kg i.v.) caused non-significant effects on HR, PR, and QRS intervals. There was significant increase in the QT, and QTc intervals ($P<0.05$). As compared with the control, the ΔQT max value was 4.3±0.8 ms (3.6%) at 40 min, and the ΔQTc max value was 9.0±2.0 ms (3.4%) at 40 min. Coadministration of MCP and CPX did not significantly alter the values obtained by MCP alone on the HR and PR interval but significantly prolonged QRS ($P<0.05$), QT, and QTc intervals ($P<0.01$). The ΔHR max value was -21.3±4.0 beats/min (-7.5%) at 10 min while the ΔPR max value was 5.7±1.0 ms (9.8%) at 10 min, the ΔQRS max value was 1.6±0.5 ms (4.9%) at 40 min, the ΔQT max value was 6.1±1.0 ms (4.7%) at 40 min, and the ΔQTc max value was 12.9±3.0 ms (4.9%) at 40-50 min (table 1). The value of each parameter at 0 min was as follows: HR, 285±6 beats/min; PR interval, 58±1.0 ms; QRS, 32±0.5 ms; QT interval, 121±3.0 ms; and QTc interval, 264±3.0 ms.

*3- Effect of drugs on ECG indices during hyper-thermia:*

As shown in fig 4, injection of MCP significantly reduced the positive chronotropic response and the enhanced A-V conduction caused by hyperthermia during the first 20 min. As compared with the control values, the ΔHR max value was reduced from 57.4±8.0 to 38.9±5.0 beats/min (-5.6%) at 10-20 min ($P<0.01$). The ΔPR max value was increased from -5.6±1.0 ms to -1.7±0.8 ms (6.5%) at 10 min ($P<0.05$). QRS duration was non-significantly changed. There were also slight increases in the QT and QTc intervals ($P=0.055$). The ΔQT max value was 3.8±1.0 ms (3.3%) at 10 min, and the ΔQTc max value was 6.5±1.0 ms (2.7%) at 10-20 min. Injection of CPX did not significantly change the hyperthermic control values of the HR or PR interval but there were significant increases in QT and QTc intervals ($P<0.05$). As compared with the hyperthermic control values, the ΔQT max value was 4.2±0.9 ms (3.7%) at 20 min, and the ΔQTc max value was 9.8±2.0 ms (4%) at 20 min. Coadministration of MCP and CPX significantly reduced the positive chronotropic response and the enhanced A-V conduction caused by hyperthermia during the first 20 min. As compared with the control values, the ΔHR max value was reduced from 57.4±8.0 to 35.6±5.0 beats/min (-6.6%) at 10-20 min ($P<0.01$). The ΔPR max value was increased from -5.6±1.0 ms to -1.9±0.5 ms (6.2%) at 10 min ($P<0.05$). There were also significant increases in QRS, QT, and QTc intervals ($P<0.05$). As compared with the hyperthermic control values, the ΔQRS max value was 1.1±0.2 ms (3.3%) at 10 min, the ΔQT max value was 6.1±0.9 ms (5.2%) at 20 min, and the ΔQTc max value was 14.0±3.0 ms (5.3%) at 20 min (table 1). The value of each parameter at 0 min was as follows: HR, 276±7.0 beats/min; PR interval, 60±1.0 ms; QRS, 32±0.5 ms; QT interval, 125±3.0 ms; and QTc interval, 268±3.0 ms.

*4. Effect of drugs on plasma potassium at normal RT and hyperthermia:*

Induction of hyperthermia caused significant elevation of plasma potassium levels ($P<0.01$). As compared with the control, the ΔK max value was 0.45 mmol/l at the peak of RT. There was good correlation between ΔRT and ΔK ($r$ = 0.9). Plasma potassium levels were not significantly changed at any point of drug administration either at normal RT or during hyperthermia (table 2). The value of each parameter at 0 min was as follows: RT, 35.9±0.1°C; plasma potassium, 2.95±0.07 mmol/l.

**Table 1:** Effect of i.v. injection of metoclopramide (MCP), ciprofloxacin (CPX), or both on Δmax changes of HR **(A)**, PR interval **(B)**, QRS duration **(C)**, QT interval **(D)**, and QTc interval **(E)**, during normothermia and hyperthermia. Each value represents the mean ±SE of five rats. *P<0.05; **P<0.01; NC = no change (Dunnett's multiple range test).

**A**

| | Normothermia | | Hyperthermia | | |
|---|---|---|---|---|---|
| | ΔHR max (beats/min) | time (min) | ΔHR max (beats/min) | time (min) | ΔRT (°C) |
| MCP | –19.3±2** | 10 | –18.5±1.7** | 20 | 1.46±0.1 |
| CPX | 6.5±0.3 | 40 | NC | - | - |
| MCP+CPX | –21.3±1.4** | 10 | –21.8±2** | 10 | 0.73±0.08 |

**B**

| | Normothermia | | Hyperthermia | | |
|---|---|---|---|---|---|
| | ΔPR max (ms) | time (min) | ΔPR max (ms) | time (min) | ΔRT (°C) |
| MCP | 5.4±1.0** | 10 | 3.9±0.5* | 10 | 0.72±0.09 |
| CPX | 1.3±0.6 | 10 | NC | - | - |
| MCP+CPX | 5.7±1.0** | 10 | 3.7±0.5* | 10 | 0.73±0.08 |

**C**

| | Normothermia | | Hyperthermia | | |
|---|---|---|---|---|---|
| | ΔQRS max (ms) | time (min) | ΔQRS max (ms) | time (min) | ΔRT (°C) |
| MCP | NC | - | NC | - | - |
| CPX | 1.2±0.3 | 40 | 0.9±0.2 | 10 | 0.73±0.08 |
| MCP+CPX | 1.6±0.5* | 40 | 1.1±0.2 | 10 | 0.71±0.06 |

**D**

| | Normothermia | | Hyperthermia | | |
|---|---|---|---|---|---|
| | ΔQT max (ms) | time (min) | ΔQT max (ms) | time (min) | ΔRT (°C) |
| MCP | 4.0±1.0 | 30 | 3.8±1 | 10 | 1.1±0.09 |
| CPX | 4.3±0.8* | 40 | 4.2±0.9* | 20 | 1.46±0.1 |
| MCP+CPX | 6.1±1.0** | 40 | 6.1±0.9* | 20 | 1.44±0.1 |

**E**

| | Normothermia | | Hyperthermia | | |
|---|---|---|---|---|---|
| | ΔQTc max (ms) | time (min) | ΔQTc max (ms) | time (min) | ΔRT (°C) |
| MCP | 5.5±1 | 50 | 6.5±1 | 10 | 1.1±0.09 |
| CPX | 9±2* | 40 | 9.8±2* | 20 | 1.46±0.1 |
| MCP+CPX | 12.9±3** | 40 | 14±3* | 20 | 1.46±0.1 |

**Table 2:** Effect of metoclopramide (MCP) and/or ciprofloxacin (CPX), on plasma potassium concentrations (mmol/L) at different degrees of rectal temperature (RT) during 80 min. Each group represents the mean ±SE of five rats. *P<0.05; **P<0.01 (Dunnett's multiple range test).

| Time (min) | RT (°C) | Plasma $K^+$ (mmol/l) | | | |
|---|---|---|---|---|---|
| | | Con | MCP | CPX | MCP+CPX |
| 20 | 37.4±0.08 | 3.18±0.08* | 3.12±0.07 | 3.2±0.06 | 3.15±0.08 |
| 40 | 38.8±0.07 | 3.40±0.09** | 3.37±0.08 | 3.43±0.09 | 3.4±0.09 |
| 60 | 38.5±0.06 | 3.37±0.07** | 3.34±0.06 | 3.29±0.08 | 3.31±0.07 |
| 80 | 38.1±0.09 | 3.3±0.06** | 3.21±0.07 | 3.25±0.06 | 3.18±0.08 |

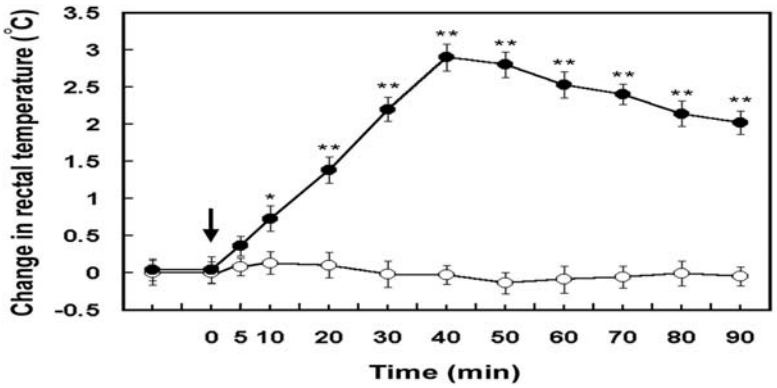


**Fig. 1.** Effect of i.c.v. injection of PGE2 (0.4 µg/kg) on rectal temperature ( ● ) compared with the respective vehicle injection ( ○ ) during 90 min duration. The average value of rectal temperature at 0 min was 35.9±0.1°C. Each point represents the mean±SE of five rats. *P<0.05; **P<0.01 (Student's *t* test).

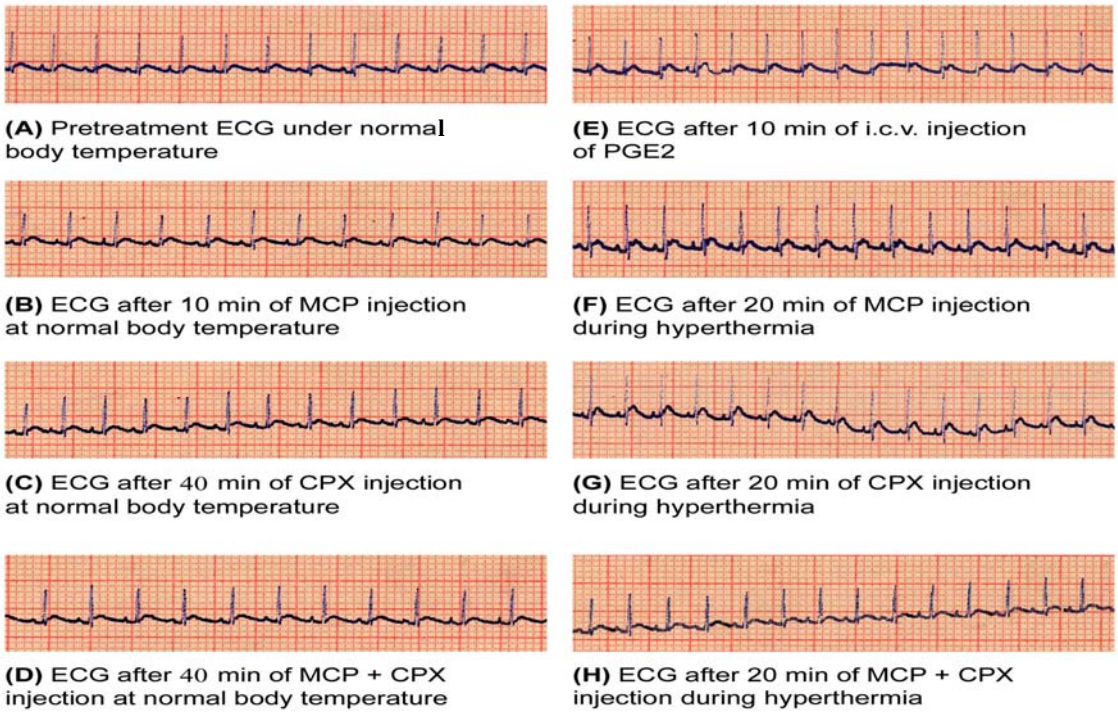


**Fig 2.** ECG traces for MCP (0.2 mg/kg i.v.) and/or CPX (20 mg/kg i.v.) at selected time points under normal and hyperthermic conditions

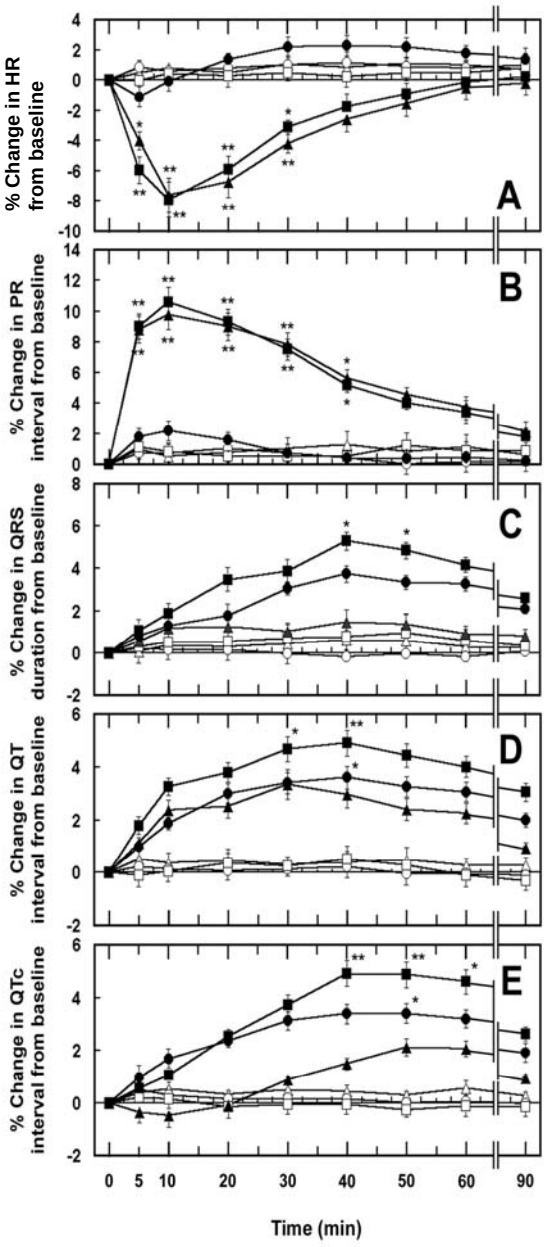


**Fig 3.** Effect of i.v. injection of MCP (0.2 mg/kg) (▲) and CPX (20 mg/kg) (●), or both (■) on Δ%HR (A), Δ%PR interval (B), Δ%QRS duration (C), Δ%QT interval (D) and Δ%QTc interval (E) as compared with the respective vehicle injection (△, ○, □) during 90-min interval at normal body temperature. Each point represents the mean ±SE of five rats. *P<0.05; **P<0.01 (Dunnett's multiple range test).

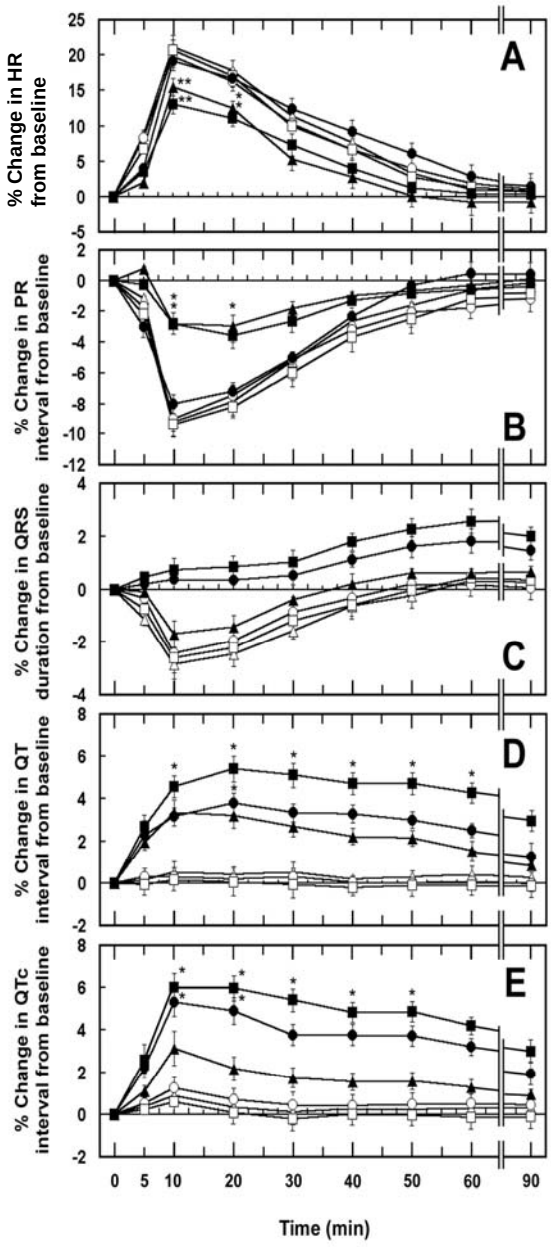


**Fig 4.** Effect of i.v. injection of MCP (0.2 mg/kg) (▲) and CPX (20 mg/kg) (●), or both (■) on Δ%HR (A), Δ%PR interval (B), Δ%QRS duration (C), Δ%QT interval (D) and Δ%QTc interval (E) as compared with the respective vehicle injection (△, ○, □) during 90-min interval at elevated body temperature. Each point represents the mean ±SE of five rats. *P<0.05; **P<0.01 (Dunnett's multiple range test).

## Discussion

The combination of MCP and CPX is not unusual in daily clinical practice, as nausea and vomiting are well known during the course of febrile illness. In this study we investigated the effect of single i.v. doses of MCP and/or CPX on the ECG parameters in anesthetized rats during 90-min duration. We chose the doses of both drugs based on the current clinical practice, and to mimic the atmosphere of a febrile condition. Hyperthermia was included in the experiment to examine its possibility as a triggering factor for any drug-induced ECG changes. The technique used in the analysis of ECGs is very sensitive in measuring minute changes because of the versatile power of Photoshop software.

It is generally recognized that hyperthermia can modulate cardiovascular responses and serum electrolyte levels. In this study an elevation of 2.9 °C resulted in marked increase in HR, decrease in PR and QRS intervals, nonspecific ST and T changes, and elevation of plasma potassium. There is substantial body of literature indicating similar results in animal experiments (17, 21, 22) and in humans (23, 24). The attenuation of vagal chronotropic responses (21, 22), peripheral capillary dilatation (25), and increased sympathetic nerve discharge (26), all might be responsible for the noted ECG effects of hyperthermia. It was also reported that hyperthermia can increase plasma potassium levels possibly due to shift of potassium from the intracellular to extracellular compartments during hyperthermia (27).

We also reported statistically significant effects of small doses of MCP and CPX on ECG parameters whether at normal body temperature or during mild-to-moderate hyperthermia. These changes were not related to changes of plasma potassium levels because none of the drugs has influenced plasma potassium during 80 min postinjection. On the other hand, hyperthermia alone had significant influences on electrocardiographic parameters, mainly the HR and conduction velocity, and plasma potassium, but was of no influence on the ECG findings mediated by the two drugs either solo or in combination.

The decrease of HR and conduction velocity caused by MCP occurred early in both conditions though less prominent during hyperthermia than in normothermia, possibly due to the attenuated vagal chronotropic responses (21, 22) and/or increased sympathetic nerve discharge (26) usually accompanying acute hyperthermia. MCP also produced slight increases in QT interval by about 4 ms in normo- and hyperthermia. These findings may partly explain the underlying mechanisms of cardiac problems associated with MCP. It is well known that dopamine receptors are mainly distributed at the neuronal level and inhibit cholinergic pathways (28). MCP, by acting as a dopamine type-2 (D2) receptor blocker, may increase the inhibitory cholinergic activity in the cardiac muscle, and on the other hand, it modifies the sympathetic drive to the heart and induces changes in autonomic cardiovascular control that may cause secondary alterations in cardiac repolarization (29).

Cardiac repolarization, reflected in the ECG by QT interval, is a delicate balance between depolarizing inward sodium and calcium currents and repolarizing outward potassium currents. It has been demonstrated that a rapid ($I_{Kr}$) and a slow ($I_{Ks}$) potassium currents are involved in QT interval and repolarization of rat ventricular cells (30). A likely mechanism for MCP-induced QT prolongation in this study is blockade of the rapid component of the cardiac delayed rectifier potassium current, which is encoded by HERG (human ether-a-go-go-related gene) (31). This supports the previous findings obtained in animals and humans on the effect of gastrointestinal prokinetics on the QT interval. In animal studies, Drolet and coworkers have demonstrated that domperidone, a closely related D2 receptor blocker, prolongs cardiac repolarization in a reverse rate-dependent manner through blocking of potassium current in isolated guinea pig hearts (32). In human studies, Ellidokuz and Kaya have shown that MCP prolongs the QT interval in healthy subjects (33), and in an elegant study on cultured cells, Claassen and Zunkler have recently demonstrated that MCP can block the HERG/$I_{Kr}$ current expressed in human embryonic kidney cells although less potent than did cisapride and domperidone (34). The poor correlation between QT and QTc that was associated with MCP injection, in this study, seems expected based on the findings of Hayes *et. al.*, who demonstrated that, in rats, the QT interval may not change appreciably with HR in some instances of vagal stimulation (35), however, a good correlation between QT and QTc was observed during hyperthermia when the vagal tone has been attenuated.

Only a few data have been published on the electrocardiographic analysis of the quinolone-induced effects on heart function, and the data presented here offer the first, albeit limited, opportunity to compare between CPX and MCP on the individual electrocardiographic parameters, under different circumstances of body temperature. In this study we did not demonstrate significant effects of 20 mg CPX/kg on the HR or conduction velocity in spite of small swing in HR and abolished by hyperthermia. This effect, though non-significant, may reflect interaction with the sympatho-vagal balance that could not be ascertained with the small dose conducted in this study. However, preclinical toxicological evaluation of fluoroquinolones has shown that they can induce cardiovascular effects such as hypotension or tachycardia after intravenous injection in several animal species. In one study conducted on anaesthetized rabbits, CPX (1–30 mg/kg i.v.) caused a transient, dose-related decrease in heart rate, but after a dose ten times higher (300 mg/kg) ventricular tachycardia and arrhythmia were also observed (36).

Fluoroquinolones share the potential, as do MCP and other drugs that prolong the QT, to block the cardiac HERG/$I_{Kr}$ current in a dose-dependent manner (37-38). It has been shown that the chemical substituent in position 5 in the fluoroquinolone ring is responsible for QT prolongation. Thus, a methyl group at position 5, as in sparafloxacin, is responsible for QT prolongation of 14 ms. An amino group at position 5, as in grepafloxacin, is associated with QT prolongation of 11 ms. A proton (H) at this position is associated with QT prolongation of 2 ms for CPX, 3 ms for gatifloxacin, 5-6 ms for moxifloxacin and levofloxacin (10, 39). In this study, CPX increased QT interval by about 4.3 ms regardless the degree of body temperature.

Although weak evidence links CPX with QT-mediated arrhythmias (40), some recent studies have demonstrated comparable risk of CPX with other fluoroquinolones. In the guinea pig isolated right ventricular myocyte model, CPX and levofloxacin similarly prolonged the action potential duration by 0.6-3.3% (41). In a HERG assay in transfected HEK 293 cells, $I_{Kr}$ inhibition for CPX, at its therapeutic concentration, was only 3.3% lower than that of sparafloxacin and grepafloxacin (42). In a more recent report, Prabhakar and Krahn have recorded marked QT prolongation with recurrent syncope and documented TdP requiring defibrillation in two female patients following CPX administration. In both cases, the QT normalized after cessation of CPX (13).

The coadministration of MCP and CPX in single i.v. doses, in this study, did not alter the electrocardiographic data obtained by MCP alone on HR and conduction velocity, but on the other side, they were able together to produce more prolongation of QT and QTc intervals. These findings were not surprising based on the data obtained by each of them alone, in this study, and previously in the literature. How much this prolongation might be dangerous, this is a good question unlike to have good answer, because the interpretation on the degree of QT or QTc interval prolongation differs from the "statistical" than the "clinical" point of view, and there is much debate on this topic in the literature (43). However, and on the basis of the findings presented here, MCP and CPX might be two of the next compounds to be added to the growing list of drugs associated with long-QT syndrome.

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