SEARCH FOR NEW DRUGS

DOMESTIC ANTIDEPRESSANTS. 2. PYRAZIDOLE (PIRLINDOLE)

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Pyrazidole is the registered trade name of (2,3,3a,4,5,6-hexahydro-8-methyl-1H-pyrazino[3,2,1-j,k]carbazole hydrochloride, which was synthesized and pharmacologically characterized at the All-Russia Institute of Pharmaceutical Chemistry in the 1960 – 1970sa [1 – 8]. Pyrazidole represents a new class of original tetracyclic antidepressants – pyrazinocarbazole derivatives – possessing certain important structural features determining both the new mechanism of action and the activity profile of this drug. The drug was certified as an antidepressant in 1975 (Registration No. 75/689/6). Pyrazidole proves to be a highly effective and safe drug [9 – 17].

Pharmacological investigations of the specific (antidepressant) activity of pyrazidole were performed using a broad set of tests on white mice, rats, cats, rabbits, and dogs. In some of these experiments, the pharmacological properties of the new drug were studied in comparison to those of imipramine (an agent blocking the uptake of monoamines) and tranylcypromine and phenelzine (irreversible selective inhibitors of monoamine oxidase). Pharmacologically effective doses of pyrazidole are 10 – 25 mg/kg for peroral administration, 5 – 10 mg/kg for intraperitoneal injections, and 1 – 2 – 5 mg/kg for intravenous infusions. The results of testing showed pyrazidole to be an antidepressant with a new activity profile [8, 18 – 23].

The experiments showed that pyrazidole (i) decreases the immobilization time and stimulates the activity of animals (mice and rats) in the behavioral "desperate" swimming test; (ii) reduces the depressant effects (hypothermia, ptosis, catalepsy) of reserpine and tetrabenazine while not inhibiting catalepsy induced by phenothiazine derivatives [19]; (iii) potentiates the effects of phenamine and *L*-DOPA upon the CNS; (iv) enhances clophelin-induced aggression; and (v) decreases apomorphine-induced hypothermia. Pyrazidole is comparable to imipramine [8] or even superior to this reference drug [19] with respect to the antireserpine effect. Although the antidepressant activity of pyrazidole is one-third of that for tranylcypromine, the former drug exhibits a three times lower toxicity than the latter. The duration of the antireserpine effect of pyrazidole is twice that of imipramine and about half that of tranylcypromine [19]. In contrast to pyrazidole, imipramine and tranylcypromine suppress phenothiazine catalepsy; note also that imipramine enhances clophelin-induced aggression only upon chronic administration [24]. On the other hand, pyrazidole, in contrast to imipramine and tranylcypromine, does significantly affect the locomotive and temperature effects of β-phenylethylamine.

Pyrazidole is capable of producing both serotoninergic and antiserotonin effects. The drug increases 5-hydroxytryptophan (5-HTP) induced head shaking and tremor in mice and potentiates the serotonin-induced pressor reaction in narcotized dogs. At the same time, pyrazidole decreases contractions in the isolated uterine horn of rat and inhibits the foot edema growth in rat caused by serotonin injections.

Pyrazidole enhances the pressor effects of noradrenaline, thyramine, and phenylethylamine in narcotized dogs, cats, and rats. However, the drug-induced increase (30 – 60%) in the pressor effects of indirectly acting amines is markedly lower as compared to the action of phenelzine (100 – 200% and even greater) [8, 18, 25]. Pyrazidole enhances adrenaline-induced hyperglycemia in rats [26]. The potentiating effect of pyrazidole in this test is not affected by phentolamine and somewhat reduced by propranolol; the effect is not observed upon adrenalectomy, but is restored after cortisole administration [27].

Pyrazidole produces a stimulating action upon the spontaneous encephalogram, ascending activation system in brain, and the functional mobility of cortical neurons. In this respect, the drug differs from imipramine and resembles phenelzine; however, the activating effect of pyrazidole is less pronounced and characterized by a slower onset (30 – 60 min) as compared to the case of phenelzine. On the

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other hand, pyrazidole, similar to imipramine and distinct from phenelzine, stimulates the limbic system as manifested by a decreased threshold of hippocampal convulsions and an increased duration of aftereffect discharges [28].

Pyrazidole, similar to imipramine and distinct from tranylcypromine, decreases the level of picrotoxin-induced tonic convulsions in rats. However neither pyrazidole nor tranylcypromine offer protection against the convulsions caused by maximum electroshock. Pyrazidole, in contrast to imipramine and tranylcypromine, does not increase the duration of sleep caused by hexobarbital and ethanol [18, 19, 29]. In a test for the effect of the drug on the passive avoidance conditional reflex, pyrazidole (similar to imipramine) showed a variable action, stimulating the reflex in doses not exceeding 5 mg/kg and suppressing the conditional reflex manifestations in a dose of 10 mg/kg or above.

An advantage of pyrazidole in comparison to drugs of the imipramine group is the absence of anticholinergic activity. Pyrazidole reduces neither the intensity nor the duration of convulsions induced by arecoline, nicotine, and oxotremorine; in large doses, pyrazidole increases (rather than decreases) the oxotremorine-induced hypothermia [8, 18, 19]. Pyrazidole did not affect depressor response to the acetylcholine injection and the electric current irritation of vagus nerve in narcotized cats [8, 30]. The drug did not show evidence of any mydriatic action [31].

The aforementioned ability of pyrazidole to increase the effects of *L*-DOPA and 5-HTP (catecholamine and indolamine precursors) and to enhance the pressor effects of thyramine and phenylethylamine is evidence that the drug may inhibit the inactivation of monoamines, thus increasing their amount and potentiating their action.

Experiments on rats *in vivo* showed that pyrazidole inhibits deamination of serotonin dopamine, and (to a lower extent) thyramine, while not affecting the deamination of phenylethylamine [32, 33]. Pyrazidole inhibits the monoamine oxidase (MAO) activity in brain to a greater extent than in liver. The MAO activity in brain is restored 24 h after the pyrazidole administration (against 6 h in liver). It was reported that pyrazidole produces no suppressing action upon nonspecific liver enzyme systems [34]. The tissue and substrate specificity of pyrazidole depend neither on the dose nor on the administration schedule (being retained for large doses and chronic administration), in contrast to acetylene amines (such as chlorgilin and deprenyl) losing their selectivity at concentrations 10 – 100 times the effective level [35, 36].

High concentrations (500 μM) of pyrazidole not only inhibit the oxidative deamination of monoamines, but produce a similar effect on the re-uptake of noradrenaline and serotonin in rat brain synaptosomes as well [37]. It was reported that the drug does not significantly affect the presynaptic release of noradrenaline (in sections of cerebral hemispheres) [38]. Pyrazidole probably inhibits the GABAergic system in brain. An indirect evidence may be the fact that diazepam (a GABAergic system activator) offers protection from convulsions induced by pyrazidole in toxic doses [39]. Pyrazidole exhibits low affinity with respect to specific "binding sites" (receptors) of tricyclic antidepressants in brain tissues [40].

The ability of activating neuromediator systems, which accounts for the antidepressant effect of pyrazidole, determines some other valuable properties of this drug as well, including the antiamnesic, antihypoxant, adaptogenic, and anticonvulsant effects. It was established that even a single peroral administration of pyrazidole in a dose of 10 mg/kg reduces the unfavorable effects of maximum electroshock and scopolamine upon the memory function in white rats [41]. The proportion of animals retaining the acquired conditional reflex of passive avoidance increases from 3 and 20% in control groups to 45 and 70% in the groups treated with pyrazidole. Repeated administration of pyrazidole in the same daily dose over a period of four days protected the memory function against the detrimental action of ethanol, as manifested by an almost threefold increase in the number of rats retaining the acquired active avoidance reflex.

The antihypoxant effect of pyrazidole is manifested in doses 2.5 – 5 times greater than the doses effective with respect to the cognitive functions. In these experiments, the drug action was most pronounced in rats with the circulatory hypoxia modeled by ligated carotid arteries (a twofold increase in survival) and with the hemic hypoxia induced by sodium nitrate (300 mg/kg, s.c.), while being less effective in the test animals with hypoxic hypoxia (modeled in a vacuum chamber). Pyrazidole also showed the ability to delay the development of fatigue: the drug increased the endurance of white mice in the test of swimming with load, while not producing a stimulant effect in the test for motor activity [42].

The anticonvulsant activity of pyrazidole is not as pronounced: a 50 mg/kg dose only slightly delays the onset of convulsions induced by thiosemicarbazide in mice, but does not reduce the loss of animals. At the same time, even smaller doses of pyrazidole enhanced the anticonvulsant effect of carbamazepine upon their combined administration [43]. Pyrazidole exhibits both the intrinsic analgesic activity and the ability to enhance the action of analgin and promedol [44].

Of special interest can be the combined administration of pyrazidole with nootropic agents and tranquilizers [45, 46]. We have established that pyracetam is capable of increasing the activity of pyrazidole and other antidepressants. This phenomenon can be used to potentiate the therapeutic effect of these antidepressants (especially in cases of drug-resistant forms of depression) or to reduce the drug dose (for decreasing the side effects). The combined administration of pyrazidole and diazepam leads to a decrease in the calming effect of the latter drug, while its anxiolytic effect is not reduced and the anticonvulsant effect even increases. These features of the pyrazidole activity (distinct from the behavior of imipramine, the presence of which decreases both calming

and anxiolytic effects of diazepam) can be used when it is necessary to inhibit the sedative action of benzodiazepines.

Pyrazidole belongs to the class of low-toxicity drugs. The LD_{50} of pyrazidole for a single peroral administration or intraperitoneal injection is 450 and 175 mg/kg in mongrel white mice and 2000 and 178 mg/kg in rats, respectively. No cases of group toxicity were reported for pyrazidole. In cats, peroral administration of pyrazidole in a dose of 50, 100, or 150 mg/kg leads to certain toxicity manifestations (vomit, convulsions, aggression), but not to the loss of test animals; in contrast, an imipramine dose of 100 mg/kg is lethal. Dogs tolerate peroral administration of pyrazidole in a dose of 75 mg/kg without visual manifestations, a dose of 150 mg/kg leads to vomit and palsied motions, and doses above 500 mg/kg are lethal. The peroral administration of imipramine leads to toxicity effects already in a dose of 60 mg/kg, as manifested by a violated coordination of movements, increased reflector response to tactile and sound irritant factors, and expanded eye pupil [47, 48].

The experimental animals also tolerate well the prolonged repeated administration of pyrazidole. Having received pyrazidole daily (except weekend) over a period of 6 months, dogs (35 and 70 mg/kg, p.o.) and rats (62.5, 125, 250 mg/kg, p.o.) did not exhibit changes in behavior or in the general sate. All the test animals showed good weight gain and exhibited no evidence of dyspepsia; the sections of internal organs did not display pathomorphological changes on the macroscopic or microscopic levels; the peripheral blood morphology as well as the biochemical characteristics of blood and urine also fell within normal limits. However, a change in the pyrazidole administration scheme for rats, whereby the animals received perorally a dose of 200 mg/kg (40 times the therapeutic level) daily over a period of one month without interrupts, leads to capillary plethora and weakly pronounced protein dystrophy in 30% of the test animals. The absence of such phenomena in the rats treated daily over a 6-month period with weekend interrupts is indirect evidence that the drug is rapidly eliminated and the drug-induced changes are reversible [49].

Investigations of the drug effect on the gastrointestinal tract in rats showed that pyrazidole decreases the basal gastric secretion (but to a lower extent than do imipramine, amitriptyline, and desipramine), while not decreasing the evacuator function of the gastrointestinal tract, the appetite (food consumption), and the bladder muscle tone [30, 50, 51]. The effect of pyrazidole on the cardiovascular system is also much less pronounced as compared to that of imipramine [52, 53]. In particular, pyrazidole produce no cardiotoxic effects observed for imipramine and other tricyclic antidepressants. In rats, the intravenous injection of pyrazidole in a dose of 20 mg/kg led only to a decrease in the heart rate, while not affecting the sinus rhythm in all animals tested. The same dose of imipramine produced an arrhythmogenic action, leading in 30% of cases to cardiac arrest and loss of the animals [53]. In dogs, a 20 mg/kg (i.v.) dose of pyrazidole led to no loss of the test animals, whereas imipramine injections in a dose exceeding 5 mg/kg were lethal [52]. Pyrazidole administration in a dose 30 times the maximum recommended human dose neither violated the course of gestation in female rats nor produced embryotoxic and teratogenic effects [47].

The absorption, distribution, and excretion of pyrazidole were studied in rats using a drug preparation with radioactive carbon label [54]. Upon a single peroral administration in a dose of 25 mg/kg, the concentration of the labeled drug was most pronounced in lungs, liver, kidneys, blood plasma, spleen, brain, thymus, heart, adrenal glands, lymph nodes, and muscles. The maximum radioactivity level in all organs was observed 1 – 3 h upon the drug administration (in brain, after 1.5 h and in plasma, after 6 h). The radioactivity half-life in the brain was 6 h, in lungs – 7 h, and in other organs, 9 – 10 h. The elimination halftime for the labeled pyrazidole preparation amounted to 8.6 h. Upon repeated administration (25 mg/kg) for 10 or 24 days, both the distribution of pyrazidole in organs and tissues and the elimination kinetics were the same as those observed for the single drug introduction.

The results of the clinical investigations showed that the therapeutic properties of pyrazidole are not completely similar to those of the known antidepressants. Pyrazidole possesses a unique spectrum of psychotropic effects: the main antidepressant (thymoanaleptic) action is combined with a special regulating influence upon the CNS, which is manifested in the activating effect for patients with depression of the apathic and anergic type, and in the calming effect for patients in agitated states. This “balancing” action of pyrazidole, markedly expanding the clinical use of this drug, accounts for its efficacy in the treatment of both simple melancholic syndromes with predominantly psychomotor retardation and a large number of atypical depression states, frequently characterized by a mixed affect [14 – 17, 55 – 57].

The thymoanaleptic action of pyrazidole is manifested by elimination of the depression symptoms, irrespective of the variant of depression. In the first stage, the drug reduces the expression of vital melancholy (frequently, up to its complete vanishing), psychic anesthesia, and psychomotor retardation; then, the drug action leads to a decrease in senescent-hypochondriac disorders, obsession syndrome, depressive delusion, and other depression menifestations. The positive effect is usually observed 3 – 5 days after the beginning of therapy and is most pronounced on reaching an optimum individual daily drug dose for each patient (in most cases, within 150 – 300 mg). The calming effect of pyrazidole, albeit much less pronounced as compared to that of sedative antidepressants, is still sufficient for the treatment of moderate anxiety depression. In heavier anxiety depression states, adding neuroleptics may be necessary. Pyrazidole administration, in contrast to that of amitriptyline, does not lead to drowsiness in the daytime.

The stimulating action of pyrazidole is softer as compared to that of the classical antidepressants belonging to

MAO inhibitors, imipramine, and other antidepressants-stimulators. Cases of hyperstimulation under the action of pyrazidole are seldom and are manifested by the appearance or enhancement of producive psychopathologic symptoms only in patients with certain variants of schizophrenic depression. From the data of various researchers, the expression of calming (sedative) and stimulating components in the spectrum of pyrazidole action may be different. In [14], both components appeared simultaneously and were independent of the drug dose; according to [17], the activating action of pyrazidole is more pronounced for a daily dose of 75 – 125 mg/kg, while the drug administration in doses exceeding 200 mg/kg is accompanied by increasing sedative action. From the data of [56 – 59], the stimulating component is pronounced earlier and stronger, while in [15] the calming component was reported to exceed the stimulating effect.

The most favorable results, rated as good or very good, were observed upon pyrazidole administration in patients with (generally, not too heavy) neurotic, adynamic, "masked" depression, and asthenodepressive states. In particular, pyrazidole was effective in patients with hypochondriac, asthenic, and depersonalization depression and in those showing rather heavy melancholic depression. On the contrary, the positive drug effect was least pronounced in cases of depressive delusion and heavy retarded anxiety depression [14 – 17, 55 – 61]. However, it was reported that the ability of pyrazidole to act upon heavy endogenous depression states (developed within the framework of maniacal-depressive psychosis or schizophrenia) increases when the drug is administered in a daily dose of 400 mg/kg [14].

Pyrazidole was administered to patients with alcoholic addiction in order to reduce depression and anxiety-depressive state manifestations, especially in the abstinence stage [62, 63]. It should be noted that pyrazidole was also rather effective in treating depressive states in patients with organic disorders [56], including cases of endogenous-organic oligophrenia characterized by increased risk of secondary (with resect to mental deficiency) psychopathologic disorders (e.g., of the depressive background development) [64].

A good tolerance of pyrazidole for patients and the absence of undesirable somatic and vegetative changes upon the drug administration were reported after all clinical investigations. In patients suffering from depression and where tricyclic antidepressants are counterindicated, for example, because of certain cardiovascular disorders and side effects (tachycardia, arrhythmia, etc.) caused by drugs belonging to this group, the administration of pyrazidole affected neither the heart rhythm nor the arterial pressure and ECG [55]. Having no prohibitions for use in patients with arterial hypertension, arrhythmias, ischemic heart disease, and cerebral atherosclerosis, pyrazidole can be recommended for the treatment of depressive states in these patients [65, 66]. The drug relieves neurotic reactions with depressive background, which arise in cases of stenocardia and myocardial infarction and complicate the course of disorders [67, 68].

Pyrazidole produced no negative effects in patients with narrow-angle glaucoma, which is an absolute counterindication for the use of tricyclic antidepressants. It was reported [55] that the treatment of depression complicated by urine retention caused by amitriptyline was successfully completed upon the passage to pyrazidole. Side effects such as xerostomia, sweating, weakness, and dysaccommodation inherent in tricyclic antidepressants are usually insignificant with pyrazidole and do not restrict its administration [14, 15, 57, 59, 60, 69 – 72]. An obvious advantage of pyrazidole is its compatibility with a wide range of drugs used for the treatment of somatic diseases, which makes it possible to use pyrazidole for treating psychic disorders in somatic patients [14, 15, 73 – 75]. In some cases, pyrazidole administration to such patients led to pronounced vegetostabilizing effect [76].

In view of the positive effect of pyrazidole upon the cognitive functions, pyrazidole may be used in the complex therapy of patients suffering from senile dementia, including Alzheimer's disease [77]. Since, as noted above, pyrazidole exhibits no negative effects upon the gastrointestinal tract, the drug can well be used for the treatment of psychic disorders in patients suffering from cardiospasms and irritable bowel syndrome [78, 79]. It was reported that pyrazidole was successfully used for treating migraine in patients with pronounced emotional disorders against a depressive syndrome background [80]. The good tolerance of pyrazidole allows this drug to be used in gerontologic practice, as well as for the therapy of younger patients, including teenagers and children aged below 6, under both clinical and ambulatory conditions [81].

Counterindications for the administration of pyrazidole are acute inflammatory liver diseases and hemopoietic system disorders. The drug cannot be administered until two weeks after the use of other antidepressants belonging to the class of MAO inhibitors. During pyrazidole administration, it is not recommended to use adrenaline and other sympathomimetics because the reaction of the organism to these agents may be enhanced against the background of the anti-MAO activity of pyrazidole.

Pyrazidole is usually administered perorally in a daily dose beginning with 0.05 – 0.075 g (50 – 75 mg) in two takes, with gradual increase of the level by 0.025 – 0.05 g steps. The therapeutic effect is typically achieved after 7 – 14 days of therapy with a daily dose of 0.15 – 0.3 g. When necessary (and provided that the drug is well tolerated) the daily dose can be increased to 0.4 g. On reaching the therapeutic effect, treatment with this individual dose of pyrazidole is continued for another 2 – 4 weeks, after which the dose is gradually decreased. In patients suffering from neurotic and reactive depressions, pyrazidole is administered in lower doses. Pyrazidole is available in the form of 0.025 and 0.05 g (25 and 50 mg) tablets in 50, 100, 500, and 1000-stick packages. The drug is stored under conditions according to List B.

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