Pyrazidol, a new drug with antidepressant properties

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Searching for new psychotropic drugs, several pyrazinoindole derivatives have been synthesized at the All Union Chemical Pharmaceutical Research Institute[1]. These compounds derive from a new heterocyclic system formed by an indole condensed with a pyrazine or piperazine ring. Structurally, they resemble harmine, reserpine and other indole alkaloids which possess psychotropic activity. As indole derivatives, they are also analogs of serotonin.

Pharmacological investigations performed in our laboratory have shown that some of these compounds possess antidepressant properties. One of the most active is the hydrochloride of 1,10-trimethylene-8-methyl-1,2,3,4-tetrahydropyrazino-(1,2 a) indole, named pyrazidol (Fig. 1) which has been introduced in medical practice as antidepressant.

[Chemical structure of pyrazidol]

Fig. 1. — Pyrazidol.

The mechanism of action of antidepressants is strictly connected with their effect on brain monoamines. According to Schiffrin's hypothesis[2], affective disorders are related to a catecholamine insufficiency or hyperactivity. Carlsson[3] emphasized the duality of monoaminergic component of depression to which either catecholamines or serotonin participate, while Lapin[4] has underlined the role of serotonin in the pathogenesis...
of these diseases. Recently, the catecholaminergic hypothesis of Schildkraut [5] about the pathogenesis of affective disorders has been completed taking into account serotonin and other neurochemical principles.

The activity of antidepressant drugs has been related to their effect on various monoaminergic processes of the brain [2, 5]. They are classically divided into two groups according to the postulated mechanism of action. The first group includes compounds which inhibit the neuronal uptake of monoamines; the second group includes the monoamine oxidase inhibitors.

Pyrazinoindole derivatives differ chemically from any known antidepressant. Pyrazidol in particular is a tetracyclic compound and its neurochemical mechanism of action includes effects characteristic of the two groups of antidepressants. The drug exerts in fact a combined action, inhibiting both neuronal uptake and monoamine oxidase activity. Moreover, it differs from the classic tricyclic antidepressants because it is devoid of anticholinergic activity.

Pyrazidol antagonizes the depressant effects of reserpine and of tetrahenazine, which is a characteristic of the representatives of both groups of antidepressants. The central noradrenergic effect of pyrazidol is instead shown by its potentiation of the amphetamine stereotyped behaviour in rats and amphetamine group-toxicity in mice. Furthermore, pyrazidol increases the tremorogenic action of tryptamine, the 1-dopa hypermotility and the 5-hydroxytryptophan-induced head-twitches. Blood pressure effects exerted by noradrenaline, serotonin, tyramine, β-phenylethylamine and tryptamine in cats and dogs are also potentiated.

These data show that pyrazidol interacts with several monoaminergic activities. In fact, the observed effects can be induced by two mechanisms, i.e., by inhibiting the neuronal uptake of the monoamines released from nerve terminals, thus enhancing their action on the postsynaptic membrane, or by decreasing their intracellular deamination, through an inhibition of mitochondrial monoamine oxidase activity.

Pyrazidol has been shown to affect both these processes. The drug inhibits the neuronal uptake of noradrenaline by rat myocardium, according to Iversen procedure. It has also been found, in a joint research with Dr. Raevsky [6] that pyrazidol inhibits the noradrenaline uptake by brain synaptosomes. In studies carried out in collaboration with Gorkin [7], it was demonstrated that pyrazidol exhibits an anti-monoamine oxidase activity. As a MAO inhibitor, pyrazidol mainly affects the deamination of serotonin and only slightly acts on the deamination of tyramine (Fig. 2). This peculiarity of pyrazidol action is of relevance in the framework of the present knowledge about the multiplicity of monoamine oxidases. It is also important from the practical point of view, since the side effects caused by typical MAO inhibitors (iproniazid, tranylcypromine) are mainly connected with their inhibitory
Fig. 2. — Inhibition of the biogenic amines deamination (%) in rat brain and liver homogenates.
Mean values (± S. E.) from five–six experiments involving inhibition of tyramine [1], dopamine [2] and serotonin [3] deamination by pyrazidol in brain (A) and liver (B). Abscissa: pyrazidol doses in mg/kg i.p.
Fig. 3. — Duration of the MAO-activity inhibition induced by pyrazidol (75 mg/kg i. p.) in rat brain and liver. Mean values (± S. E.) from three–six experiments (with two parallel estimations in each experiment) involving inhibition of tyramine [1], dopamine [2] and serotonin [3] in brain (A) and liver (B). Abscissa: time after the administration.
effect on the deamination of tyramine. Moreover, the anti-MAO action of pyrazidol is reversible and of short duration. In fact, while the effects of iproniazid persists for several days [8], that of pyrazidol — according to our results — lasts for only a few hours (Fig. 3).

The combined mechanism of action of pyrazidol has considerable interest since it may play a definite role in the mode of action and in the therapeutic effect of this derivative.

Up to date, pyrazidol has been clinically studied in about 1000 patients with various types of depressions. Favourable results have been obtained in percentages ranging from 65 to 85% of the cases, according to the severity of the clinical forms. Side effects were rarely observed in the course of pyrazidol therapy. The lack of anticholinergic activity allows pyrazidol to be administered to patients in whom treatment with classic antidepressants (amitryptiline, etc.) is contraindicated. On the basis of these results, the drug can be classified as a new antidepressant whose chemical properties resemble the drugs belonging to the median part of the Kielholz classification of antidepressants [9].

Summary. — During the search for new psychotropic drugs, a group of pyrazinoindole derivatives have been synthetized at the All Union Chemical Pharmaceutical Research Institute. Especially effective and having antidepressant activities is the hydrochloride of 1,10-trimethylene-8-methyl-1,2,3,4-tetrahydropyrazino (1,2-a) indole, named pyrazidol. Pyrazidol differs from any already known antidepressant for its chemical structure, the general pattern of activity and its neurochemical mechanism of action. The drug combines an inhibiting action on the neuronal uptake of monoamines with a monoamineoxidase inhibiting activity. As MAO-inhibitor, pyrazidol mainly impairs serotonin deamination, and acts only slightly on tyramine deamination. Furthermore, the anti-MAO action of pyrazidol is of short duration. Then, pyrazidol constitutes a drug with a particular profile of therapeutic activity.

REFERENCES


