



THE EXPERIENCE OF USING DRUG MIRTAZAPINE IN COMPREHENSIVE THERAPY OF IDIOPATHIC CYSTITIS IN CATS

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ABSTRACT

The article presents the results of research on the experience of using drug Mirtazapine in combination therapy of idiopathic cystitis in cats. It has been found that the use of Mirtazapine for cats with idiopathic cystitis at the dosage of 1.88 mg per day for two weeks improves the overall state and cognitive functions. The drug has a pronounced analgesic effect. Mirtazapine does not cause changes in the hematological parameters of cats. In addition, injection of Mirtazapine reduces the pH value of urine after 14 days by 6.7 %, after 30 days — by 10.7 %, and after 60 days — by 10.3 %, compared to the first day. A decrease of 3.5 % (30 days) and 7.6% (60 days) of pH was also noted in animals in the second group. All of these allow concluding the reasonability of using Mirtazapine for cats with idiopathic cystitis.

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Keywords: Mirtazapine, cats, idiopathic cystitis, urine

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Introduction

Domestic cats are very susceptible to various stress factors that affect the physical and psychological state of a cat and may cause several behavioral disorders. The most common stress factors are changes in the lifestyle, appearance of children or new animals in the family, conflicts between other cats, and much more. Cats living in a state of stress can give up food, show aggression, excessive licking, or house soiling.

For domestic cats, stressors have additive effects, which means that when multiple stressors affect an animal simultaneously the resulting response to the stress is much higher than if the animal was exposed to only one stressor.

Stress factors can provoke manifestations of clinical symptoms of idiopathic cystitis by activating the efferent part of the sympathetic nervous system that stimulates dorsal root ganglia. The latter react to the effects with the induction of releasing neuropeptides and neurotransmitters in the peripheral tissues, which are responsible for the development of an inflammatory reaction and the emergence of the feeling of pain [1-4].

At the moment, it is known that idiopathic cystitis in cats is a systemic state caused by changes in the nervous system, the hypothalamic-pituitary-adrenal axis, in the bladder, the trigger of this state being stress.

Due to the effect of "uncontrollable stress", various dysfunctions develop in animals, such as the development of repetitive, stereotyped, or compulsive behavior [5]. Prolonged exposure to the physiological stress response may lead to the development of pathological processes in the organism of the animal. A striking example of this is the idiopathic dysfunction of the lower urinary tract in cats [6].

Numerous studies show that antidepressants are an effective means for the treatment of several pain syndromes. Clinical and experimental data support the hypothesis that the analgesic properties of this group of medicinal drugs have independent nature and are not secondary to their primary antidepressant effect [7].

There are quite many drugs with anxiolytic action. One of them is Mirtazapine, which is a tetracyclic antidepressant with mainly sedative action. It belongs to a new class of psychotropic drugs named noradrenergic, and to serotonergic antidepressants with a new profile of pharmacological activity [7]. Mirtazapine can also block H1 receptors, which explains its slight sedative effect [8]. The drug has an anxiolytic action, improves the sleep quality; at therapeutic dosages, Mirtazapine has virtually no anticholinergic action, has no effect on the cardiovascular system, and is well tolerated by patients [9]. However, despite numerous positive qualities of Mirtazapine, its use in veterinary practice is not well known yet.

The aim of this investigation was to study the effects of drug Mirtazapine in the course of treatment of idiopathic cystitis in cats.

Materials and Methods:

The study was performed on the basis of veterinary clinic Powderpill-service (Penza), veterinary clinic Zoo Planet (Zarechny, Penza region), and the FSBEI Saratov State Agricultural University. For the study, two groups of cats aged one to four years were formed, six animals in each.

All animals had been kept completely at home and had mostly been eating dry feed. Clinical examination included urinalysis, full blood examination and biochemical blood essay, ultrasound examination of the urinary system, and X-ray examination of the bladder.

The hematological parameters were determined on hematologic analyzer IDEXX Laser Cyte (USA), the biochemical parameters — on analyzer IDEXX Catalyst (USA), common urine analysis — on analyzer CL-50 Plus Urine Analyzer (USA), urine density was determined with a refractometer, and urine sediment was examined by microscopic examination directly at the clinic upon animals' admission. Ultrasound examination was performed on unit Mindray DP 6600, and X-ray examination — on X-ray machine Porta 120 with digitizing on DR panel AKFA.

The male cats in the first group, along with the main treatment, were prescribed oral administration of Mirtazapine at the dosage of 1.88 mg daily for two weeks; further, the drug was given at the same dosage every other day for two months. In case of a recidivation of the disease, studies were performed in the same scope.

Digital material was subjected to statistical analysis with calculation of the Student's t-criterion on a personal computer with the standard variation statistics program in Microsoft Excel.

Results:

The first stage of the research was studying the spread of urological syndrome in cats, compared to the total number of diseases. The results are shown in Table 1.

Table 1. Percentage of patients with the urological syndrome to the total number of diseases

Year	The number of cases with various pathologies	The number of cases with the urological syndrome	% of urological pathologies of the total number
2013	4,862	580	12
2014	5,486	658	12
2015	5,637	845	15
2016	5,891	1,001	17
2017	5,923	889	15

It was found that the percentage of patients with the urological syndrome to the total number of diseases was 12 to 17 %. The highest percentage of patients with urological problems was noted in 2016 and amounted to 17 %.

Idiopathic cystitis is characterized by abnormal behavior of the animal during urination after excluding other disorders such as urolithiasis, bacterial urinary tract infections, anatomical abnormalities, and neoplasms [1]. Idiopathic cystitis has less pronounced seasonality, but a slight increase in the autumn and spring is noted.

Idiopathic cystitis is more frequently observed in sterilized cats (31 % of all cases) (Fig. 1).

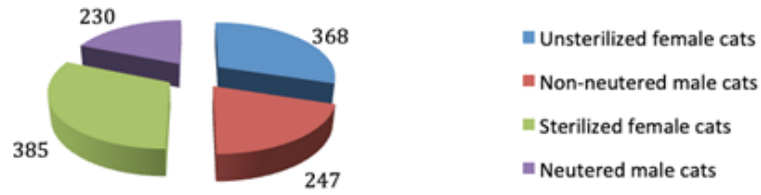


Figure 1. Idiopathic cystitis incidence rate, depending on gender (n=1,230)

Female cats, on the contrary, are more often prone to idiopathic cystitis, regardless of the activity of the reproductive system functioning (29.92 % and 31.4 %, respectively). In the male cats, little difference was noted in the spread of the disease, depending on the physiological state: the noncastrated male cats — 20.08 %, and the castrated male cats — 18.69 % of the total number of the animals with the disease.

During an ultrasound examination, symptoms of bladder inflammation were found in all animals (Fig. 2), without concretions, which fact was also confirmed by X-ray examination (Fig. 3).



Figure 2. Ultrasound examination of a cat. Bladder inflammation.

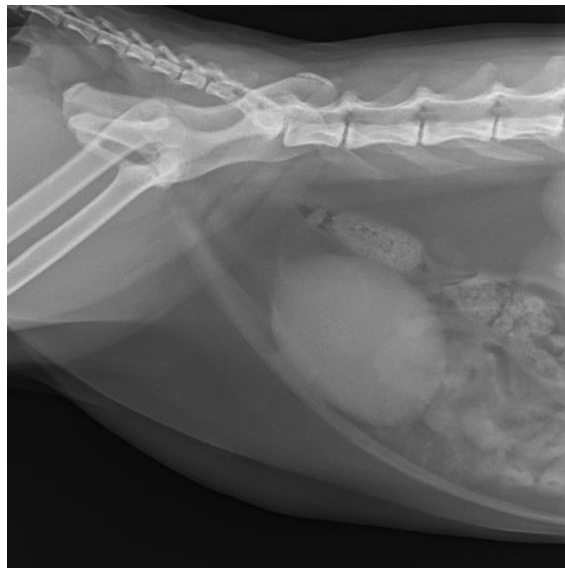


Figure 3. X-ray study of a cat. Bladder inflammation.

The results of studying the influence of drug Mirtazapine on the physicochemical properties of cat urine are shown in Table 2.

Table 2. Physicochemical properties of cat urine after using drug Mirtazapine

Group of animals	Indicator				recidivation
	pH	SG	LEU	BLD	
Day 1					
Group 1	7.0 ± 0.005	1.049 ± 0.003	++	+++	0
Group 2	7.1 ± 0.003	1.050 ± 0.002	++	+++	0
Day 14					
Group 1	6.53 ± 0.001	1.048 ± 0.003	+	+	0
Group 2	7.0 ± 0.003	1.050 ± 0.001	++	+++	2
Day 30					
Group 1	6.25 ± 0.002*	1.046 ± 0.001	-	-	0
Group 2	6.85 ± 0.003	1.048 ± 0.003	+	-	0
Day 60					
Group 1	6.28 ± 0.003*	1.046 ± 0.002	-	-	0
Group 2	6.56 ± 0.003	1.044 ± 0.002	-	+	1

Note: (*) P≤0.050

It was found that injecting Mirtazapine had reduced the pH value of urine after 14 days by 6.7 %, after 30 days — by 10.7 %, and after 60 days — by 10.3 %, compared to the first day. A decrease of 3.5 % (30 days) and 7.6 % (60 days) in pH was also noted in the animals in the second group.

All cats had high erythrocytes, neutrophils, and epithelial cells count, some cats had crystals of struvites. After the treatment, leukocytes and neutrophils were not found in the animals of the first group, and single erythrocytes were found in the animals of the second group. Within 60 days, no recurrence of the disease was observed in any cat in the experimental group.

The results of clinical blood analysis are shown in Table 3.

Table 3. Hematological parameters of the cats after administration of Mirtazapine

Indicator	Unit of measurement	Norm	Day 1	Day 14	Day 30	Day 60
RBC (erythrocytes)	10 ¹² /l	5.00–10	6.90 ± 0.03	6.88 ± 0.05	7.52 ± 0.04	7.23 ± 0.06
HCT (hematocrit)	%	30–45	33.0 ± 0.66	33.3 ± 0.33	34.6 ± 0.54	34.8 ± 0.52
HGB (hemoglobin)	g/l	9–15.1	14.1 ± 0.63	14.5 ± 0.31	15.0 ± 0.31	15.1 ± 0.21
MCV (mean corpuscular volume)	fL	41–58	52.64 ± 1.51	54.56 ± 1.61	55.36 ± 1.31	54.00 ± 1.42
MCH (mean corpuscular hemoglobin)	pg	12.0–20.00	18.9 ± 0.21	19.4 ± 0.62	19.3 ± 0.72	19.2 ± 0.41
MCHC (mean cell hemoglobin concentration)	g/l	29.0–37.5	33.8 ± 0.62	33.5 ± 0.52	35.0 ± 0.86	35.6 ± 0.41
RDW (red cell distribution width)	%	17.3–22.0	19.2 ± 0.39	20.1 ± 0.74	19.9 ± 0.51	20.0 ± 0.62
Reticulocytes	K/ml	3.0–50.0	15.6 ± 0.61	16.1 ± 0.48	15.9 ± 0.33	16.3 ± 0.27
Leukocytes	10 ⁹ /l	5.50–19.50	8.55 ± 0.16	9.03 ± 0.05	9.00 ± 0.49	9.73 ± 0.23
Neutrophils	10 ⁹ /l	2.5–12.5	5.8 ± 0.28	5.5 ± 0.003	5.3 ± 0.31	5.5 ± 0.11
Lymphocytes	10 ⁹ /l	0.40–6.80	2.18 ± 0.01	2.3 ± 0.03	3.5 ± 0.52	3.3 ± 0.52
Monocytes	10 ⁹ /l	0.15–1.7	0.36 ± 0.005	0.20 ± 0.001	0.40 ± 0.002	0.42 ± 0.003
Eosinophils	10 ⁹ /l	0.10–0.79	0.19 ± 0.003	0.34 ± 0.003	0.37 ± 0.001	0.35 ± 0.001
Basophils	10 ⁹ /l	0.00–0.10	0.02 ± 0.001	0.01 ± 0.001	0.00	0.00
Platelets	K/ml	175–600	581.2 ± 12.53	539.8 ± 15.00	556.3 ± 10.53	581.4 ± 12.5

Note: M ± m are the mean value and its error

Comparing the results of the studies to the reference values in Table 3 showed no valid fluctuations. The erythrocyte count by days 30 and 60 after the administration of Mirtazapine increased by 8.3 % and 4.8 %, respectively, compared to the initial values. In addition, a decrease was noted in the number of segmentonuclear neutrophils by 5.1 % and 8.6 %, compared to the initial level. The initial basophils count was $0.02 \pm 0.001 \times 10^9/l$, on day 14 this figure dropped twice, and by day 30, basophils were not detected.

Biochemical analysis of blood was made on the first day of the study, on days 14, 30, and 60, and included determination of the following parameters: glucose, creatinine, urea, total protein, albumin, globulin, alanine aminotransferase (ALT), symmetric dimethylarginine, alkaline phosphatase, and gamma-glutamyltranspeptidase (GGT). The mean values are shown in Table 4.

Table 4. Biochemical parameters of cat blood after the administration of drug Mirtazapine

Indicator	Unit of measurement	Norm	Day 1	Day 14	Day 30	Day 60
Glucose	Mmol/l	4.11–8.84	7.42±0.42	7.39±0.41	8.00±0.63	7.83±0.33
Creatinine	Mmol/l	71 – 212	131.2±1.95	154.9±2.03	153.8±2.64	158.4±2.9
Urea	Mmol/l	5.7– 12.9	8.0 ± 0.83	8.3± 0.39	8.5± 0.33	8.2 ± 0.71
Symmetric dimethylarginine	g/l	0 – 1.4	0.8± 0.003	0.8±0.002	0.9±0.001	0.8 ± 0.03
Total protein	g/l	57 – 89	79.8± 1.00	83.6±1.01	85.7± 1.5	87.7± 1.01
Albumin	g/l	22 – 40	30.5±0.66	32.4±0.74	34.3±0.66	30.5± 1.52
Globulin	g/l	28 – 51	49.6±0.98	51.6±1.52	51.3±0.41	57.8± 2.00
ALT	units/l	12 – 130	58.2±0.83	59.9±1.73	58.9±2.00	60.5± 2.04
Alkaline phosphatase	units/l	14 – 111	46.1±0.31	50.00±1.03	50.3±1.63	51.5±0.55
GGT	units/l	0 – 4	0,83±0,02	0	0	0

Note: $M \pm m$ are the mean value and its error

During the study, no significant deviations were noted in the biochemical parameters upon the administration of Mirtazapine in the specified dosage and frequency (Table 4).

The owners of the cats in the experimental group noted improved appetite and overall state from the first days of Mirtazapine administration, with that, the slight sedative effect was observed in two cats, which did not affect the appetite. With the use of Mirtazapine in the specified dosage, excessive vocalization was observed in one cat out of six. All owners reported improvement of the cognitive functions, improved interest in playing games and company; during the research, an average increase in the weight by 300 g was observed. The sedative effect was virtually not observed after Mirtazapine started being administered once in two days. Within 2.5 months, no cat in the experimental group showed recurrence of the disease. In the reference group, three cats were taken to the clinic with relevant symptoms.

Discussion:

Idiopathic cystitis in cats is a diagnostic term used to refer to several pathological states of cats that affect the bladder and the urethra and may be associated with urination in inappropriate places. Idiopathic cystitis is characteristic of young and middle-aged cats. It is a frequent disease; its share is 60 – 70 % of all lower urinary tract diseases in cats [4].

Male and female cats suffer equally from idiopathic cystitis, although neutered male and female cats are at a greater risk than their non-neutered peers. The peak of risk is observed in two- to six-year-old cats living all the time indoors with people [5]. Idiopathic cystitis in cats tends to recidivate. Each time the symptoms reappear, a basic examination is to be made.

Since the symptoms of idiopathic cystitis may disappear spontaneously without therapy, and suddenly reappear after various time intervals, it is difficult to understand which therapy is more effective. Since there is no specific treatment for idiopathic cystitis, therapy is aimed at reducing the pain and improving the overall state of a cat.

Conclusion:

The use of Mirtazapine for cats with idiopathic cystitis at the dosage of 1.88 mg per day for two weeks improves the overall state and cognitive functions. The drug has a pronounced analgesic effect. It is, however, worth noting manifestations of the sedative effect in the first two weeks of drug administration. In this case, one should also ambiguously treat the weight gain, since excessive weight is a problem for many cats living indoors.

Mirtazapine does not cause changes in the hematological parameters of cats. Besides, injection of Mirtazapine reduces the pH value of urine after 14 days by 6.7 %, after 30 days — by 10.7 %, and after 60 days — by 10.3 %, compared to the first day. The decreased in pH by 3.5 % (30 days) and 7.6 % (60 days) was also noted in the animals in the second group. All this allows concluding the reasonability of using Mirtazapine for cats with idiopathic cystitis.

References

1. Buffington CA, Chew DJ, Kendall MS, Scrivani PV, Thompson SB, Blaisdell JL, Woodworth BE. Clinical evaluation of cats with nonobstructive urinary tract diseases. *Journal of the American Veterinary Medical Association*. 1997 Jan;210(1):46-50.
2. Tony Buffington CA. Comorbidity of interstitial cystitis with other unexplained clinical conditions. *The Journal of urology*. 2004 Oct;172(4 Part 1):1242-8.
3. Buffington CT, Westropp JL, Chew DJ, Bolus RR. Risk factors associated with clinical signs of lower urinary tract disease in indoor-housed cats. *Journal of the American Veterinary Medical Association*. 2006 Mar 1;228(5):722-5.

4. Buffington CT, Westropp JL, Chew DJ, Bolus RR. Clinical evaluation of multimodal environmental modification (MEMO) in the management of cats with idiopathic cystitis. *Journal of feline medicine and surgery*. 2006 Aug;8(4):261-8.
5. Mason GJ. Stereotypies: a critical review. *Animal behaviour*. 1991 Jun 1;41(6):1015-37.
6. Cameron ME, Casey RA, Bradshaw JW, Waran NK, Gunn-Moore DA. A study of the environmental and behavioural factors involved in the triggering of idiopathic cystitis in the domestic cat. *BCAVA Congress 2001 Scientific Proceedings*. 200;505.
7. Sitsen, J.M.A., Zivkov, M. Mirtazapine: clinical profile. *CNS Drugs*. 1995; 4(1): 39-48.
8. De Boer TH, Nefkens F, Van Helvoirt A, Van Delft AM. Differences in modulation of noradrenergic and serotonergic transmission by the alpha-2 adrenoceptor antagonists, mirtazapine, mianserin and idazoxan. *Journal of Pharmacology and Experimental Therapeutics*. 1996 May 1;277(2):852-60.
9. Bomholt SF, Mikkelsen JD, Blackburn-Munro G. Antinociceptive effects of the antidepressants amitriptyline, duloxetine, mirtazapine and citalopram in animal models of acute, persistent and neuropathic pain. *Neuropharmacology*. 2005 Feb 1;48(2):252-63.