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RESEARCH ARTICLE

EVALUATION OF ANTIDIABETIC DRUG ALOGLIPTIN FOR THE TREATMENT OF INFLAMMATION IN RATS

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ABSTRACT
Objective: The present study was planned to evaluate the Alogliptin (Anti diabetic drug) for the treatment of inflammation in experimental models in rats.
Methods: Total of 5 groups of wister rats of either sex weighing 180- 220 g, selected for the study of 2 animal model were kept at ambient temperature of 28±2°C and relative humidity of 45 to 55% with a 12:12 h light/dark cycle. The animals were fasted for 12 h before commencing the experiment with water ad libitum. Fasting was continued till completion of the experiment. Group A was served as normal toxicant control treated with toxicant Carrageenan (model 1) and Histamine (model 2), group B with Ibuprofen (40 mg/Kg p.o.) served as standard, groups C, D and E administered with Alogliptin (low, medium and high doses p.o) respectively in each model. The Groups B, C, D and E were administered with 0.1 ml of 1% w/v of carrageenan in model 1,Histamine in model 2 into sub plantar region of right hind paw of rats 1 h after the administration of Ibuprofen/ Alogliptin. Immediately thereafter the oedema volumes of the injected paws were measured plethysmographically at prefixed time intervals.
Results: The Alogliptin with three selected doses i.e. 1, 2 and 3 mg/kg/day have exhibited a significant reduction in paw oedema volume at 4th h in carrageenan 36.92%, 51.49%, 65.46% and histamine 27.41%, 48.24%, 69.07% respectively. Ibuprofen (40 mg/kg) was used as standard reference thus standard drug has exhibited time dependent reduction in oedema volume.
Conclusion: The results of recent studies suggest that dipeptidyl-peptidase-4 inhibitors (Alogliptin) have anti inflammatory effect on experimental models in rats.
Keywords: Alogliptin, anti inflammatory, dipeptidyl-peptidase-4, carrageenan, histamine.

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INTRODUCTION
In the present evaluation, we have selected a Alogliptin (Anti diabetic drug) in which variety of pharmacological features are abundant. However, to date anti-inflammatory activities of this drug have not been reported. Its medicinal properties of dipeptidyl peptidase 4 inhibitors (DPP-4) reported by the researchers to opt for the assessment of anti-inflammatory activities in various experimental animal models. Dipeptidyl peptidase-4 (DPP-4) inhibitors are novel oral antihyperglycemic agents for treating type 2 diabetes mellitus patients. Recent studies suggest that several DPP-4inhibitors exert suppressing inflammatory reactions. However, whether or not DPP-4inhibitors suppress arterial inflammation and intimal hyperplasia after injury remains undetermined. Alogliptin (2-({6-[(3R)-3-aminopiperidinyl-1-yl]-3-methyl-2, 4-dioxo-3,4-dihydropyrimidin-1(2H)yl} methyl) benzonitrilemonobenzoate) (AGP) is a selective DPP-4 inhibitor that has improves glycemic control. However, it remains unknown whether AGP has anti-inflammatoryeffects[1-7]. DPP4 was first discovered by Hopsu-Havu and Glenner in 1966[8]. This protein is also called CD26 and is a ubiquitously expressed 110-kDa glycoprotein that belongs to the type 2 transmembrane protein family[9]. As a member of the serine peptidase/prolyl oligopeptidase family, DPP4 is often sub classified based on its structure and function as follows: membrane-bound peptidase (fibroblast activation protein (FAP)/seprase), resident cytoplasmic enzyme (DPP8 and DPP9), and nonenzymatic member (DPP6 and DPP10). These proteins share a typical α/β-hydrolase fold. DPP4 comprises four domains: a short cytoplasmic domain, a transmembrane domain, a flexible stalk segment, and the extracellular domain, which is further separated by a glycosylated region, the cysteine-rich region, and the catalytic region[10]. DPP4 can cleave dozens of peptides,

including chemokines, neuropeptides, and regulatory peptides, containing a proline or alanine residue at position 2 of the amino-terminal region[11]. Despite the preference for proline at position 2, alternate residues at the penultimate position are also cleaved by DPP4, indicating a required stereochemistry for cleavage. This DPP4 cleavage at post-proline peptide bonds inactivates peptides and/ or generates new bioactive peptides, thereby regulating diverse biological processes.

DM is a low-grade systemic inflammatory disease. Suppressing inflammation slows the progression of DM. In addition to preserving glucose homeostasis, DPP4 inhibitors exert pleiotropic actions, such as anti-inflammatory effects. Alogliptin inhibits Toll-like receptor-4-mediated extracellular matrix signal-regulated kinase (ERK) activation and ERK-dependent matrix metalloproteinase expression in U937 histiocytes[12-13]. DPP4 inhibitors reduce cy-clooxygenase-2, IL-1β, macrophage inflammatory pro-tein-2, and TLR-4-mediated IL-6 expression in Zucker Diabetic Fatty rat[14], diabetic apolipoprotein E-deficient mice[15], and C57BL/6J-obese/obese mice[16], which parallels recovery from disease. It is speculated that the anti-inflammatory properties of DPP4 inhibitors may be largely beneficial for DM. Alogliptin was first approved by the Pharmaceuticals and Medical Devices Agency of Japan in 2010 and by the FDA in 2013 for treating T_2DM. It is a potent and highly selective inhibitor of DPP4 with a mean IC_{50} of 6.9 nM and 1,000-fold increased selectivity for DPP4 compared with that of the closely related serine proteases DPP2, DPP8, DPP9, FAP/ seprase, prolyl endopeptidase, and tryptase[17]. Alogliptin exhibits favorable pharma-cokinetic, pharmacodynamic, and pharmacologic safety profiles. Therefore, alogliptin as a monotherapy or add-on to metformin, pioglitazone, glipizide, glibenclamide, voglibose, or insulin significantly improves glycemic control compared with placebo or active comparators in adult and elderly patients with inadequately controlled T_2DM[18-19]. Because the kidney is the main excretion route for alogliptin, accounting for 60% to 71% of excretion, the oral dose should be reduced or withdrawn in patients with renal impairment[18].

Thus for its medicinal properties reported in the texts prompted us to select Evaluation of Alogliptin for the treatment of inflammation in different experimental animal models.

MATERIALS AND METHODS

Determination of anti-inflammatory activity:

Carrageenan induced paw edema:

Group A: Toxicant control (0.1 ml of 1% w/v Carrageenan, hind paw)
Group B: Standard (Ibuprofen 40 mg/Kg, p.o)
Group C: Alogliptin (1 mg/Kg/day p.o)
Group D: Alogliptin (2 mg/Kg/day p.o)
Group E: Alogliptin (3 mg/Kg/day p.o)

Experimental Procedure

Total 5 groups of Wister albino rats of either sex weighing 180- 220 g, selected for the study were kept in colony cages at ambient temperature of 28±2°C and relative humidity of 45 to 55% with a 12:12 h light/dark cycle. The animals were fasted for 12 h before commencing the experiment with water ad libitum. The fasting was continued till completion of the experiment. Group A was served as normal toxicant control treated with toxicant carrageenan, group B with Ibuprofen (40 mg/kg p.o.) served as standard, groups C, D and E administered with Alogliptin (low, medium and high doses p.o) respectively. The rats in Groups B, C, D and E were administered with 0.1 ml of 1% w/v of carrageenan into sub plantar region of right hind paw of rats 1 h after the administration of Ibuprofen/Alogliptin. Immediately thereafter the oedema volumes of the injected paws were measured plethysmographically at prefixed time intervals[20-23].

2. Histamine induced paw edema:

Group A: Toxicant control (0.1 ml of 1% w/v histamine, hind paw)
Group B: Standard (Ibuprofen 40 mg/Kg)
Group C: Alogliptin (1 mg/Kg/day p.o)
Group D: Alogliptin (2 mg/Kg/day p.o)
Group E: Alogliptin (3 mg/Kg/day p.o)

Experimental Procedure

Permission was granted from Innovative college of pharmacy, Greater Noida, India to conduct experiment on animals (1346/po/Re/s/10/CPCSEA). 5 groups of Wister albino rats of either sex weighing 180- 220 g, selected for the study were kept in colony cages at ambient temperature of 28±2°C and relative humidity of 45 to 55% with a 12:12 h light/dark cycle. The animals were fasted for 12 h before commencing the experiment with water ad libitum. The fasting was continued till completion of the experiment. Group A was served as normal toxicant control treated with toxicant Histamine, group B with Ibuprofen (40 mg/kg p.o.) served as standard, groups C, D and E administered with Alogliptin (low, medium and high doses p.o) respectively. The rats in Groups B, C, D and E were administered with 0.1 ml of 1% w/v of Histamine into sub plantar region of right hind paw of rats 1 h after the administration of Ibuprofen/ Alogliptin. Immediately thereafter the oedema volumes of the injected paws were measured plethysmographically at prefixed time intervals.

For comparison purpose, the volume of oedema was measured at prefixed time intervals. The difference between paw volumes of the treated animals was measured and the mean oedema volume was calculated[20-23]. Percentage reduction in oedema volume was calculated by using the formula,

$$\text{Percentage reduction} = \frac{Vo - Vt}{Vo} X100$$

Where, Vo = Volume of the paw of control at time‘t’, Vt = Volume of the paw of drug treated at time‘t’.

Statistical analysis

All results will be expressed as mean ± SEM from 6 animals. Statistical difference in mean will be analyzed using one-way ANOVA (analysis of variance) followed by Post hoc test (Dunnett‘s‘t’ test). $P< 0.05^{*}$, 0.01^{**} and 0.001^{***} will be considered as statistically significant.

RESULTS

1. Anti-inflammatory activity of Alogliptin in Carrageenan induced paw oedema model in rats:

The Alogliptin with three selected doses i.e. 1, 2 and 3 mg/kg/day have exhibited a significant reduction in paw oedema volume in carrageenan induced paw oedema in rats at different time intervals. Results are tabulated in Table 1. Ibuprofen (40 mg/Kg) was used as standard reference and it has significantly reduced paw oedema volume by 32.97% at 1st h, 57.48% at 2nd h, 70.94% at 3rd h and 82.03% at 4th h, thus standard drug has exhibited time dependent reduction in oedema volume. During 1st h of study Alogliptin with low, medium and high doses have significantly reduced oedema volume by 14.05%, 26.75%, and 45.67% respectively, which was found to be a time dependent effect.

Table 1: Anti-inflammatory effects of *Alogliptin* in Carrageenan induced paw oedema model in rats at different time intervals

S. N.	Groups	Treatment	1 h	% ROV	2 h	% ROV	3 h	% ROV	4 h	% ROV
A	Toxicant	Carrageenan (1% w/v)	0.370± 0.018	--	0.461± 0.017	--	0.475± 0.020	--	0.501± 0.017	--
B	Standard	Ibuprofen 40 mg/kg	0.248± 0.025***	32.97	0.196± 0.024***	57.48	0.138± 0.008***	70.94	0.090± 0.017***	82.03
C	*Alogliptin*	1 mg/kg	0.318± 0.020ns	14.05	0.338± 0.027ns	26.68	0.340± 0.017*	28.42	0.316± 0.015**	36.92
D	*Alogliptin*	2 mg/kg	0.271± 0.021ns	26.75	0.285± 0.024**	38.17	0.275± 0.013***	42.10	0.243± 0.014***	51.49
E	*Alogliptin*	3 mg/kg	0.201± 0.013*	45.67	0.216± 0.010***	53.14	0.186± 0.016***	60.84	0.173± 0.017***	65.46

n = 6, Significant at P < 0.05*, 0.01** and 0.001***, ns = not significant. ROV- Reduction of Oedema Volume.

During second hour of the study Alogliptin with low, medium and high doses have significantly reduced oedema volume by 26.68%, 38.17%, 53.14% respectively a time dependent effect. During 3rd h of study Alogliptin with low, medium and high doses have significantly reduced oedema volume by 28.42%, 42.10%, 60.84% respectively a time dependent effect was noted. During fourth hour of study Alogliptin with low, medium and high doses have significantly reduced oedema volume by 36.92%, 51.49%, 65.46% respectively a time dependent effect was noted and result are graphically represented in Figure 1.

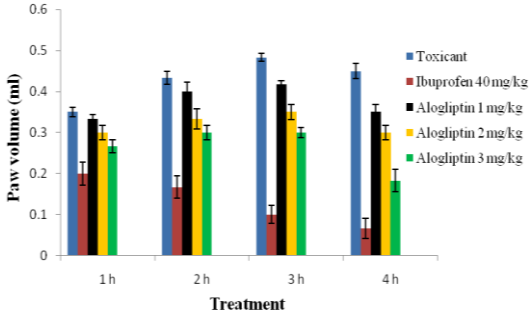

Figure 1: Anti-inflammatory activity of Alogliptin in carrageenan induced paw oedema model in rats

2. Anti-inflammatory activity of Alogliptin in Histamine induced paw oedema model in rats:

The Alogliptin with three selected doses i.e. 1, 2 and 3 mg/Kg have exhibited a significant reduction in paw oedema volume in histamine induced paw oedema in rats at different time intervals. Results are tabulated in Table 2. Ibuprofen (40 mg/Kg) was used as standard reference and it has significantly reduced paw oedema volume by 58.73% at first hour, 70.90% at second hour, 84.72% at third hour and 91.22% at fourth hour, thus exhibited a time dependent reduction in oedema volume. During first hour of study Alogliptin with low, medium and high doses have significantly reduced oedema volume by 9.25%, 20.63%, 39.68% respectively, which was found to be a time dependent effect. During second hour of study Alogliptin with low, medium and high doses have significantly reduced oedema volume by 14.77%, 26.59%, 45.90% respectively noted a time dependent effect. During third hour of study Alogliptin with low, medium and high doses have significantly reduced oedema volume by 19.95%, 34.62%, 54.58% respectively a time dependent effect was noted. During fourth hour of study Alogliptin with low, medium and high doses have significantly reduced oedema volume by 27.41%, 48.24%, 69.07% respectively a time dependent effect was noted and result are graphically represented in Figure 2.

DISCUSSION

The present study is the first providing evidence that DPP-IV inhibition with Alogliptin has protective effects of diabetic animals by a mechanism independent of enhanced insulin secretion. In the system of medicine a very good numbers of anti diabetic's medicine are reported to produce anti-inflammatory activities. Hence in the present study a plant by name Alogliptin has considered to evaluate its anti-inflammatory activities scientifically. For this Alogliptin were tested against different inflammatory models in rats. Carrageenan induced paw oedema model is used for screening of NSAIDs and inflammation produced by its biphasic in nature with the release of serotonin, bradykinin and histamine at I Phase followed by release of prostaglandins in II Phase which is shown in Table 1 and Figure 1.

Table 2: Anti-inflammatory effects of *Alogliptin* in Histamine induced paw oedema model in rats at different time intervals

S. No.	Groups	Treatment	1 h	% ROV	2 h	% ROV	3 h	% ROV	4 h	% ROV
A	Toxicant	Histamine (1% w/v)	0.378± 0.011	--	0.440± 0.019	--	0.491± 0.008	--	0.456± 0.015	--
B	Standard	Ibuprofen 40 mg/kg	0.156± 0.015***	58.73	0.128± 0.013***	70.90	0.075± 0.021***	84.72	0.040± 0.019***	91.22
C	*Alogliptin*	1 mg/kg	0.343± 0.024ns	9.25	0.375± 0.023ns	14.77	0.393± 0.010**	19.95	0.331± 0.015***	27.41
D	*Alogliptin*	2 mg/kg	0.300± 0.018*	20.63	0.323± 0.029***	26.59	0.321± 0.010***	34.62	0.236± 0.015***	48.24
E	*Alogliptin*	3 mg/kg	0.228± 0.016***	39.68	0.238± 0.015***	45.90	0.223± 0.010***	54.58	0.141± 0.015***	69.07

n = 6, Significant at P < 0.05*, 0.01** and 0.001***, ns = not significant. ROV- Reduction of Oedema Volume

Histamine being an important mediator of inflammation and also a potent vasodilator that causes increase in vascular permeability. In both phases due to release of these mediators cause pain and fever and Alogliptin significantly reduced paw oedema in II Phase of the inflammation indicating there effect on prostaglandins which is shown in Table 2 and Figure 2.

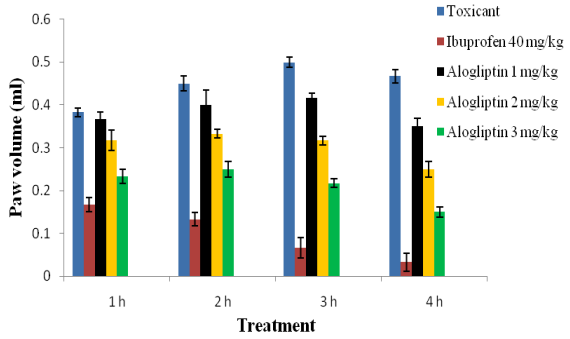

Figure 2: Anti-inflammatory activity of Alogliptin in histamine induced paw oedema model in rats

The present study evaluation of Anti diabetic drug Alogliptin confirms a positive anti inflammatory effect, hence these might have contributed for the anti-inflammatory activity.

CONCLUSION

The results of recent studies suggest that dipeptidyl-peptidase-4 inhibitors (Alogliptin) have anti inflammatory effect on experimental models in rats.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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