SEARCH FOR NEW DRUGS

DOMESTIC ANTIDEPRESSANTS. 2. PYRAZIDOLE (PIRLINDOLE)

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Original article submitted May 18, 2000.

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 – 1970s [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). 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 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 serotonergic 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 cortisone 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 tyramine 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) tyramine, 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 chlorgolin 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 antiemetic, antihypoxant, adaptogenic, and anticonvulsant effects. It was established that even a single peroral administration of pyrazidole in a dose of 15 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 33% 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