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Phenoxybenzamine Treatment Is Insufficient to Prevent the Stress-induced Effects in Rat Gastrointestinal Tract

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Abstract: Phenoxybenzamine (POB) as an irreversible α-adrenoceptor antagonist was used to evaluate any possible therapeutic effects on stress-induced disorders in defecation in rats. In this study restriction stress was conducted on control and treated groups of rats with 0.1 and 1% of POB in a 2 mg kg^{-1} dose. After performing of restriction and drug administration, the frequency and weight of dropped faecal pellets were determined between 0-6, 6-12 and 12-24 h. The observed data showed no significant differences between control and treated animals ($p>0.05$). Present data suggest that although no significant differences have been observed in this trial but it could not be excluded due to other pharmacokinetic factors of phenoxybenzamine, which requires further studies to be conducted to elucidate more detail about it.

Key words: Phenoxybenzamine, adrenoceptor, rat, defecation

INTRODUCTION

Phenoxybenzamine (POB) is a non-selective α-adrenoceptor antagonist, which binds irreversibly and covalently to its target receptors. Over the last recent years, POB has been used as a antispasmoic agent to minimize adrenergic-mediated vasoconstriction of the radial artery (Taggart *et al*., 2000). POB also is approved for the treatment of diaphoresis and hypertension associated with pheochromocytoma (Te, 2002). Topical administration of POB resulted in a 24 h half-life in human, which is relatively longer than that other vasodilators (Cable *et al*., 1998).

There are some indications for POB in veterinary medicine such as administration for decrease of the maximal urethral pressure and blood pressure in dogs, treatment of severe non responsive diarrhea in the horse and management of feline urinary tract disease (Hood *et al*., 1982; Marks *et al*., 1996; Fischer *et al*., 2003).

Experimental studies on laboratory animals showed that POB blocked the enhancing effect of substance P on the twitch induced by transmural nerve stimulation in guinea pig vas deferens (von Euler and Hedqvist, 1974). Moreover, it has also been demonstrated that POB abolished the 5-hydroxytriptamine-and histamine-induced cerebral artery contractions in dogs (Tanaka and Nakayama, 1998).

At the same time it is known that released corticotropin-releasing hormone from Central Nerve System (CNS) by stress peripherally increase the release of 5-hydroxytriptamine (*5-HT*). Furthermore, it is well established that *5-HT* is one of the elements, which stimulates defecation through the *5-HT* receptors (Miyata *et al*., 1998).

In the light of the important role of *5-HT* on defecation and reported antagonistic effect of POB on *5-HT* induced contractions, hence we aimed to investigate the possible effect of POB on stress-induced defecation in rat to clarify the possible therapeutic effect.

MATERIALS AND METHODS

Animal preparation: Study was conducted on 18 Wister rat (9 male and 9 female, ~250 g), which the legality of study on animals was approved by the Institutional animal care and use committee of Urmia University and was undertaken with new EU guide to the care and use of the laboratory animals. A week before experiments all rats transferred to the laboratory and acclimatized for the laboratory atmosphere. Animals were free to access to the food and water. They fed during the study from same source, which they were feeding before transferring to the research place. Rats were randomly divided to the three groups with 6 rats (3 male and 3 female) in each group and they kept in the research cage during the study. The first group was chosen as a control and other two groups as test groups.

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Chemicals: Phenoxybenzamine hydrochloride (POB) was purchased from Sigma Chemical company (Germany). Physiologic serum (saline) was obtained from I.P.P.C. (Iran). All other chemicals were in analytical grade. Different concentrations of the POB (0.1 and 1%, w/v) were prepared in sterile Physiologic Buffered Saline (PBS).

Animal experiments: Two test groups (A and B) were dosed interaperitoneally (i.p.) 2 mg kg^{-1} (b.w.) POB with different concentrations of 0.1 and 1%. The control group was received only vehicle of the POB. All rats in three groups were restrained in a fibreglass restrainer for 2 min and immediately after that were administered the placebo and test drug. Following first restriction and treatment process, all rats were placed individually in plastic cages, which are proposed as a repeated stress because of individuality and away from community and the number and weight of faecal pellets were determined during 0-6, 6-12 and 12-24 h.

Statistical analysis: All numerical data was represented as mean ± SD. Differences between control and two test groups at different time points and various concentration of given compound were analyses by using a two way ANOVA test, which followed by bonferoni test in case of any significant differences. A $p<0.05$ was considered as significant.

RESULTS

As shown in Table 1, neither weight of collected feces pellets nor frequency of defecation showed significant differences ($p>0.05$). However, despite of long period of time for feces collection between 12 till 24 h (2-fold longer than 6-12 h) after treatment, the weight of collected feces pellets showed reduction of the weight but not frequency of defecation either in control and treated groups.

DISCUSSION

In this study with using POB as a classical irreversible α-adrenoceprtor antagonist, we field to show any significant differences in frequency and amount of eliminated faeces between control and treated groups of rats.

Previous studies showed that POB not only irreversibly blocks the α-adrenoceptors but also H_1-histamine and muscarinic acetylcholine receptors, as well (Van der Graaf and Stam, 1999; Eglen *et al*., 1994). In the light of the above mentioned characteristic of chosen drug for this trial it was assumed that giving POB should block the sympathetically-driven decrease (stress-induced sympathetic effects in this study), in gastrointestinal motility and reduce the tone pf the various intestinal sphincters (Bodenstein *et al*., 2005). This would lead to increase in gastric emptying and upper intestinal activity. Moreover, among the many proposed actions of 5-HT is a pathological involvement in the mechanisms of at least some types of watery diarrhea and disturbed defecation. These effects are evoked by increased propulsive activity of the intestine and/or by increases in the volume of fluid that is accumulated within the lumen, depending on the severity and type of the disturbance (Banner *et al*., 1996).

At the other hand recently, it is shown that selective 5-HT4 receptor antagonism prevented disruption in defecation behaviours indicating of major role of exo-or endogenous enteric 5-HT (Sanger *et al*., 2000). However, in this direction it is also demonstrated that selective antagonists at the 5-HT4 receptor do not affect normal, healthy gut function (Sanger *et al*., 1998). All together above mentioned discussion indicating of having a major role of 5-HT receptors in defecation processes and also showing an increase of defecation frequency due to stress, which indeed in our study we proposed to have stress as an initiative factor to test the capability of POB.

Very recently *et al*. (2005), demonstrated that POB ameliorated anorexia indicating that the adrenoceptors are involved in 5-HT function (Bellinger *et al*., 2005). Therefore the philosophy behind this study was to clarify any possible effect of POB on stress-induced defecation.

It is well documented that the elimination of pharmacological receptors by irreversible competitive antagonist-which in this trial activated 5-HT receptors was proposed to be objective of treatment-depends on both the concentration used and the incubation time in

Table 1: The weight (W) of collected feces (g) and frequency (F) of defecation of control and treated rats with POB at different time points and at various concentration (N = 6); group A received 0.1% and group B has been administered 1% of POB with 2 mg kg^{-1} b.w

	Time					
	0-6		6-12		12-24	
Groups	W	F	W	F	W	F
Control	1.40±0.3	2	1.22±0.48	2	0.79±0.38	2
Group A	1.00±0.42	2	0.89±0.36	2	0.67±0.20	2
Group B	1.25±0.46	2	1.23±0.44	2	0.78±0.15	2

case of *in vitro* experiments and *in vivo* situation biological half-life of used compound (Bodenstein *et al*., 2005). As it mentioned above POB showed capability to antagonize the 5-HT receptor as well (Range *et al*., 2003). Since POB is bound covalently to the receptor, thus it is long lasting compound and due to this obvious reason we chose to perform the study till 24 h after treatment.

As we could not be able to demonstrate any significant differences between various treated groups and between treated and control groups in this study, thus it might reflect that either given concentrations of drug were not adequate to exert any considerable effects, or biological half-life of the used drug is shorter than examined time points in current study.

In conclusion, according to present results we could not exclude any possible therapeutic use of POB in treatment of various forms of gastrointestinal disorders and indeed further studies have to direct to clarify the precise elimination half-life time of the POB in different species of animals and human.

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