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PIROXICAM MAY CAUSE PARKINSONISM IN HUMANS: A MINI REVIEW

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Abstract

Parkinsonism is a neuro-degenerative disease caused by destruction or impairment of basal ganglia which secretes dopamine from dopaminergic nerve that is connected to cholinergic nerve that secretes acetylcholine leading to decreased level of dopamine production. Piroxicam when administered to monogastric animals caused Parkinson-like effects characterize by opistothonus, torticollis, hypotention and sedation which are extrapyramidal. Therefore piroxicam may cause damage to basal ganglia resulting cholinergic effect. However, hydroxylated and carboxybenzothiazine metabolites of piroxicam must have been responsible for dopaminergic effect similar to that of fluphenazine in dose-dependent fashion.

Keywords: Piroxicam, parkinsonism, acetylcholine, dopamine, basal ganglia

Introduction

Piroxicam, a non-steroidal anti-inflammatory, antipyretic, analgesic drug [1], renders neuroprotection in cerebral ishaemia at low doses [2]. But disruption of Poly(ADP-ribose) polymerase gene disrupting renders mice resistant to cerebral ischaemia [3]. Higher doses (500-1000mg/kg) caused torticollis, opistothonus, lethargy, hypotension and so it has tendency to produce extrapyramidal effects [4] similar to that of typical antipsychotic (e.g. fluphenazine), which antagonizes dopamine receptors in the limbic system, the frontal cortex, the basal ganglia and the pathway to release of prolactin [5]. Extrapyramidal effect is a mimicry of parkinsonism [6]. Hence, all drugs that exhibit extra pyramidal effects have potential of inducing or exacerbating Parkinsonism in humans.

Piroxicam: The possible cause of parkinsonism

Parkinsonism being a neurologic syndrome resulting from deficiency dopamine is a consequence of degenerative changes in the basal ganglia characterized by rhythmic muscular tremors, rigidity of movement, testination, droopy posture, mask life faces and progressive supranuclear palsy [7]. Therefore, extrapyramidal signs seen in mice and rat at dose less than 500mg/kg and in guinea pigs, chickens, cockerels, broilers, turkeys and dogs at dose less than 1000mg/kg may be suggestive of damage to basal ganglia [4]. The human brain is composed of 15 billion neurons and below the cortex is the limbic system which has basal ganglia as component. The limbic system maintains homeostasis and controls emotions [8]. Drug-induced parkinsonism (DIP) is the second-most common etiology of parkinsonism in the elderly after Parkinson disease (PD). But the two are indistinguishable. Drugs that cause parkinsonism are typical anti-psychotics, gastrointestinal prokinetics, calcium channel blockers, atypical antipsychotics, and anti-epileptics. The clinical manifestations of DIP are classically bilateral and symmetric parkinsonism without tremor at rest. About 2.7% of DIP patients show symmetrical parkinsonism and tremor at rest. Typical antipsychotics such as fluphenazine [6] and piroxicam may cause parkinsonism in human and Parkinson-like condition in animals [4], respectively. The pathophysiology of DIP is related to drug-induced changes in the basal ganglia motor circuit secondary to dopaminergic receptor damage or blockade. Since these effects are limited to presynaptic dopaminergic receptors, presynaptic dopaminergic neurons in the stritum may be intact. Dopamine transporter (DAT) imaging is useful in diagnosing presynaptic parkinsonism. DAT uptake in the straitum is significantly

decreased even in the early stage of PD, and this characteristic may help in differentiating PD from DIP which may have a significant and longstanding effect on patients' daily lives. Therefore patients' neurological signs should be monitored when dopamine blockers are prescribed especially for parkinsonism and other movement disorders [9]. There is no prevalence and incidence of DIP, 40% of patients given chlorpromazine showed parkinsonism [10]. DIP is the second most common cause of parkinsonism, accounting for 2.7% [11]. PD affects only 1-2% of the adult population over 55 years old and neurotropic viruses can induce encephalopathies with a consequence of parkinsonism. The viruses are influenza, coxsackie, Japanese encephalitis B, St. Louis, West Nile and HIV viruses. Von Economo's encephalopathy can also cause parkinsonism [12]. However secondary parkinsonism caused by drugs and toxins is characterized by tremor, bradykinesia, rigidity and postural instability. n contrast PD could be idiopathic and is treatable [13]. Anti-breast cancer such as cyclophosphamide and busulphan caused parkinsonism in chronic myelogenous leukemia abated by levodopa (600mg) and gemcitabine caused parkinsonism abated by levodopa (1500mg) and never manifested again. Carboplatin and paclitaxel (anti-squamous cells carcinomas) caused parkinsonism abated by levodopa (1000 mg/kg) and never manifested again [14]. Occupational causes of parkinsonism are associated with exposure to manganese, carbon disulfide, organic solvents, carbon monoxides and N-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MTPT) [15]. MPTP produces neuropathological and clinical abnormalities in primates and rodents that closely resemble idiopathic parkinsonism. But N-Methyl-4-phenylpyridine (MPPT), a metabolite of MPTP formed by monoamine oxidase B, is accumulated in striated and cortical synaptosomes by the dopamine and norepinephrine uptake systems, respectively. But MPTP is not accumulated [16]. Analgesic overuse causes chronic daily headache and severe dyskinesia may result from obsessive use of dopamine replacement therapy [14]. Manganese, an essential element necessary for physiological processes, support development, growth and neuronal function, accumulates in the basal ganglia and causes parkinsomian – like syndrome referred to as manganism. Manganese-induced parkinsonism and PD are similar in their pathophysiological mechanisms and motor symptoms with striking differences in the clinical and pathologic manifestations [18]. Magnetic resonance spectroscopy is used to diagnose PD, PID and idiopathic parkinsonism [19]. Specific signs and minimal response to levodopa treatment suggest other causes of parkinsonism. So parkinsonism should be considered as differential in patients who have falls and exhibit general functional decline [20]. But methamphetamine users are almost twice as likely as non-users to develop parkinsonism, despite differences in

methamphetamine abuse and parkinsonism distinct symptomatic profiles [21]. But 3% to 6% of parkinsonism is vascular resulting from cerebrovascular disease such as hypertension leading to strategic infarcts of subcortical gray matter nuclei, diffused white matter, ischaemic lesions and less commonly large vessel infarcts. The affected person is older, with gait difficulties, poor levodopa responsiveness, falls, cognitive impairment and dementia [22].

Structure – activity relationship of piroxicam and parkinsonism

The extrapyramidal effects caused by piroxicam may be structurally activity based, since it is abated by atropine, suggesting the involvement of acetylcholine [4]. However, antimuscarinic drugs reduce the excitatory cholinergic activity within the striatum and restore dopaminergic-cholinergic balance. Example of the anticholinergics used in parkinsonism is benztropine [6]. The extrapyramidal motor activities caused by piroxicam may be due to pyridyl – N and O of the amide group [23], Methyl-Oxygen-Oxygen (M-O-O) and Nitrogen (N) functional groups which are structurally related to Sulphur – Oxygen – Oxygen (S-O-O) and Nitrogen (N) of piroxicam that are either methylated or hydrogenated may also contribute to penetration of piroxicam and damage CNS. The antimuscarinic effect exhibited by piroxicam may be due to replacement of Sulphur in the group (S-O-O) by methyl group in vivo. Whereas the nitrogen group may be responsible for cholinergic effect in ganglia and striated muscle [24] as seen in a tetanic spasm in which the spine and extremeties are bent with convexity forward, the body resting on the head and the heels (opisthotonos) and a contraction of the muscle of the neck, chiefly those supplied by accessory nerve (XI); the head is drawn to one side and usually rotated so that the chin points to the other side (torticollis or wryneck), usually observed in mammals [7]. The conversion of piroxicam to a metabolite that caused extrapyramidal effects may be by methylation [24] and the penetration of piroxicam into brain may be by redox chemical delivery system. Brain uptake of piroxicam may be positively correlated with lipid solubility at high doses or negatively correlated with hydrogen bonding and due to damage of meninges [23] especially when piroxicam causes parkinsonism, suggesting that antioxidants can be used to abate parkinsonism.

The dopamine D_3 receptor (D_3R) has been implicated in substance abuse and neuropsychiatric disorders with the high sequence homology between the D_3R and D_2R. Therefore dopamine has made the development of D_3R – selective compounds challenging [25]. But piroxicam is convertible in vivo to hydroxymethylated metabolite which may be

converted in vivo to barbiturates such as thiopentone and thiamylal. Hence piroxicam metabolites may act via dopamine, adrenaline, histamine, melatonin and potassium channel receptors causing CNS depression signifying that hydroxylation, cyclodehydration and carboxylation of piroxicam may be used to counteract, abate or eliminate the extrapyramidal effects produced by piroxicam [26]. Therefore, piroxicam also acts on sub-cortical sites such as thalamus and hypothalamus and lacks affinity for morphine receptors, tolerance and drug dependence in patients. The N – heterocyclic carboxamides are generally more acidic than the corresponding N – aryl carboxamides, and this enhanced acidity was attributed to stabilization of the enolate anion by the pyridine nitrogen atom [27]. Therefore piroxicam is unique because of its CNS effects [28]. Neuro-inflammation and angiogenesis have been involved in the pathogenesis of parkinsonism. However, piroxicam may have neuro-protection if co-administered with levodopa in order to ensure longevity of its action and to delay the development of dyskinesia [29]. This anti-parkinsonism effect may be due to the effect of piroxicam metabolites that have depressant activity via dopaminergic receptor [26], similar to that of a typical antipsychotic, fluphenazine [30]. Hence drugs that have heteroatoms including those that are tautomeric may cause Stevens-Johnson syndrome [31].

Conclusion

Piroxicam is converted to acetylcholine-like metabolite in vivo and may damage or impair the function of basal ganglia invariably causing Parkinson-like condition at higher doses. However, after a long stay period of piroxicam in the body, it can be converted to CNS depressing metabolites which may abate parkinsonism.

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References

[1] Tripathi KD. Essentials of Medical Pharmacology, 7th ed., Jaypee Brothers Medical Publishers, New Delhi, 2003; p 1002.

[2] Bhattacharya P, Pandey AK, Paul S, et al. Aquaporin – 4 inhibition mediates piroxicam-induced neuro-protection against focal cerebral ischaemia/perfusion injury in rodents. Plus One 2013; 8(9): 1 – 13.

[3] Eliasson MJL, Sampei K, Mandir AS, et al. Poly (ADP-ribose) polymerase gene disruption renders mice resistant to cerebral ischaemia. Nat Med 1997; 3(10): 1089 – 1095.

[4] Saganuwan SA, Orinya OA. Toxico-neurological effects of piroxicam in monogastric animals. J. Exper. Neurosc. 2016; 10:121 – 120.

[5] Ballington DA, Laughinlin MM. Pharmacology, 5th ed., Med Tec, Scientific International, Pvt. Ltd., New Delhi, India, 2014; p. 916.

[6] Kapoor AK, Raju SM. Illustrated Medical Pharmacology, Jaypee Brothers Medical Publishers (p) Ltd., New Delhi, India, 2013; p. 874.

[7] Stegman JK. Stedman's Medical Dictionary, 28th ed., Lippincott Williams & Wilkins, A Wolters Kluwer Company, Baltimore, USA, 2006; p. 2169.

[8] Danesh HB. The Psychology of Spirituality from Divided Self to Integrated self, Sterling Publishers Private Ltd., New Delhi, India, 2006; p. 270.

[9] Shin HW, Chung SJ. Drug-induced parkinsonism. J Clin Neurol 2012; 8(1); 15 – 21.

[10] Hall RA, Jackson RB, Swain JM. Neurotoxic reaction resulting from chlorpromazine administration. JAMA, 1956; 161: 214 – 218.

[11] Barbosa MT, Caramelli P, Maia DP, C. at al. Parkinsonism and parkinson's disease in the elderly: a community based survey in Brazil (the Bambui study) Mov. Disorder 2006; 21: 800 – 808.

[12] Jang H, Boltz DA, Webster RG, et al. Viral parkinsonism. Biochem Biophy Act 2000; 1792: 714 – 721.

[13] Molho ES, Factor SA. Secondary causes of parkinsonism. In: Parkinson's Disease and Movement Disorders, Human Press, 2000; p. 211 – 228.

[14] Susman E. Chemo-induced parkinsonism controlled with levodopa. Oncol Time 2001; 23(12): 59.

[15] Tanner CM. Occupational and environmental causes of parkinsonism. Occup Med 1991; 7(3): 503 – 513.

[16] Javitch JA, Amato RJD, Strittmatter SM, et al. Parkinsonism-inducing neurotoxin, N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine: uptake of the metabolite N-methyl-4-phenylpyridine by dopamine neurons explains selective toxicity. Proc Natl Acad Sci USA 1985; 2173 – 2177.

[17] Grosset KA, Grosset DG. Prescribed drugs and neurological complications. J Neurol Neurosurg Psych 2004; 75:3.

[18] Kwakye G, Paoliello MMB, Mukhopadhyay S, et al. Manganese-induced parkinsonism and parkinson's disease: shared and distinguishable features. Int J Environ Res Public Healt 2015; 12:7519 – 7540.

[19] Gulin O. Magnetic Resonance Spectroscopy of Degenerative Brain Diseases, Springer, London 2016; p. 268.

[20] Frank C, Pari G, Rossiter JP. Approach to diagnosis of Parkinson disease. Canad Family Physic 2006; 52: 862 – 868.

[21] Granado N, Ares-Santos S, Moratalla R. Methamphetamine and parkinsom's disease. Parkinson's Dis 2013; ID308052:10

[22] Vale TC, Barbosa MT, Caramelli P, et al. Vascular parkinsonism and cognitive impairment. Damat. Neuropsychol. 2012; 6(3): 137 – 144.

[23] Saganuwan SA. Physicochemical and structure-activity properties of piroxicam – a mini review. Comparat Clin Pathol 2016; 25(5): 941 – 945.

[24] Saganuwan SA. In vivo piroxicam metabolites: possible source for synthesis of central nervous system acting drugs. Centr Nerv Syst Agent Med Chem 2017; 17(1): 1 – 6.

[25] Newman AH, Beuming T, Banala AK, et al. Molecular determinants of selectivity and efficacy at the dopamine D_3 receptor. J Med Chem 2012; 55(5): 6689 – 6699.

[26] Saganuwan SA. In vivo piroxicam metabolites. Possible source for synthesis of central nervous system (CNS) acting depressants. Centr Nerv Syst Agent Med Chem 2017; 1:1 – 6.

[27] Siddiqui WA. Synthesis of piroxicam-related heterocyclic molecules and evaluation of their biological activities. Ph.D. Thesis. Government College University, Cahore, Pakistan, 2007.

[28] Thomae K. Pharmacology of indoxicam, a new non-steroidal anti-inflammatory drug with an improved safety profile through preferential inhibitor of COX_2. Br. J. Rheumatol. 1966; 35(1): 4 – 12.

[29] Teema AM, Zaitone SA, Moustafa YM. Ibuprofen or piroxicam protects nigral neurons and delays the development of L-dopa induced dyskinesia in rats with experimental parkinsonism: Influence on angiogenesis. Neuropharmacol 2016; 107: 432 – 451.

[30] Saganuwan SA. Fluphenazine (a typical antipsychotic) has a purgative effect on turkey. J Neurosci 2015, 50(3): 112 – 122.

[31] Saganuwan SA. Therapeutic causes of Stevens-Johnson syndrome-a min review. Ope Access J toxicol 2018;1(2):1-4.