Bronchodilator and Positive Inotropic Activity of Pyridazine Compound Zardaverine as a Phosphodiesterase Isozymes Inhibitor

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Abstract: The zardaverine is a pyridazinone derivative that has been initiated as an effective broncho-dilatory agent. It is also uses as a positive inotropic agent. The effect of zardaverine is due to the inhibition of phasphodiestrase (PDE) activity. The zardaverine acts on the different PDE isozymes and showed selective PDE-III and PDE-IV isozymes inhibitory activity. The zardaverine reduced the cyclic GMP-controllable PDE III isoenzyme and the rolipram- controllable PDE-IV isoenzyme from canine trachea and human polymorphonuclear (PMN) cells. The zardaverine influenced the calmodulin-motivated PDE-I isoenzyme, the cGMP-motivated PDE-II isoenzyme and the cGMP-specific PDE-V isoenzyme slightly at level up to 100 μM. The zardaverine inhibited the ADP-induced human platelets aggregation. This reduction was synergistically increasing by the adenylate cyclase activators like prostaglandin E_1 (PGE_1) and forskolin. The zardaverine was reduced the zymosan-induced superoxide anion formation in human PMN cells. This activity was raised by adenylate cyclase activators.

Keywords: Pyridazinone, phosphodiesterase, zardaverine, bronchodilator.

INTRODUCTION

In recent years huge numbers of pyridazinone derivatives are reported as pharmacologically active compounds and possess almost all type biological activities such as antimicrobial, anti-inflammatory, analgesic, herbicidal, antifeedant, anticancer, antipyretics, antisecretory, antiphlogistics, antiulcer, antidepressants, anxiolytics, neuroleptics, sedative-hypnotics, tranquillizers, GABA antagonists, anticonvulsants, immunosuppressant and other some other types of pharmacological properties [1-5]. Large numbers of pyridazinone compounds were also well recognized as intermediates for drugs and agrochemicals. The cardiovascular applications of pyridazine analogues are also very well know. These cardiovascular activities are principally antihyper-tensive, antiplatelets, antithrombotics, vasodilatators, selective β-blockers, cardiotonics, antiarrhythmics, and hypocholesterolaemic activities [6,7].

The cyclic nucleotides arbitrate lots of diverse effects in mammalian cells like 3',5'-cyclic nucleotides hydrolysis to the subsequent nucleoside 5'-monophosphates and regulated the cyclic nucleotide levels. The advance of PDE inhibitors is to raise the cyclic nucleotide intracellular strength as an essential biological effect to dealing of various diseases. The PDE inhibitors may have possible therapeutic importance, such as heart failure, thrombosis, hypertension, obstructive airways disease and inflammation [8]. The PDE inhibitors are employed therapeutically and their efficacy has been restricted by the adverse actions and low effectiveness. Various types of PDEs have been known in various tissues, such as platelets, tracheal smooth muscle and cardiac muscle [8,9].

ZARDAVERINE WORKS AS PHOSPHODIES-TERASE III AND IV INHIBITOR

The pyridazinone derivative, zardaverine is chemically 6-(4-difluoromethoxy-3-methoxy-phenyl)-3(*2H*)pyridazinone compound (Figure **1**). It has a powerful bronchodilator and positive inotropic activity. The zardaverine is acts by reducing the phosphodiesterase (PDE) enzymes [10-12]. The zardaverine act on on various PDE isozymes in the different tissues, and it inhibited the cyclic GMP-reducible PDE-III activity in human platelets and the rolipram-reducible PDE-IV activity in canine trachea and human polymorphonuclear (PMN) cells. Zardaverine also influence the calmodulin-motivated PDE-I, the cGMP-motivated PDE-II and the cGMP-specific PDE-V isoenzyme on some extent at levels up to 100μM. The zardaverine inhibited the ADP-provoked human platelets aggregation and reduction was synergistically recovered by adenylate cyclase activators like prostaglandin E_1 (PGE_1) and forskolin. The zardaverine was inhibited zymosan-provoked superoxide anion production and effects were improved by the adenylate cyclase activators in human. It is probably to developed selective and probably clinically valuable PDE inhibitors. The inotropic effectiveness of zardaverine is approximately 10 times more than that for bronchodilator activity. It raises intracellular cyclic AMP levels by reduction of PDE activity [10-15].

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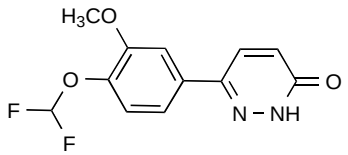

Figure 1: Structure of pyridazinone derivative, Zardaverine.

The PDE isozymes are differing in their physical characteristics and pharmacokinetics, substrate specificities, subcellular localization and tissue circulation [15]. The effect of diverse enzymes and their contribution in regulation of signal transmission within cells is weakly understood. Some of the isozymes inhibitors have been possess isozyme selectivity [9]. Some of the selective inhibitors are used pharmacologically. The inhibitory activity of zardaverine on PDE isozymes, platelets, homogenates were utilized as enzyme sources, one isozyme is mainly effective. The PDE-IB from bovine brain, is a calmodulin-sensitive and exhibited selectivity for cGMP [16], cGMP-motivated PDE-II acquired from cardiac ventricle; PDE-III attained from cardiac ventricle and platelets; the PDE-IV from cardiac ventricle and canine trachea were utilized; the cGMP specific PDE-V was attained from human platelets [17-19]. The reduction of PDE-III effectiveness from human platelets and PDE-IV from canine trachea in different levels of zardaverine, established a somewhat elevated affinity of zardaverine for PDE-IV compared to PDE-III. The effectiveness of zardaverine as well as other compounds as inhibitors of the various PDE isozymes, in difference to PDE III and IV, effectiveness of PDE I, II and V were affected at zardaverine levels above 100μM. Therefore, zardaverine was exhibited at least 100-times selectivity for PDE-III and PDE-IV over PDE-I, PDE-II and PDE-V isoenzymes.

The comparable selectivity was established in other pyridazinone compound, B832-07, but at variation, it is about 30-time more effective PDE-III inhibitory activity than PDE-IV inhibitory activity. The B832-145, a another compound of this group and exhibited significant PDE-IV selectivity as contrast to zardaverine [20,21]. Zardaverine inhibited platelets aggregation induced by diverse agonists such as platelet activating factor (PAF), adenosine diphosphate (ADP), collagen and arachidonic acid (AA). The zardaverine was platelet aggregation inhibitor in the level of 1.5 to 16.2 μM. The anti-platelet aggregation effect of zardaverine was improved in the existence of adenylate cyclase activators and steady with a synergistic relation between zardaverine and adenylate cyclase activators. Zardaverine compared to B832-07 was about three-time more effective and B832-145 about two-time less effective as platelet aggregation inhibitors. The xanthenes IBMX, enprofylline and theophylline were weak inhibitor of platelet aggregation with IC_{50} values of 17.8, 316 and 50μM, respectively [14]. The superoxide anion production motivated by zymosan was time and dose dependent. In the deficiency of any adenylate cyclase activator, zymosan-induced O^{2-} release is inhibited by zardaverine. The PGE_2 and forskolin is synergistically raised the inhibitory activity of zardaverine in a dose-dependent way. The platelet aggregation inhibitory action, xanthines IBMX, enprofylline and theophylline were relatively weak inhibitory actions of O^{2-}release. The motapizone in PMN cells was approximately 18,000-times more effective than that for platelet aggregation inhibitory action. Milrinone was approximately 300-times, CI 930 approximately 500-times, and B832-07 approximately 20-times less effective as inhibitors of O^{2-} release than platelet aggregation inhibitors. In contrast, rolipram and Ro 20-1724 was approximately 700-times more effective in PMN cells than in platelets. The PDE isozymes inhibitions on the cellular level and revealed that a high correlation between aggregation inhibition and PDE-III inhibition and between O^{2-}release inhibition and PDE-IV inhibition [14].

Several different isozymes were used to evaluate the PDE isozymes selectivity of zardaverine. PDE III and PDE-IV were originated in homogenates of tracheal tissue [21,22]. These two isozymes, the cGMP-inhibited PDE-III and cAMP-specific PDE-IV [9,23]. The PDE-III and PDE-IV inhibition, three PDE III/IV inhibitors groups can be categorized:

a) agents like milrinone, motapizone and CI 930 are selective PDE-III;

b) PDE-IV selective inhibitor agents like Ro 20-1724 and rolipram

c) agents combine PDE-III and PDE-IV inhibitory action, like zardaverine.

Zardaverine is a PDE III and PDE IV inhibitory agent having $1C_{50}$ values ranging from 0.56 to 1.7μM and showed 80-1700-times selectivity for PDE III and PDE IV isozymes contrast to PDE-I, PDE-II and PDE-V. The zardaverine was showed a low preference for PDE-IV inhibition over the PDE-III. The PDE-III or PDE-IV isozymes are exist in various human tissues [22,24]. Various PDE inhibitory agents with selectivity for either PDE-III or PDE-IV were able of inducing relaxation or

avoiding agonist-induced constriction. The existence of both isozymes in tracheal smooth muscle [25], the reduction of both PDE-III and PDE-IV isozymes by zardaverine have bronchodilatory action. The existence of a PDE isozyme does not prove it significant for the regulation of cAMP substance in cells.

The interactions between adenylate cyclase activators and PDE inhibitors, zardaverine inhibited platelet aggregation with IC_{50} values ranging from 1.5 to 16μM. Zardaverine was inhibited zymosan-stimulated superoxide anion liberate from PMN cells with an IC_{50} of 0.6μM. Zardaverine is, about three times more active in PMN cells than in platelets. In platelets and PMN cells, joining adenylate cyclase activators with zardaverine, marked raise of the PDE inhibitory action. In platelets, zardaverine and adenylate cyclase activators act synergistically to raise cAMP level, whereas in PMN cells a more complex interaction. Zardaverine is considerably lower than IC_{50} values for PDE inhibition may make raise in cAMP level in target cells, thereby reducing or preventing cell activation. The inhibitions of platelet aggregation and superoxide anion release from PMN cells by PDE inhibitors [14]. Selectivity for PDE III inhibitors was potent in platelets, whereas selectivity for PDE-IV was potent inhibitors of O^{2-}release in PMN cells. The PDE-III is vital for flexible cAMP level in human platelets, whereas PDE-IV is the major isozyme in PMN cells. Zardaverine does not have an inhibitory activity on PMN ceils-but also persuades the action of other inflammatory cells. The zardaverine and rolipram was inhibited zymosan-induced O^{2-} generation. The inhibition was examined at 0.1μM zardaverine. The PDE-III inhibitors did not affect cell activation at level up to 100μM. The inhibition of O^{2-} release from eosinophils is arbitrated by PDE-IV. The zardaverine also have basics to inhibited establishment of pro-inflammatory cells and probably considered as an anti-inflammatory agent. The treatment of inflammatory diseases, zardaverine is an anti-obstructive drug, that by asset of PDE-III and PDE-IV isozymes inhibitor, have anti-inflammatory, bronchodilator and cardiovascular effectiveness [26-30].

CONCLUSION

The pyridazine nucleus is present in various active compounds that exhibited diverse pharmacological activities. Due to this reason pyridazine derivatives hold considerable attention comparative to the producing of drug intermediates and physiologically effective organic molecules. Though, several pyridazinone agents have been reported as cardiovascular agents. These activities of pyridazine nucleus prompted us to develop new pyridazinone compounds with potent cardiac activity. Pyridazinone compounds have focused our attentions because of their easy functionalization and make them new and effective compounds for designing and development of novel compounds for future prospects.

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