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Effect of metaclopramide on urinary bladder smooth muscle contraction-relaxation mechanism

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ABSTRACT

Objectives: Metoclopramide, a dopamine receptor antagonist, a benzamide, is a commonly used antiemetic drug in many diseases with nausea and vomiting. The aim of this study is to examine the effects of metoclopramide, which is also used in urinary system infections, on the urinary bladder contraction-relaxation mechanism.

Methods: In the study, bladder tissue strips obtained from adult female Wistar rats in diestrus were placed in an isolated organ bath containing Krebs solution. The effect of metoclopramide at concentrations of 10 µM and 20 µM on sections where spontaneous contractions were observed under 1.5 g of tension was investigated.

Results: Metaclopramide caused a statistically significant increase in the area under the contraction curve (AUC) and peak to peak (p-p) parameters of spontaneous bladder contractions at concentrations of 10 and 20 µM ($p < 0.01$).

Conclusions: Metaclopramide has an activator effect on spontaneous bladder contractions. This effect should be taken into consideration in clinical use, especially when used in urinary system infections.

Keywords: Metoclopramide, urinary bladder, isometric contraction, rat

Metoclopramide (MCP) is an antiemetic with central and peripheral effects that increases the motility of the gastrointestinal system and accelerates gastric emptying [1, 2]. It is an antiemetic agent used in the prevention and treatment of nausea and vomiting due to acute migraine or urinary tract infections and after chemotherapy and radiotherapy. It may also cause side effects such as movement disorders of the extrapyramidal system [2]. MCP has a peripheral effect in accelerating gastric emptying and a central effect in reducing nausea and vomiting. MCP acts as a dopamine 2 and serotonin (5HT-3) receptor antagonist. It acts by blocking the dopamine receptor and stimulating the acetylcholine receptors in the stomach muscles [3]. MCP is widely used as a motility agent due to its contractile effects on gastrointestinal (GI) smooth muscle. MCP is widely used as an antiemetic agent, especially in patients receiving chemotherapy. Cholinergic reactions on smooth muscles are dominant in the periphery [4]. Its main antiemetic effect is through central dopaminergic antagonism [4].

This agent also has important effects on the urinary system. The effects of MCP on detrusor smooth muscle were studied using a canine model. Data from this animal model have been demonstrated by metoclopramide, a decrease in bladder capacity, an increase in

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detrusor micturition pressure, and a decrease in post-void residual volume [5]. Since urethral relaxation is an important factor in vesical micturition, the effect of metoclopramide on urethral pressure has also been studied and it has been shown to reduce urethral closing pressure [6]. One of the most common cases of emesis is urinary tract infections. In this case, the most preferred anti-emetic drug is MCP. Although it is frequently used in urinary system infections, its effectiveness on bladder activation is unknown. Therefore, in this study, it was aimed to investigate the effects of MCP on the contraction-relaxation of the bladder smooth muscle.

METHODS

Animals

In the study, 8 intact female Wistar rats, weighing 180-200 g, obtained from Fırat University Experimental Research Center were used. Rats were kept in plastic cages at 21°C room temperature, 12 hours light and 12 hours dark period. They were fed with tap water in glass bottles and special rat food in the form of pellets.

In Vitro Bladder Contraction Test

The rats decapitated on the day of the experiment and pelvic cavities were opened by cutting from the midline. The bladder tissues were rapidly excised and carefully separated from the surrounding tissues. The sections obtained from the bladder were opened by cutting vertically. Strips of 1.5×5 mm were obtained from the bladder tissue and placed in an organ bath pre-filled with crebs solution given the electrolyte composition: (118 mM NaCl, 4.7 mM KCl, 1.2 mM MgSO4, 15.8 mM NaHCO3, 1.18 mM KH2PO4, 11.5 mM glucose and 2.4 mM CaCl2, 0.016 mM EDTA). The temperature of the organ bath was kept at 37 °C. 95% O_2 and 5% CO_2 were continuously supplied to the bath solution. Each bladder strip was placed in the organ bath under the optimum resting force of 1.5 g and allowed to equilibrate for 90 minutes prior to drug administration.

Spontaneous contractions were obtained depending on the tension. The strain level in the suspended sections below 1.5 g remained constant throughout the experimental period. During this time, the bladder strips were washed every 15 minutes with fresh physiological solution. Each experiment was repeated using fresh bladder strips from different rats. The contractile forces were recorded isometrically using a force transducer connected to an amplifier and then to the data acquisition system. After the regulation period, 2 separate doses of MCP at concentrations of 10 µM and 20 µM were administered non-cumulatively. The effects of MCP on spontaneous bladder contractions were measured by changes in mean peak to peak (p-p) and area under the contraction curve (AUC). During the control period, contraction activity (mean p-p and AUC) was taken as 100%. AUC and p-p values of contractions before and after the application were normalized as % change.

Statistical Analysis

Statistical analysis of the data were evaluated using the Paired T test in the SPSS 22.0 program. All values were determined as mean ± standard deviation (mean ± SD). For all analysis, $p < 0.05$ was considered statistically significant.

RESULTS

MCP caused a statistically significant increase in p-p and AUC values of spontaneous bladder contractions at 10 and 20 µM doses (Figs.1 and 2). After the 10 µM dose was applied, the p-p values of contractions were calculated as 288 ± 134 and AUC values as 248 ± 94. The p-p values of contractions after MCP applied at 20 µM concentrations were calculated as 236 ± 90 and AUC values as 243 ± 126. It was observed that the p-p ($p = 0.005$ and $p = 0.004$) and AUC values significantly increased ($p = 0.003$ and $p = 0.01$) compared to the pre-administration values of MCP applied at concentrations of 10 and 20 µM. The original traces obtained at 10 and 20 µM doses in isolated organ bath are shown in Figs. 3 and 4, respectively.

DISCUSSION

MCP has an activator effect on spontaneous bladder contractions. In the study, it was shown that after MCP was applied to the bladder sections showing spontaneous contraction, there was a significant increase in the p-p and AUC values of contractions. MCP has

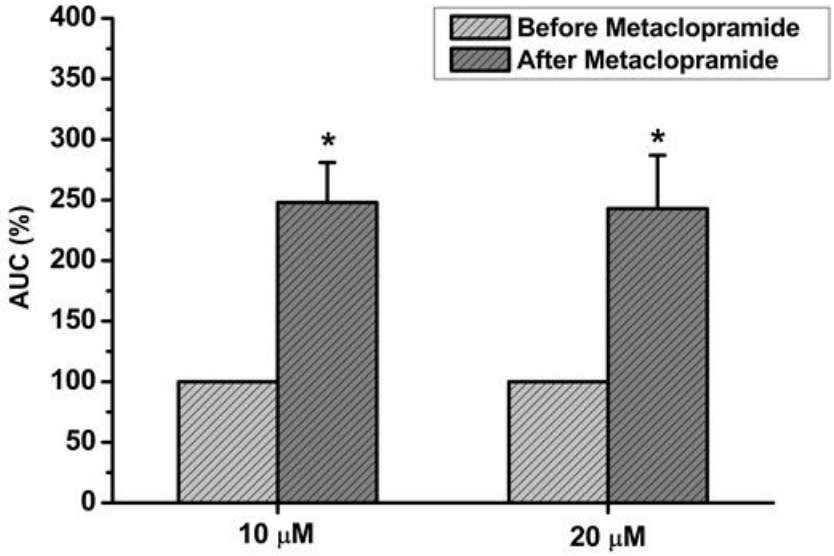

Fig. 1. **Effects of metoclopramide on AUC measurements in bladder contractions. * $p < 0.001$.**

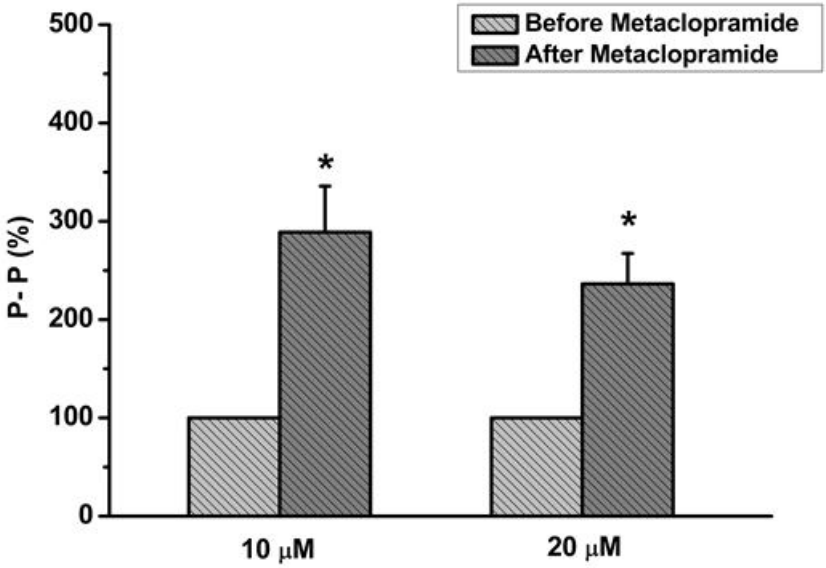

Fig. 2. **Effects of metoclopramide on peak-to-peak (p-p) measurements in bladder contractions. * $p < 0.001$.**

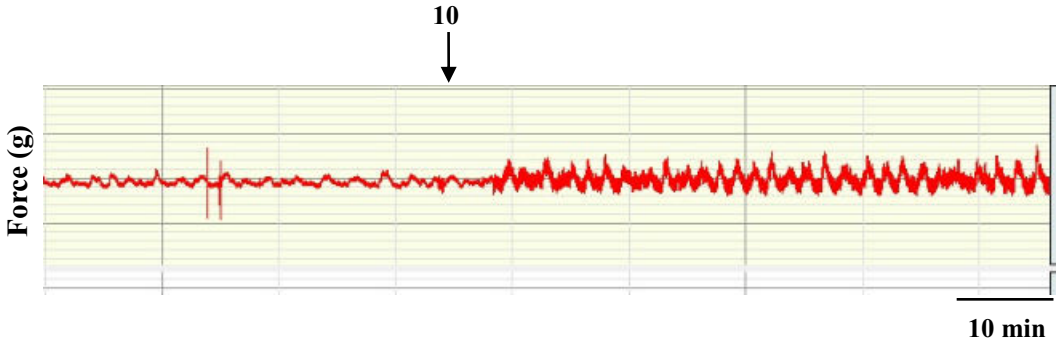

Fig. 3. **Original trace obtained when a 10 µM dose of metoclopramide was administered in an isolated organ bath.**

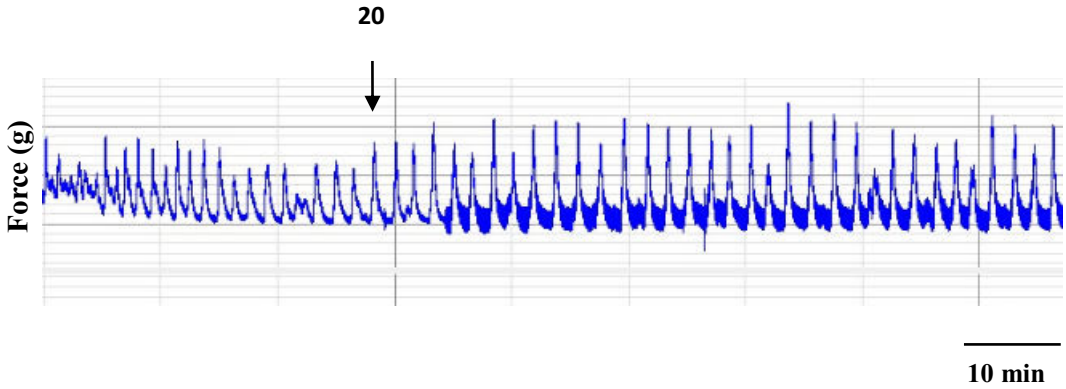

Fig. 4. Original trace obtained when 20 µM dose of metoclopramide was administered in isolated organ bath.

proven useful as a motility agent due to its ability to induce smooth muscle contraction in the gastrointestinal tract. Previous research had characterized the contractile effects on various parts of the urinary tract. In a study, the effect of MCP on detrusor smooth muscle was investigated using an in-vitro guinea pig bladder strip model. In the study, the effects of MCP were compared with those obtained in combination with atropine and acetylcholine.

MCP has been shown to exhibit inhibitory activity on guinea pig detrusor strips at low doses and stimulatory activity at higher doses. Acetylcholine has been observed to attenuate the contraction effect at low doses, but increase this effect at higher doses. Atropine reduces the contraction effect of MCP but increases the relaxation effect. Analysis of these interactions shows that MCP exerts a direct effect on bladder smooth muscle [7]. Nestler *et al*. [8] published a case report showing improvement in bladder function with spontaneous micturition after treatment with MCP in a diabetic man who needed intermittent catheterization with diabetic gastroparesis.

Reports on the possible effects of MCP treatment on the urinary tract are limited. In a clinical study conducted in ten patients with chronic neurological disorders, Vaidyanathan *et al*. [9] noted that administration of MCP in one third of these patients showed a return of detrusor reflex activity within minutes. However, the effects of MCP, a commonly used agent in lower urinary tract infections, on the bladder contraction relaxation mechanism are unknown. Therefore, in our study, we examined the possible effects of MCP on bladder contractions and found that MCP has an activator effect on bladder contractions. It can be said that this effect may be effective in reversing bladder smooth muscle reflex activity in patients with various chronic nervous system disorders characterized by a clinically seen neurogenic bladder.

CONCLUSION

It is clear that an effective and safe agent in the medical treatment of neurogenic bladder will have significant benefits in treatment. In this study, it is thought that MCP is effective in inducing bladder contractions and may have beneficial effects in such patients. This effect should be taken into account in clinical use.

Authors' Contribution

Study Conception: ZE, GZ, OB, IS, AY, EK; Study Design: ZE, GZ, OB, IS, AY, EK; Supervision: ZE, GZ, OB, IS, AY, EK; Funding: N/A; Materials: GZ, OB, IS, AY; Data Collection and/or Processing: ZE, EK, GZ, IS; Statistical Analysis and/or Data Interpretation: ZE, IS, OB, EK; Literature Review: ZE, EK; Manuscript Preparation: ZE, EK and Critical Review: ZE, IS, OB, AY, GZ, EK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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