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Selective effects of alfuzosin and doxazosin with intraduodenal administration on urethral pressure of cats[1]

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KEY WORDS alfuzosin; doxazosin; adrenergic alpha-antagonists; blood pressure; urethra; hypogastric plexus; electric stimulation

ABSTRACT

AIM: To observe the selective effects of alfuzosin (Alf) and doxazosin (Dox) on the urethral pressure by different administration routes. **METHODS**: The urethral pressure of the anesthetized cat was increased by electric stimulation of the hypogastric nerve. The different effects of Alf or Dox on the arterial blood pressure and urethral pressure between intraduodenal administration (id) and intravenous infusion (iv) were compared. **RESULTS**: When the hypogastric nerve was stimulated by electric stimulation (10 Hz, 25 V), the ratios of $ED_{20(BP)}/ED_{50(UP)}$ id to $ED_{20(BP)}/ED_{50(UP)}$ iv were 10.9:4.3 for Alf, and 3.1:2.1 for Dox. The reduction in urethral pressure induced by id Alf was greater than that by iv Alf. Dox did not show any difference in its effects by 2 administration routes. **CONCLUSION**: Intraduodenal administration of Alf, but not Dox, selectively decreased the urethral pressure elevated by electric stimulation. The uroselectivity of id Alf was not due to the species difference in its bioavailability and biotransformation.

INTRODUCTION

The human prostate, prostatic capsule, bladder neck, and proximal urethra are innervated by sympathetic nerves, from which norepinephrine (NE) released causes the contraction of prostate and urethra via α_1-adrenoceptors, producing an increase in urethral pressure or resistance. These changes are associated with the urethral obstruction by benign prostatic hyperplasia (BPH)[1,2]. α_1-Adrenoceptor antagonists decrease urethral pressure and resistance, and improve the urethral obstruction symptoms of BPH[1-3]. However, blocking of α_1-adrenoceptors in cardiovascular system produces several side-effects of postural hypotension, syncope, and asthenia, which limit the use of α_1-adrenoceptor antagonists in clinics.

Lefevre-Borg *et al*[4] reported the tissue selectivity of alfuzosin (Alf) by intraduodenal administration (id) in comparison with intravenous infusion (iv). They observed the drug effects on the urethral pressure (UP) in cats, but not on the blood pressure (BP) in conscious spontaneously hypertensive rats (SHR). The possibility of different bioavailability of id between rats and cats was not excluded in their experiments, that is, the bioavailability of Alf in cats and rats might be different. On the other hand, clinical trials demonstrate that doxazosin (Dox) is an effective agent for the treatment of symptomatic BPH in both normotensive and hypertensive patients[5], and Dox also improves urinary symptoms of men with lower urinary tract symptoms believed secondary to BPH[6]. The other study demonstrates that Dox is more effective in the patients younger than 60 years old[7], but there is no study to show the effects of Dox on the UP and BP by different administration routes. In this study, we attempted to investigate whether the id Alf and Dox produced a selective inhibition of UP increased by sympathetic nerve stimulation.

MATERIALS AND METHODS

Cats Adult cats ($\hat{\delta}$, $n = 72$, $3.8 \pm s$ 1.0 kg) were obtained from Experimental Animal Center of Hebei Medical University (Certificate № 04036).

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Chemicals Alf and Dox synthesized by Dr NIE Xin-Yong and LIU Yu-Ting (Hebei Drug Research Institute) were in white crystalline powder that had no particular odor. Alf was soluable in water with bitter (mp 235 ℃ and $E^{1\%}_{1cm}$ 1158). Dox was soluable in Me_2SO (mp 265 – 267 ℃ and $E^{1\%}_{1cm}$ 1278). In the present study, Dox was dissolved in 50 % (vol/vol) Me_2SO, and the solvent had no effect on the UP and BP. UP before and after solvent were (23.8 ± 4.1) and (22.2 ± 3.7) kPa, and BP before and after solvent were (2.8 ± 0.4) and (2.8 ± 0.4) kPa, respectively, $n = 5$, $P > 0.05$. Other drugs were dissolved in normal saline.

Surgery Cats were anesthetized with urethane (75 mg·kg^{-1}, iv) and chloralase (35 mg·kg^{-1}, iv). BP of the left carotid artery was measured with pressure transducer and recorded on a polygraph (RM – 6200, Nihon Kohden). A polyethylene cannula (d = 1.5 *mm* – 2.5 *mm*) was introduced through the bladder neck and advanced into the first half of the urethra about 1 cm as the inflow side. The cannula was held at the bladder neck with a ligature. An other cannula was inserted from the penis near to the prostatic urethra portion as an outflow side. The prostatic urethra portion was perfused with 37 ℃ normal saline at 0.5 mL·min^{-1}.

Electric stimulation The hypogastic nerves were isolated and positioned on bipolar platinum electrodes, which were bathed in 37 ℃ paraffin. The nerves were stimulated with square-wave pulses of 0.05 ms duration and 25 V, over a frequency range of 2 – 20 Hz for 5 s at 2-min intervals.

Intraduodenal administration Dox (0.025 – 0.8 mg·kg^{-1}) or Alf (0.1 – 3.0 mg·kg^{-1}) was administered via the intraduodenal route. The UP and BP were observed before and after the drugs. Since the maximal effects of Dox and Alf appeared 120 and 60 min, respectively, after medication, the responses were recorded before treatment and 120 min after Dox, and 60 min after Alf.

Intravenous infusion Dox (0.003 – 3.0 mg·kg^{-1}) or Alf (0.001 – 1.0 mg·kg^{-1}) was infused via the femoral vein. Since the maximal effects on BP appeared 30 s after Dox and 1 min after Alf, and those on UP occurred 7 min after Dox and 5 min after Alf, the responses were recorded before treatment and 30 s, 7 min after Dox; 1 min, 5 min after Alf, respectively.

Statistical analysis Data were expressed as $\bar{x} \pm s$, and $ED_{20(BP)}$ (producing a 20 % decrease in BP) and $ED_{50(UP)}$ (producing a 50 % reduction in UP) were calculated with weighted probit analysis (Bliss and Finney. Using NDST ver 4.2, 1996, Sun RY, *et al*, editors). Comparisons of the ratios ($ED_{20(BP)}$/$ED_{50(UP)}$) between 2 administration routes were analyzed by unpaired t test.

RESULTS

Effects of id Alf and Dox In the anesthetized cat, electric stimulation of the hypogastric nerves increased UP in a frequency-dependent manner. UP were (5.8 ± 0.50), (12.8 ± 2.26), (18.3 ± 1.80), and (24.3 ± 5.60) kPa at 2, 5, 10, and 20 Hz, respectively, $n = 5$. Alf and Dox administered id produced a dose-related inhibition of the increase in UP induced by nerve stimulation (Tab 1).

Tab 1. Regression analysis of the reduction in urethral pressure caused by Dox and Alf administered intraduodenaly in the anesthetized cats. $n = 5$ cats.

Frequency/ Hz	ED_{50}/ mg·kg^{-1}	95 % confidence limits/ mg·kg^{-1}
Doxazosin		
2	0.041	0.023 – 0.074
5	0.056	0.040 – 0.078
10	0.064	0.056 – 0.073
20	0.091	0.067 – 0.123
Alfuzosin		
2	0.201	0.107 – 0.411
5	0.181	0.133 – 0.245
10	0.275	0.203 – 0.427
20	0.610	0.399 – 0.938

Alf and Dox id decreased BP dose-dependently, and the values of $ED_{20(BP)}$ were 2.959 ± 0.419 mg·kg^{-1} for Alf ($n = 20$), and 0.194 ± 0.025 mg·kg^{-1} for Dox ($n = 20$).

The ratios of $ED_{20(BP)}/ED_{50(UP)}$ at 2, 5, 10, and 20 Hz stimulation for id Alf were 4.9 – 14.8, and for id Dox were 2.1 – 4.9. The ratios of id Alf or Dox were reverse to stimulation frequency (Tab 2).

Effects of iv Alf and Dox Alf and Dox iv produced dose-related inhibitions to UP induced by nerve stimulation at 10 Hz and to BP. The values of

Tab 2. $ED_{20(BP)}/ED_{50(UP)}$ ratio of intraduodenal administration of Alf and Dox. $n = 5$ cats.

Frequency/Hz	$ED_{20(BP)}/ED_{50(UP)}$ ratio	
	Alfuzosin	Doxazosin
2	14.8 ± 1.8	4.9 ± 0.6
5	16.2 ± 2.4	3.5 ± 0.8
10	10.9 ± 1.2	3.1 ± 0.8
20	4.9 ± 0.6	2.13 ± 0.22

$ED_{50(UP)}$ for Alf and Dox were 0.051 ± 0.025 mg·kg^{-1} and 0.075 ± 0.008 mg·kg^{-1} ($n = 5$), respectively, and those of $ED_{20(BP)}$ for Alf and Dox were 0.222 ± 0.088 mg·kg^{-1} and 0.172 ± 0.038 mg·kg^{-1} ($n = 5$), respectively. The ratios of $ED_{20(BP)}/ED_{50(UP)}$ at 10 Hz stimulation were 4.3 ± 0.96 for Alf and 2.12 ± 0.29 for Dox, respectively.

The ratio of $ED_{20(BP)}/ED_{50(UP)}$ of id/iv was 10.9/4.3 for Alf, and 3.1/2.1 for Dox when the hypogastric nerve was stimulated at 10 Hz. Statistical analysis with a paired t test showed that there was a reduction in UP but not in BP when Alf was administered id except for the large dose (3.0 mg·kg^{-1}). However, iv Alf did not show the same phenomena (Tab 3).

Preferential effects by Dox on UP were not observed in both administration routes (Tab 4).

DISCUSSION

The results of the present study showed that Alf produced a preferential relaxation in urethral tract of the anesthetized cat when the agent was given via intraduodenal route, in comparison with intravenous route, and this kind of preferential effect was not observed in the experiments with Dox.

At present, α_1-adrenoceptor antagonists are usually considered as the first-line therapy for BPH[8]. However, their vasodilatory-related adverse effects[9] limit the clinical use. In the present study, we observed the effects of Alf administered by both routes of intraduodenal and intravenous administrations in the same species (anesthetized cats), and got a similar result to the report [1]. Therefore, we further confirmed that Alf was a useful agent to preferentially decrease the urethral resistance when it was administered by intraduodenal route. A possible reason of species difference in bioavailability and biotransformation

Tab 3. Effects of id and iv Alf on UP and BP responses to eletric stimulation (25 V, 10 Hz) in anesthetized cats. $^bP < 0.05$, $^cP < 0.01$ *vs* before drug. $n = 5$ cats.

Alfzosin/mg·kg^{-1}	Before drug	After drug	Change/%
id			
Urethral pressure (kPa)		(60 min)	
0.1	3.2 ± 1.1	2.1 ± 0.7^c	−33.3 ± 9.1
0.3	3.1 ± 0.8	1.5 ± 0.4^c	−50.0 ± 14.1
1.0	3.1 ± 1.2	1.0 ± 0.4^c	−67.7 ± 11.4
3.0	2.7 ± 0.8	0.49 ± 0.16^c	−77.4 ± 7.4
Blood pressure (kPa)			
0.1	21.5 ± 3.3	21.9 ± 3.4	2.7 ± 1.6
0.3	21.5 ± 2.7	20.5 ± 2.7	−4.5 ± 1.3
1.0	22.7 ± 4.3	20.6 ± 3.7	−9.3 ± 2.5
3.0	21.5 ± 4.5	17.0 ± 2.9^b	−20.4 ± 4.3
iv			
Urethral pressure (kPa)		(5 min)	
0.001	3.4 ± 0.7	3.0 ± 0.8	−12.5 ± 5.3
0.01	3.1 ± 0.8	2.1 ± 0.9^b	−33.4 ± 10.9
0.1	3.2 ± 0.9	1.2 ± 0.5^c	−61.8 ± 12.0
1.0	3.3 ± 0.7	0.65 ± 0.23^c	−78.6 ± 9.6
Blood pressure (kPa)		(1 min)	
0.001	19.8 ± 3.2	19.2 ± 3.0	−4.3 ± 1.1
0.01	21.4 ± 3.7	19.6 ± 3.4	−7.9 ± 1.9
0.1	19.3 ± 2.7	15.8 ± 2.6^b	−10.4 ± 5.4
1.0	20.3 ± 1.8	14.8 ± 1.3^c	−22.8 ± 5.3

Tab 4. Effects of id and iv Dox on UP and BP responses to eletric stimulation (25 V, 10 Hz) in anesthetized cats. $^bP < 0.05$, $^cP < 0.01$ *vs* before drug. $n = 5$ cats.

Doxzosin/mg·kg^{-1}	Before drug	After drug	Change/%
id			
Urethral pressure (kPa)		(120 min)	
0.025	2.44 ± 0.24	1.77 ± 0.16^c	−27.6 ± 2.0
0.05	2.3 ± 0.4	1.3 ± 0.3^b	−41.2 ± 1.5
0.1	2.1 ± 0.4	0.79 ± 0.11^c	−62.3 ± 3.5
0.2	1.9 ± 0.7	0.40 ± 0.11^c	−78.5 ± 3.0
Blood pressure (kPa)			
0.025	25.0 ± 2.3	22.1 ± 1.7	−4.1 ± 2.0
0.05	22.1 ± 1.9	18.4 ± 1.7^b	−9.3 ± 2.1
0.1	20.7 ± 2.0	16.2 ± 2.0^b	−14.4 ± 2.4
0.2	24.5 ± 0.8	17.0 ± 0.7^c	−23.5 ± 1.5
iv			
Urethral pressure (kPa)		(7 min)	
0.003	1.79 ± 0.15	1.57 ± 0.12^c	−12.3 ± 3.4
0.03	1.5 ± 0.4	1.1 ± 0.3^b	−33.4 ± 5.0
0.3	1.6 ± 0.2	0.50 ± 0.21^c	−61.8 ± 13.6
3.0	1.77 ± 0.14	0.0 ± 0.0^c	−100.0 ± 0.0
Blood pressure (kPa)		(0.5 min)	
0.003	23.1 ± 2.7	22.1 ± 2.6	−4.6 ± 0.5
0.03	22.6 ± 1.5	19.2 ± 1.8^c	−15.9 ± 6.4
0.3	22.6 ± 2.7	17.6 ± 1.6^c	−22.0 ± 2.8
3.0	23.9 ± 2.2	13.3 ± 0.7^c	−44.5 ± 2.8

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between cat and rat for Alf was excluded by our present experiments. Furthermore, we found that the selectivity in urinary tract of Alf administered intraduodenaly was decreased markedly at higher frequency stimulation from more than 10 times (2 - 10 Hz) to 4.9 times (20 Hz, Tab 2). Further experiments are needed to clarify whether intravenous administration of Alf will produce the same phenomena.

It has been recognized that multiple subtypes (α_{1A}, α_{1B}, α_{1D}) of the α_1-receptor exist[10], but the functional relevance of these subtypes in terms of contraction of urethral and vascular smooth muscle is far from being fully understood. Radioligand binding experiment showed that prazosin, alfuzosin, and terazosin were not selective antagonists for any particular α_1-subtype[11]. Moreover, Alf did not show an affinity for histamine, dopamine, serotonin, benzodiazepine receptors, muscarinic receptors, and β-adrenoceptors[12]. On the other hand, this preferential effect on urethral responses was not observed in Dox in the same experiments, althouth Dox is also a selective α_1-adrenoceptor blocker. The mechanism of the uroselectivity of Alf is still unclear, and further study will be nessary.

In summary, the results of the present study show that intraduodenal administration of Alf, but not Dox, selectively decreases the urethral pressure increased by electrical stimulation, and the uroselectivity of Alf might be due to its biotransformation.

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阿芙唑嗪及多沙唑嗪十二指肠给药对猫尿道压的选择性作用[1]

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关键词 阿芙唑嗪；多沙唑嗪；肾上腺素 α-受体拮抗剂；血压；尿道；腹下神经丛；电刺激

目的：观察不同给药途径对阿芙唑嗪(Alf)和多沙唑嗪(Dox)降尿道压的选择性作用. **方法**：电刺激麻醉猫腹下神经以升高尿道压. 比较十二指肠和静脉两种途径给药时，Alf 和 Dox 降低平均动脉血压(MBP)及尿道压(UP)的作用. **结果**：相同电刺激条件下(10 Hz, 25 V)，Alf 肠道给药与静脉给药时 $ED_{20(BP)}/ED_{50(UP)}$ 比值为 10.9∶4.3；Dox 两种给药途径的比值为 3.1∶2.1. Alf 十二指肠给药降尿道压作用的选择性优于静脉给药，Dox 两种给药途径的作用无显著性差异. **结论**：Alf 胃肠道给药时，选择性降低电刺激诱发的尿道压升高，而 Dox 无此特点. Alf 对尿道的选择性作用与药物生物利用度和生物转化的种属差异无关.

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