Pharmacological Research, Vol. 36, No. 1, 1997

PIRLINDOLE: A SELECTIVE REVERSIBLE INHIBITOR OF MONOAMINE OXIDASE A. A REVIEW OF ITS PRECLINICAL PROPERTIES

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Accepted 30 May 1997

Pirlindole is a tetracyclic compound that has been characterized as a potential antidepressant drug. It has pharmacological characteristics in common with both tricyclic antidepressants and classical irreversible monoamine oxidase inhibitors. Its main mechanism of action consists of a selective and reversible inhibition of monoamine oxidase A. Secondarily, it exerts an inhibitory effect on noradrenaline and 5-hydroxytryptamine reuptakes. It has no effect on the dopaminergic and cholinergic systems. It has only a low potential for amplifying tyramine and noradrenaline pressor effect, which makes one expect that it will not be at the basis of a 'cheese effect'. Pirlindole has an absolute bioavailability of between 20 and 30% due to an extensive first-pass effect. Orally, the T_{max} varies between 2.5 and 6 h in the rat and 0.8 and 2 h in the dog. Two phases of elimination (7.5 and 34–70 h) are measured in the rat and three phases in the dog (1.3, 10.8 and 185 h); it is extensively metabolized. The rat eliminates mainly unconjugated products while the dog eliminates mostly conjugated products. Acute and chronic toxicological studies have not revealed potentially dangerous effects of the drug at the usual doses. It does not present measurable mutagenic, clastogenic or carcinogenic properties. Thus, pirlindole shows pharmacological, pharmacokinetic and toxicological properties which make it suitable for the management of depression.

KEY WORDS: pirlindole, reversible inhibitor of monoamine oxidase A, antidepressant.

INTRODUCTION

Pirlindole hydrochloride (2,3,3a,4,5,6-hexahydro-8-methyl-1*H*-pyrazino [3,2,1-*jk*]-carbazole HCl) (pyrazidol) (Fig. 1) is a tetracyclic molecule that had been synthesized in the USSR by the end of the 1960s and now there has been a renewal of interest in it due to its original mechanism of action. It acts as a selective and reversible inhibitor of monoamine oxidase A (RIMA), is active in several pre-clinical tests predictive of antidepressant properties and is now in late clinical phase III in major depression. It possesses an asymmetrical carbon (Fig. 1) and is thus constituted of two enantiomers (*R*-(−)-pirlindole and *S*-(+)-pirlindole) in a ratio of 50:50. The three molecules are active and show the same antidepressant profile with some slight differences, the racemic compound constituting a golden mean between the two enantiomers. The aim of this paper is to give an overview of the pre-clinical (pharmacology, pharmacokinetics and toxicology) properties of pirlindole.

Pharmacology

Special pharmacodynamics

Behavioural pharmacology (Table I). Pirlindole is active in the Porsolt's model (forced swimming test) in which it significantly decreases the immobility time when acutely (10–20 mg kg^{-1} i.p. in the rat [1] and 5–25 mg kg^{-1} i.p. in the mouse [2–4]) or chronically (10 mg kg^{-1} i.p. twice daily for 14 days in the mouse [2]) administered. Its potency is equivalent to that of classical tricyclic antidepressants such as imipramine, amitriptyline or desipramine and to that of classical monoamine oxidase inhibitors (MAOIs) such as tranylcypromine. The two enantiomers of pirlindole are also active in the forced swimming procedure in the mouse: *R*-(−)-pirlindole decreases

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1043–6618/97/070023–11/$25.00/0/fr970196

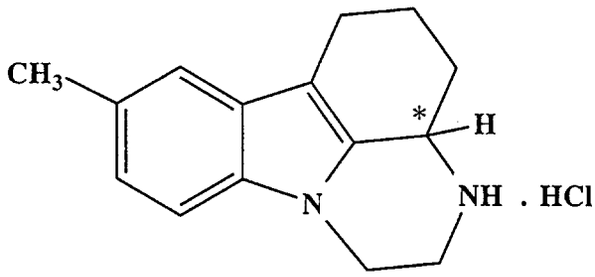

Fig. 1. Molecular formula of pirlindole hydrochloride. * asymmetric carbon.

the immobility time at the dose of 1 mg kg^{-1} i.p. and is inactive for higher doses. *S*-(+)-pirlindole decreases the immobility time at 25 mg kg^{-1} i.p. while lower and higher doses are inactive. The racemic compound is active between 5 and 25 mg kg^{-1} i.p. with a clear dose–effect relationship [4].

The lesion of the rat internal capsule at the level of the fornical decussation reduces the electrical self-stimulation of the medial forebrain bundle. This hypoactive reward system presents some analogy with depression. Pirlindole (10 mg kg^{-1} i.p.) chronically administered for 5 days produces an increase in self-stimulation behaviour, an effect also encountered with other antidepressants such as imipramine (5–10 mg kg^{-1} i.p.) or tranylcypromine (5 mg kg^{-1} i.p.) [5].

Following the exposure to an inescapable electric shock, a marked deficit in the learning of escape/avoidance performance is generally observed in the mouse. This deficit can specifically be modulated and improved by antidepressants. This is also the case with a chronic (7–14 days) administration of pirlindole (10 mg kg^{-1} i.p.) [2].

Like other antidepressants, pirlindole (1–50 mg kg^{-1} i.p. [1, 6, 7], 2.5–50 mg kg^{-1} p.o. [8, 9]) is able to antagonize the reserpine-induced blepharoptosis and hypothermia in mice and also the tetrabenazine-induced blepharoptosis (25 mg kg^{-1} p.o. in the mouse [6], ED_{50} = 13.66 mg kg^{-1} i.p. in the rat [1]) and catalepsy (ED_{50} = 13.39 mg kg^{-1} i.p. in the rat [1]).

Pirlindole (10–25 mg kg^{-1} p.o. [6], 5–20 mg kg^{-1} i.p. [10]) like imipramine [6], nialamide [10] and clorgyline [10] exerts a dose-dependent potentiation of amphetamine stereotypy in the rat, but it is largely less active than the three other compounds.

Pirlindole (25 mg kg^{-1} s.c. [6], 1–25 mg kg^{-1} i.p. [7] or 25 mg kg^{-1} p.o. [8]), contrary to imipramine (25 mg kg^{-1} s.c.) and amitriptyline (25 mg kg^{-1} s.c.) is unable to antagonize apomorphine-induced hypothermia in the mouse. It (ED_{50} > 65 mg kg^{-1} i.p.) does not antagonize fluphenazine-induced catalepsy in the rat contrary to imipramine (ED_{50} = 26.9 mg kg^{-1} i.p.) and tranylcypromine (ED_{50} = 4.6 mg kg^{-1} i.p.) [1].

The increase in ipsilateral rotations in the rat in response to *d*-amphetamine after destruction of the mesostriatal dopaminergic system with 6-hydroxydopamine is related to the release of dopamine and to the blockade of its reuptake. Nomifensine (5–20 mg kg^{-1} i.p.) is able to attenuate these rotations by

Table I
Comparison of the behavioural and electrophysiological properties of pirlindole (PIRL), tricyclic andidepressants (TCAs) and non-selective monoamine oxidase inhibitors (MAOIs)

Pharmacological tests	*PIRL*	*TCAs*	*MAOIs*
Decrease of immobility in the forced swimming test (Porsolt's model)	‡	‡	‡
Inhibition of electrical self-stimulation	‡	‡	‡
Inhibition of the deficit in escape/avoidance learning due to an inescapable shock	‡	‡	‡
Antagonism of reserpine-induced blepharoptosis and hypothermia	‡	‡	‡
Antagonism of tetrabenazine-induced blepharoptosis and catalepsy	‡	‡	‡
Potentiation of amphetamine stereotypy	†	‡	‡
Antagonism of apomorphine-induced hypothermia	*	‡	—
Antagonism of fluphenazine-induced catalepsy	*	‡	‡
Potentiation of 5-hydroxytryptophan-induced head twitches	†	*	‡
Potentiation of tryptamine-induced clonic seizures	†	*	‡
Antagonism of oxotremorine-induced hypothermia and tremors	*	‡	*
Antagonism of diazepam-induced sedation	‡	§	—
Inhibition of the anxiolytic effect of diazepam	*	†	—
Prevention of loss of the righting reflex induced by nitrazepam	‡	‡	—
Decrease of the firing rate of NA and 5-HT neurons	*	‡	*
EEG modifications (activation pattern)	‡	—	§

Notes: *inactive; †mild effect; ‡significant effect; §significant opposite effect; —not tested.

a selective inhibition of dopamine reuptake. Pirlindole (5–20 mg kg^{-1} i.p.) appears completely inactive in this test [10].

Pirlindole ($ED_{50} = 20$ mg kg^{-1} i.p. [6–7] or 11.4 mg kg^{-1} i.p. [1]) potentiates the 5-hydroxytryptophan-induced head twitches in mice. In contrast, imipramine ($ED_{50} > 50$ mg kg^{-1} i.p.) showed no effect in this test. Tranylcypromine showed an $ED_{50} = 1.41$ mg kg^{-1} i.p. [1].

Pirlindole ($ED_{50} = 25$ mg kg^{-1} p.o. [6] or 11.07 mg kg^{-1} i.p. [1]) potentiates the clonic seizures induced by tryptamine in the rat. In contrast, imipramine ($ED_{50} > 35$ mg kg^{-1} i.p.) is inactive in this test. Tranylcypromine showed an $ED_{50} = 0.99$ mg kg^{-1} i.p. [1].

Contrary to imipramine, nomifensine, viloxazine, maprotiline and mianserin, pirlindole (25 mg kg^{-1} s.c., 50 mg kg^{-1} p.o. or 30 mg kg^{-1} i.p.) like tranylcypromine (8 mg kg^{-1} i.p.) appears unable to antagonize oxotremorine-induced hypothermia or tremors in the mouse [1, 6, 9]. It has no effect on the convulsant activity of arecoline [8] or nicotine in mice [9].

In mice and rats, pirlindole (10–25 mg kg^{-1} p.o.) is able to antagonize the sedative action of diazepam while imipramine (10–25 mg kg^{-1} p.o.) reinforces this effect. However, pirlindole has no effect on the anxiolytic activity of diazepam but imipramine decreases this activity. Pirlindole, like imipramine, is able to prevent the loss of the righting reflex due to the administration of nitrazepam (25 mg kg^{-1} i.p.) [11].

Pirlindole (100–250 mg kg^{-1} p.o.) has no effect on the sleeping time induced by hexobarbital or amobarbital [6] and it does not potentiate the hypnotic effect of hexenal in the rat [9].

The risk of drug addiction with pirlindole is very low since experiments in Rhesus monkeys demonstrate that it (0.01–1.00 mg kg^{-1} i.v.) did not reinforce intravenous self-administration behaviour [12].

Electrophysiology (Table I). Pirlindole (1 mg kg^{-1} min^{-1} i.v. during 10 min) does not significantly modify the firing rate of neurons in the locus coeruleus and in the dorsal raphe nucleus of the rat. It therefore seems to have no influence on the electrical activity of central noradrenergic and serotonergic neurons. In this respect, it differs from tricyclic antidepressants and selective serotonin reuptake inhibitors that decrease the firing rate of monoaminergic neurons. Pirlindole is more comparable to clorgyline, another MAOI, that does not modify the electrical activity of the locus coeruleus and dorsal raphe nucleus neurons [13].

In the squirrel monkey, pirlindole (5 mg kg^{-1} p.o.) produces EEG modifications (increase in higher frequencies, beta and gamma waves) indicative of central nervous system activation without any overt motor stimulating activity. The situation is different with tranylcypromine (5 mg kg^{-1} p.o.) that produces a shift to lower frequencies [5]. Low doses of clonidine induce a synchronization of the EEG in the rabbit and particularly an increase of 60% in the relative power of the theta rhythm. Pirlindole (10 mg kg^{-1} i.v.) is able to antagonize the clonidine synchronizing effect [14]. On the contrary, high doses of clonidine induce a desynchronization in all the brain structures with a complete disappearance of delta and theta rhythms. Pirlindole (10 mg kg^{-1} i.v.) amplifies this desynchronization phenomenon [14].

Neurochemistry (Table II). *In vitro*, pirlindole inhibits rat brain MAO-A with an $IC_{50} = 250$ nM [15, 16] and heart MAO-A with an $IC_{50} = 34.2$ nM [15]. The two enantiomers of pirlindole are active with IC_{50}s respectively equal to 380 nM for *R*-(−)-pirlindole and 170 nM for *S*-(+)-pirlindole. Brain and heart MAO-B inhibition is obtained with much higher K_i, respectively 52,100 nM and 59,900 nM [15, 17]. *Ex vivo*, the inhibition of rat MAO activity with pirlindole (10–150 mg kg^{-1} i.p.) is the most important in the brain where it returns to baseline after 24 h. In the liver, deamination of serotonin is inhibited by 35–50% within 30 min while the deamination of tyramine and dopamine remains unaffected. The maximal inhibition of deamination of tyramine, dopamine and serotonin is observed after 3 h and returns to normal values within 6 h after the administration [6]. Another study shows that 1 h after injection of pirlindole (10 mg kg^{-1} i.p.) in rats, MAO activity is unchanged in the liver while enzyme activity in the brain is reduced to half of its initial value. This result is probably due to the fact that pirlindole reaches higher concentrations in the brain than elsewhere in the organism. Comparatively, pargyline (10 mg kg^{-1} i.p.) induces a strong and irreversible MAO inhibition both in the liver and in the brain [18]. A recent study [16] demonstrates that the ED_{50} of pirlindole for the selective inhibition of MAO-A in the rat is equal to 21 mg kg^{-1} i.p.. For the two enantiomers of pirlindole the ED_{50}s are respectively, equal to 32.5 mg kg^{-1} i.p. for *R*-(−)-pirlindole and 16 mg kg^{-1} i.p. for *S*-(+)-pirlindole. On the contrary, MAO-B is inhibited by approximately 30% for the highest dose of both the racemic compound and the two enantiomers (50 mg kg^{-1} i.p.). The extrapolation of the ED_{50} for the selective inhibition of MAO-B with pirlindole gives a value equal to 163 mg kg^{-1} i.p.

In vitro, using rat brain synaptosomes, the IC_{50} of pirlindole for catecholamines and serotonin uptake inhibition is always superior to 1 μM [18]. In rat cerebral cortex slices the IC_{50} for the inhibition of the reuptake of [^{3}H]noradrenaline and [^{3}H]serotonin are 6.7 and 7.9 μM, respectively. Comparatively the IC_{50} of imipramine are 0.2 and 0.44 μM, respectively [3]. A recent study demonstrates that racemic pirlindole or its *R*-(−) and *S*-(+) enantiomers inhibit NA

Table II
Comparison of the inhibitory potencies of reversible *vs* irreversible MAOIs on rat brain MAO-A and B activity *in vitro* and *ex vivo*

Compound	*IC_{50} (μM)*			*ED_{50} (μmol kg^{-1})*		
	MAO-A	*MAO-B*	*MAO-B / MAO-A*	*MAO-A*	*MAO-B*	*MAO-B / MAO-A*
Pirlindole*	0.25	52.1	208	92.5	721	7.8
Moclobemide†	6	> 1.000	> 170	8	78	9.8
Brofaromine†	0.013	31	2,400	5	> 1,000	> 200
Phenelzine†	0.015	0.033	2.2	72	91	1.3
Isocarboxazid†	0.30	0.018	0.06	17	7	0.4
Tranylcypromine†	0.18	0.74	4.1	12	4	0.3

*Results of Gérardy and Dresse [16] and Schraven and Reibert [15].
†Adapted from Da Prada *et al.* 1989, *J. Neurol Transm*., **28** (Suppl.) 5–20.
Preclinical profiles of the novel reversible MAO-A inhibitors, moclobemide and brofaromine, in comparison with irreversible MAO inhibitors.

reuptake in rat brain synaptosomes with an IC_{50} equal to 28.5, 10.0 and 17.7 μM, respectively [19]. In fact the results seem to depend largely on the choice of the preparation used to determine inhibition of reuptake. For serotonin, pirlindole presents an IC_{50} equal to 3.7, 74.7 and 26.2 μM according to the preparation, rat cortex homogenates, human cortex homogenates and rat brain synaptosomal preparations, respectively [19]. No affinity is detected for the dopamine reuptake with concentrations up to 0.1 mM [19]. In rat synaptosomal preparations, pirlindole (up to 50 μM) does not affect [^{3}H]GABA and [^{3}H]glutamate uptakes [2]. Peripherally, in rat heart, pirlindole (1 μM) inhibits noradrenaline uptake by 64% while imipramine (1 μM) inhibits this uptake by 53% [6].

For concentrations up to 10 μM, pirlindole does not produce any effect on the spontaneous release of dopamine. A slight but significant increase of the electrically-stimulated release of dopamine was measured for concentrations situated between 0.1 nM and 10 nM [20]. Pirlindole increases the electrically-induced release of noradrenaline and serotonin by a factor of 2 in rat cortex slices at concentrations respectively equal to 4.5 and 34 μM. Imipramine induces the same effect at 0.26 and 4.9 μM [3].

In vivo, in rat cortex slices, pirlindole (30 mg kg^{-1} i.p.) has no effect on [^{3}H]noradrenaline uptake but inhibits [^{3}H]serotonin uptake by 23%. Comparatively, imipramine (20 mg kg^{-1} i.p.) inhibits the two uptakes by 46 and 15%, respectively [7]. When chronically administered, pirlindole (10 mg kg^{-1} p.o. during 20 days) induces an increase in the affinity of α_1 and β adrenergic receptors and an increase in the α_2 receptor number without any effect on 5-HT2 receptors in the rat prefrontal cortex. In the hippocampus, it produces an increase in the number of α_1 and α_2 receptors and an increase in the affinity of β and 5-HT2 receptors [21]. These results are not confirmed by another study showing that pirlindole (10 or 20 mg kg^{-1} p.o. twice daily for 18 days) decreases the K_d value of [^{3}H]prazosin binding without affecting [^{3}H]dihydroalprenolol binding parameters [7].

Pirlindole (10–40 mg kg^{-1} s.c. [22], 50 mg kg^{-1} i.p. [23]) causes a clear elevation of noradrenaline levels in all rat brain structures but particularly in the hypothalamus. The same phenomenon is observed with tranylcypromine (5 mg kg^{-1} s.c.). No significant modification is observed for dopamine and HVA levels. Pirlindole (40 mg kg^{-1} s.c. [22], 50 mg kg^{-1} i.p. [23]) leads to a significant elevation of serotonin levels in the hypothalamus, cortex and raphe nucleus and to an increase in 5-HIAA levels only in the raphe nucleus. In another study, pirlindole (25 mg kg^{-1} i.p. administered three times within 24 h) increases the level of serotonin by 37% and decreases the level of 5-HIAA in the rat [24].

General pharmacodynamics

Nervous system (Table III). In the Irwin test, non-toxic but high doses (up to 324 mg kg^{-1} i.p.) of pirlindole lead to ataxia, marked motor disturbances, tremor and clonic spasms. The same observation is made with imipramine and tranylcypromine. The drug has anticonvulsive properties in the mouse since it protects against picrotoxin-induced tonic spasms (15–30 mg kg^{-1} i.p.) of the pelvic limbs [25]. Pirlindole does not produce any sedative effect in the mouse up to 40 mg kg^{-1} i.p. and no induction of sleep can be detected in the hexobarbital test. In contrast, imipramine and tranylcypromine are active in this test [25]. Like imipramine, pirlindole (10–30 mg kg^{-1} i.p.) has analgesic properties in various tests such as acetic acid-induced stretch reflexes in the mouse and carrageenin-induced paw edema in the rat as well as a local anaesthetic effect (0.3% solution) in the guinea pig [25].

Cardiovascular system (Table III). Pirlindole produces no change in the awakened dog ECG from 1.5 to 25 mg kg^{-1} p.o. On the contrary with imipramine,

Table III
Comparison of the general pharmacodynamic properties of pirlindole (PIRL), tricyclic antidepressants (TCAs) and non-selective monoamine oxidase inhibitors (MAOIs)

Pharmacological tests	*PIRL*	*TCAs*	*MAOIs*
Central nervous system			
Irwin test: ataxia, motor disturbances, tremor and clonic spasms	†	†	†
Antagonism of picrotoxin-induced tonic spasms	‡	‡	‡
Potentiation of sedation-induced by hexobarbital	*	‡	‡
Analgesic effect in the acid-induced stretch reflexes and carrageenin-induced paw edema tests	‡	‡	‡
Cardiovascular system			
Changes in the ECG of awakened dogs	*	‡	§
Changes in blood pressure in the dog	†	‡	‡
Changes in cardiac contractility in the dog	*	‡	§
Decrease in blood pressure in the spontaneous hypertensive rat	‡	‡	‡
Increase of the pressor effect of tyramine:			
intensity	†	§	‡
duration	†	§	‡
Increase of the pressor effect of noradrenaline	†	‡	§
Inhibition of platelet aggregation	†	*	*

Notes: *inactive; †mild effect; ‡significant effect; §not tested.

changes start from 6 mg kg^{-1} p.o. and at 15 mg kg^{-1} p.o. a myocardial ischemia is noted. By the intravenous route, pirlindole has only mild effects on dog blood pressure (up to 10 mg kg^{-1} i.v.), whereas imipramine and tranylcypromine exhibit toxic effects at this dose. Contrary to imipramine, for example, pirlindole has no effect on the contractility of the heart [26, 27]. In the anaesthetized cat, pirlindole (0.5–10 mg kg^{-1} i.v.) produces a dose-dependent decrease in arterial pressure with a return to baseline within 15 min. Imipramine produces a more marked hypotensive effect and a respiratory arrest is recorded at 5 mg kg^{-1} i.v. [28]. Pirlindole (25 mg kg^{-1} p.o.), imipramine (25 mg kg^{-1} p.o.) and tranylcypromine (5 mg kg^{-1} p.o.) lead to a significant decrease in blood pressure in the spontaneous hypertensive rat [25]. In the rat, the pressor effect of tyramine is increased by pirlindole (25 mg kg^{-1} p.o.), moclobemide (25 mg kg^{-1} p.o.) and tranylcypromine (2.5 mg kg^{-1} p.o.). The effect of tranylcypromine is 12 times more important than that of moclobemide and pirlindole and lasts at least 24 h while it lasts 3 h with pirlindole and 6 h with moclobemide [29]. In a second series of experiments using the intravenous route, pirlindole (2.5 mg kg^{-1} i.v.) and moclobemide (2.5 mg kg^{-1} i.v.) are only able to prolong and not to amplify the tyramine effect during 1 h [29]. In the anaesthetized dog, the pressor effect of tyramine is increased by pirlindole only above 5 mg kg^{-1} i.v., whereas it is potentiated by tranylcypromine at 0.3 mg kg^{-1} i.v. [30]. In the dog, the pressor effect of noradrenaline is amplified (26%) by pirlindole only from 10 mg kg^{-1} i.v. [27]. Imipramine on the other hand significantly potentiates the noradrenaline effect by 50%, 52% and 67% at 1.0, 2.5 and 5 mg kg^{-1} i.v., respectively [27]. Pirlindole (100 mg kg^{-1} p.o.) slightly inhibits platelet aggregation in the rat while imipramine and tranylcypromine do not affect or slightly increase aggregation [25]. *In vitro*, pirlindole (3 μg/ml) prolongs the refractory period of the electrically-induced contraction of rabbit's cardiac auricle [28].

Other systems. Pirlindole (30 mg kg^{-1} s.c.) only leads to a minimal inhibition of the period of intestinal transit in the mouse. In contrast, the same dose of imipramine causes an inhibition of peristalsis in all animals [25]. At 50 mg kg^{-1} p.o. in the rat, pirlindole leads to a marginal inhibition of diuresis while at 5 mg kg^{-1} p.o. it non-significantly elevates it. It causes a moderate elevation in sodium and potassium elimination with almost an unchanged chloride elimination [25]. Pirlindole is able to inhibit electrically-induced contractions of the rat vas deferens. Low concentrations (0.1–1.0 μg ml^{-1}) increase the contractions induced by noradrenaline while higher concentrations (> 10 μg/ ml^{-1}) induce the inverse effect. When contractions are induced by $BaCl_2$, pirlindole is spasmolytic from a concentration of 50 μg ml^{-1} [31]. Finally, pirlindole does not influence metabolic parameters in animals. In the rat, after a chronic administration of pirlindole (20 mg kg^{-1} day^{-1} p.o. for 7 days), cholesterol, triglycerides, sugar, uric acid, body weight and food consumption are not affected. An increase in liver weight of 7% is measured as well as a slight reduction in VLDL and LDL with an increase in HDL [32]. In the rat and the rabbit, pirlindole (5–20 mg kg^{-1} p.o.) has no influence on blood glucose concentration [33, 34].

Pharmacokinetics

Absorption and elimination Single doses of pirlindole have been administered in the rat by the intravenous (1 mg kg^{-1} bolus) and oral (5 mg kg^{-1}) routes. Radioactive substances used are 1,2-pyrazine-[^{14}C]pirlindole and phenyl-U-[^{14}C]pirlindole. Absorption seems to be nearly complete. Indeed, the percentage of radioactivity found in urine and faeces is similar after p.o. and i.v. administration (about 50–60% in urine and 40–45% in faeces within 24 h in both cases) [35]. The elimination by the lung is minimal. No difference is noted between males and females. By the intravenous route, three phases of elimination are measured, respectively of 15 min, 2–3 h and 20–30 h [35]. By the oral route, two phases of elimination are measured, respectively of 7.5 h and 34–70 h [35]. The lagtime for oral absorption is short (0.13 h) and the T_{max} varies between 2.5 and 6 h. The percentage of radioactivity found in the bile attests that pirlindole and/or its metabolites were subject to an enterohepatic circulation [35].

Single doses of pirlindole have been administered in the dog by the intravenous (1 mg kg^{-1} bolus [36], 1.0–1.1 mg kg^{-1} infusion 0.1 mg kg^{-1} min^{-1} [37, 38], $\pm$5 mg kg^{-1} [39]) and oral (5 mg kg^{-1} [36, 39] and 10 mg kg^{-1} [38, 40]) routes. Radioactive substances used are 1,2-pyrazine-[^{14}C]pirlindole and phenyl-U-[^{14}C]pirlindole. Absorption seems to be nearly complete. Indeed, the percentage of radioactivity found in urine and faeces is similar after p.o. and i.v. administration (about 50–70% in urine and 25–45% in faeces within 24 h in both cases) [36, 39]. No significant difference is noted between males and females. Elimination of pirlindole from the plasma is triphasic, with half-lives of 1.3, 10.8 and 185 h after oral intake of 5 mg kg^{-1} [39]. Values are 3.8, 23.7 and 180 h after i.v. administration [39]. The lagtime for oral absorption is short (0.03 h) and the T_{max} varies between 0.8 and 2 h [36–39]. Plasma levels of unmetabolized pirlindole after oral intake suggest that the compound has an absolute bioavailability of 20–30%, probably due to an extensive first-pass effect [37, 38].

In vitro, $\pm$95% of pirlindole is bound to plasma proteins in rats, dogs and men [40, 41], which probably explains its relatively long terminal half-life.

A pharmacokinetic study has been conducted in male and female dogs after repeated administration (10–20–40 mg kg^{-1} p.o. during 1 year) of pirlindole. The amplitude of blood level is strictly dose-dependent. Kinetic differences between males and females are not observed. The results attest that there is no accumulation of pirlindole and its fluorescent metabolites since plasma levels are similar to those measured after a single administration [42].

Distribution

Distribution of pirlindole after intravenous (5 mg kg^{-1} [43]) or oral (25 mg kg^{-1} [43, 44]) administration has been studied in the rat. The pattern of distribution in the rat system after i.v. or p.o. administration are relatively similar and no important differences are noted between males and females. Maximal concentrations are reached in most organs after 1–3 h (1.5 h in the brain). In the central nervous system, the distribution of the radioactivity is heterogenous; high amounts are found in the neocortex, hippocampus, thalamus and spinal cord, for instance. The blood–brain barrier crossing is judged slight or distinct. Concerning other organs, radioactivity is also high in the lungs, liver, kidneys, spleen and various glands. It is observed only transiently in the genitalia and bone marrow. The blood–placenta crossing has not been tested. After the oral administration, the percentage of radioactivity eliminated in urines and stools has also been evaluated. Globally, 40–60% are eliminated after 24 h and 80–85% after 48 h [44]. Pirlindole is also discharged into the gastro-intestinal tract via the glandular stomach and is probably made available again for gastro-intestinal absorption [43].

Metabolism

Metabolism of pirlindole has been studied in the rat and the dog using the intravenous (5 mg kg^{-1}) and oral (5 mg kg^{-1}) routes [45]. On the whole, pirlindole is extensively metabolized and the unchanged compound is only found in trace amounts in the urine ($< 1\%$). The rat eliminates mainly unconjugated products (70–75%) while the dog mainly eliminates conjugated products (60–70%) [45]. Thin layer chromatography shows that the main part of the radioactivity is found in two zones (B + C), each of them representing a triplet. At the level of B, a derivative of a carboxylic acid of pirlindole is detected and a hydroxy derivative has also been detected in the dog [45].

Toxicity

Single dose toxicity Studies on the acute toxicity of pirlindole have been conducted in various strains of rats [46, 47] and mice [48, 49] (40–50 animals per strain) after oral or intravenous administration. Signs of toxicity appear as tremors, tonic-clonic spasms and respiratory distress. For high intravenous doses, deaths occur after 1–2 min and for high oral doses, they occur after 15–60 min. Calculated LD_{50} values are variable according to the strains studied. They are situated between 442 and 930 mg kg^{-1} in the mouse and 2,295 and 4,919 mg kg^{-1} in the rat after oral administration. LD_{50}s after i.v. administration are 67 or 82 mg kg^{-1} in the mouse and 79 mg kg^{-1} in the rat. There are no sex differences in acute toxicity. The minimal lethal dose is equal to 400 mg kg^{-1} p.o and 71 mg kg^{-1} i.v. in the mouse and to 2,449 mg kg^{-1} p.o. and 50 mg kg^{-1} i.v. in the rat. The maximal non-lethal dose is equal to 320 mg kg^{-1} p.o. in the mouse. Extensive cutaneous necroses

are observed at the injection site. They must be due to the pH of the solutions which is strongly acidic.

Repeated dose toxicity

Study performed during 5 weeks in the rat [50]. Pirlindole was administered p.o. together with the food to groups of ten male and female Wistar rats during 5 weeks. Doses were 20, 60 and 180 mg kg^{-1}. In groups receiving 20 and 60 mg kg^{-1}, no abnormalities are found. In the 180 mg kg^{-1} group, one male died. Several slight abnormalities can be found in the other animals, like a slowing down of the weight increase. Biological tests show slight signs of anaemia and increased blood urea levels. Pathological examination only reveals an increased amount of glycogen in the liver.

Study performed during 4 weeks in the dog [51]. Encapsulated pirlindole was given orally to groups of three dogs of either sex at 10, 25, 50 and 100 mg kg^{-1} during 4 weeks. No abnormalities are found at 10 mg kg^{-1}. At 25 and 50 mg kg^{-1}, a dose-dependent slowing down of weight increase is detected (13% at 50 mg kg^{-1}), as well as vomiting and tonic-clonic spasms. Pathological inspection reveals areas of necrosis in the hepatic parenchyma. The dose of 100 mg kg^{-1} is found to be lethal for most animals.

Study performed during 12 weeks in the dog [52]. Encapsulated pirlindole was given orally before feeding to 12 male Beagle dogs at 20 mg kg^{-1} during 12 weeks. After 4 weeks, an unilateral moderate decrease in testicular diameter is measured and after 8 and 12 weeks this modification becomes bilateral. This testicular involution is reversible within 4–12 weeks after drug withdrawal. The course of body weight development in the treated animals corresponds to that of the control and no behavioural abnormality is observed. Sexual behaviour remains normal. The determination of LH, testosterone and thyroid hormone levels does not show any drug-related modifications compared to the control group.

Study performed during 1 year in the rat [53]. Groups of 25 rats of either sex were treated orally with 20, 60 and 180 mg kg^{-1} of pirlindole during 1 year. Their characteristics were compared to that of 25 control animals. At 20 mg kg^{-1}, pirlindole does not produce any abnormality. At 60 and 180 mg kg^{-1}, hyperexcitability is noted after 6 months and consists of increased movements of the head and paws, scratching and tremor. Polydipsia and proteinuria can also be observed. After 10 months, breathing difficulties are also noted, as well as a slowing down in weight increase (only at 180 mg kg^{-1} in females). Biological tests reveal no abnormalities. Pathological investigations show focal pleural lesions in five animals in the 180 mg kg^{-1} group. The relative weight of some organs (lung, liver, testes, adrenal, thyroid and brain can be increased and lipidosis is observed with the highest dose.

Study performed during 1 year in the dog [54]. Groups of four dogs of either sex were treated orally during 1 year with doses of 10, 20 or 40 mg kg^{-1} pirlindole. Animals were between 1 and 2 years old at the start of the experiment. No abnormality is found at 10 mg kg^{-1}. Higher doses produce several disturbances, among which vomiting and slowed weight increase, as well as dose-dependent atrophy of the germinal epithelium in the testicular parenchyma, accompanied by a reduction in the number of spermatozoids. In the middle and large dose groups the mucosa of the gall bladder becomes severely hypertrophic and there is an increase in mucosal production. Two animals from the middle and four animals from the large dose group show a hepatocellular fatty degeneration. At 40 mg kg^{-1}, tonic–clonic movements and seizure-like episodes are also noted, as well as hypersialorrhoea. Biological findings are negative.

Study performed during 91 weeks in the rat [55]. During an oncogenic/carcinogenic study performed during 24 months in the rat, an interim toxicity study has been conducted after 91 weeks of treatment. Groups of 50 rats of either sex were treated orally via the food with 100 (5.4–6.9 mg kg^{-1}), 400 (21.6–27.7 mg kg^{-1}) or 1,600 (87.9–117.2 mg kg^{-1}) ppm per day. The percentage of death does not differ between control and treated animals (26 and 34% in control animals, 8 and 12% in the 100 ppm group, 8 and 14 in the 400 ppm group, 4 and 22% in the 1,600 ppm group). A significant decrease in body weight gain is measured in the females of the 400 ppm group and in both males and females of the 1,600 ppm group. Relative food consumption is increased in the females of the 1,600 ppm groups. The results ascertained during post-mortem examinations occur with the same incidence in control animals and in the animals being treated with pirlindole. The test results so far give no indication for a cancerogenic effect of pirlindole in rats.

Reproduction toxicity

Fertility and reproduction capacity [56]. This study was performed on 256 Wistar rats. The experimental protocol was as follows: the population was divided in eight groups of 32 animals (four male and four female groups) receiving either the vehicle (group I) or pirlindole via the food at 200 (group II), 600 (group III) or 1,800 (group IV) ppm (F_0 generation). When considering the food intake, these doses correspond to 15 (group II), 45 (group III) or 180 (group IV) mg kg^{-1}. Pirlindole was given before mating (60 days before) and during the pregnancy and lactation (21 days). After 21 days of pregnancy, 20 animals were killed in each group and foetuses

were examined. The other animals had their litter. Young animals (F_1 generation) received the substance via the milk. After the weaning, they also received the substance until their adult life. Two or three animals per litter were put together with the opposite sex, while avoiding any consanguinity. After birth and breeding of generation F_2, the study was terminated. The behaviour of the mothers is not influenced by pirlindole. At 1,800 ppm, the weight of the animals is slightly reduced during the whole treatment period. In the different groups, 32 (group I), 30 (group II), 29 (group III) and 29 (group IV) females have been mounted. Pregnancies are not observed in eight, nine, five and six females, respectively (no sperm found in the vagina in some cases), although fertility of the males is 100% when they are put together with other untreated females. Overall, no influence of pirlindole can be detected on the F_0 generation. The number of living foetuses is slightly, but not significantly reduced by pirlindole. No dead foetuses are found, although the number of resorptions increases at 1,800 ppm, which means the beginning of foetal toxicity. Development of foetuses (weight and height) is normal. At 1,800 ppm, one case of microphtalmia and one case of skeletal abnormalities are detected. Two abnormal foetuses are observed in the control group. Pathological examination reveals no drug-induced foetal abnormalities. As far as completed pregnancies are concerned, no abnormalities are observed. At 1,800 ppm, young animals have a slight slowing down of weight increase. However, the viability index is unaffected by the drug. The development of the F_1 generation goes on normally. No abnormality is detected in the behaviour of the animals. Pathological investigations reveal spontaneous dilatations of the renal pelvis, whose occurrence is unaffected by pirlindole. Copulatory behaviour of the F_1 animals is found to be normal. Their fertility index is equal in all groups. However, the number of resorptions and the foetal mortality rate are increased in the 1,800 ppm group. The viability index of the F_2 generation is slightly reduced in groups III and IV. The development of these animals is normal in all groups.

Embryotoxicity [57, 58]. In a first study [57], pirlindole was administered orally to groups of 20 female Wistar rats from the 7th to the 16th day of pregnancy. Doses were 20, 100 or 500 mg kg^{-1}. On day 21 of the pregnancy, animals were sacrificed, and foetuses as well as mothers were examined thoroughly. At 20 mg kg^{-1}, all but one pregnancy are complete. All mothers are healthy and behave normally. The number of living foetuses is normal, as are the number of corpora lutea and the implantations. The placenta is normal. The weight and height of the foetuses are also normal. At 100 mg kg^{-1}, all maternal parameters are normal as in the previous group. However, two kinds of abnormality are found in this group and the 500 mg kg^{-1} group. There is one diaphragmatic hernia in the 100 mg kg^{-1} group and another one in the 500 mg kg^{-1} group. Moreover, three anal atresias are found in foetuses from a single litter in the 500 mg kg^{-1} group. However, these abnormalities are not found in a second series of experiments using the same doses. All other findings concerning foetuses in this group are negative. At 500 mg kg^{-1}, strong maternal toxicity is observed. More than half of the mothers dies. Food intake and weight increase are reduced and the number of resorptions increases. The weight of the placentas decreases, as does the number of foetuses. However, beside the abnormalities observed as described above, no other significant disturbances are noted when examining the foetuses.

In a second study [58] performed on Russian rabbits, pirlindole was administered via an oesophageal sound to groups of 15 female rabbits from the 7th to the 19th day of pregnancy. Doses used were 8, 50 and 320 mg kg^{-1}. On the 29th day of pregnancy, mothers were killed and foetuses were examined. At 8 mg kg^{-1}, no abnormalities are found. At 50 mg kg^{-1}, one foetus has an umbilical hernia and another has a shortening of the paws. All other foetuses are normal, as are the conditions of the pregnancy (normal weight increase, no abortion, no prematurity). The 320 mg kg^{-1} dose is very toxic for the mothers. Food intake is strongly reduced and the weight curve is inverted. There are severe abortions and premature births. Resorptions are also increased. Pathological examination only reveals isolated necroses of adipose tissue in the mothers. No drug-induced foetal abnormalities are found.

A peri- and post-natal reproduction study [59] was performed on Wistar rats in order to determine possible peri- and post-natal toxic effects of pirlindole. The drug was administered to groups of 20 fertilized females via an oesophageal sound from the 17th day of pregnancy to the 21st day after birth. Doses were 16, 50 and 160 mg kg^{-1} per day. The behaviour of the young animals was thoroughly studied and pathological examination of the young animals and the mothers was performed at the end of the experiment. No drug-induced abnormalities are detected at 16 mg kg^{-1}. Mothers show toxic effects at 50 mg kg^{-1}. One of them dies. Five others have an increased motility and tremor. At this dose, some young animals have a necrosis of the tip of the tail. All other parameters are normal. The 160 mg kg^{-1} dose is strongly toxic. Abnormalities of the maternal behaviour described above are enhanced. The number and weight of the young animals are clearly reduced. However, no drug-induced anatomical abnormalities can be detected even at this high dose.

Mutagenic potential

Test of Ames [60]. Pirlindole was tested in the test of Ames using four strains of *Salmonella typhimurium* (TA 98, TA 1537, TA 100, TA 1535) in the presence or absence of a rat liver preparation (S-9

mix). These strains have a high rate of frame-shift mutations or base substitutions. Pirlindole was tested at different concentrations up to 0.5 mg per plate because of its low solubility and bactericidal effect at higher doses. No mutagenic effect of pirlindole is detected in this model with or without S-9 mix. Procarbazin, steptozotocin, 9-aminoacridine and 2-aminoanthracene produce a clear mutagenic effect.

Test of the micronucleus [61]. The effect of pirlindole in the test of the micronucleus was also examined. The substance was given orally, twice at a 24-h interval to groups of five male and female NMRI mice. Doses were 5, 40 or 320 mg kg^{-1}. Cyclophosphamide (10, 40 and 160 mg kg^{-1}) was used as a positive control. Femoral bone marrow was taken 6 h after the second administration and erythrocytes were examined. Pirlindole does not increase at any dose the number of polychromatic erythrocytes with micronuclei.

Test of chromatid exchanges [62]. A third test was conducted in Chinese hamsters. One single oral dose of 430 or 2,150 mg kg^{-1} pirlindole was given to groups of eight male or female Chinese hamsters and sister chromatid exchange analysis was performed. No effect of pirlindole is detected in this model. Cyclophosphamide (13.3 mg kg^{-1}) significantly increases the number of sister chromatid exchanges.

Oncogenic / carcinogenic potential A longitudinal study was performed in Wistar rats in order to look for a possible carcinogenic effect of pirlindole. Groups of 50 male and female animals were treated with 100, 400 or 1,600 ppm pirlindole in the food. When taking into account food intake, these doses correspond respectively to 5.4–6.9 mg kg^{-1}, 21.6–27.7 mg kg^{-1} or 87.9–117.2 mg kg^{-1}. One-hundred control animals of either sex were also observed. Animals were treated for 24 months and observed during a further 6-month period. An intermediate study conducted after 91 weeks of administration did not reveal any oncogenic/carcinogenic tendency [55]. Complete pathological investigations were performed at the end of the study. Weight increase is reduced dose-dependently at 400 and 1,600 ppm. The number of deaths is similar in all groups and the occurrence of tumours is not influenced by the drug. Finally, no drug-induced abnormalities are detected histologically [63].

CONCLUSION

As it has been demonstrated in pre-clinical tests (Table I), such as the Porsolt's model or the antagonism of reserpine-induced blepharoptosis and hypothermia, pirlindole can be characterized as a potential antidepressant drug. It has some characteristics in common with both tricyclic antidepressants and classical MAOIs. Its main mechanism of action, demonstrated both *in vitro* and *ex vivo* (Table II), consists of a selective and reversible inhibition of MAO-A. *In vitro*, pirlindole has a 200-fold selectivity for MAO-A *vs* MAO-B and *ex vivo* an eight-fold selectivity for MAO-A *vs* MAO-B. These values are comparable to that observed with another well-recognized RIMA, moclobemide (Table II). Pirlindole seems to be devoid of interaction with the dopaminergic system (no effect on apomorphine-induced hypothermia and no antagonism of fluphenazine-induced catalepsy) and more interestingly, compared to tricyclic antidepressants, with the cholinergic system (no effect on oxotremorine-induced hypothermia and on arecoline-induced convulsions) (Table II). Some authors have also reported that pirlindole inhibits the neuronal reuptake of noradrenaline and serotonin without affinity for the dopamine reuptake site. Recent studies show that this activity is secondary and functional only at high concentrations (at least in the range of 1 μM–100 μM). However, this relative bivalent activity, inhibition of MAO-A on one hand and inhibition of NA and/or 5-HT reuptake on the other hand, could explain why in behavioural procedures, pirlindole presents characteristics of both tricyclic antidepressants and non-selective irreversible MAOIs.

Compared to tricyclic antidepressants and non-selective MAO inhibitors, pirlindole appears as a safe drug due to its very low level of interaction with the cardiovascular system and to its low potential for amplifying tyramine and noradrenaline pressor effect (Table III).

The oral absorption of pirlindole seems nearly complete but plasma levels of unmetabolized pirlindole suggest that the compound has an absolute bioavailability between 20 and 30%, probably due to an extensive first-pass effect. No differences have been noted between males and females. Orally, the T_{max} varies between 2.5 and 6 h in the rat and 0.8 and 2 h in the dog. In the rat, two phases of elimination are measured, 7.5 and 34–70 h, respectively. In the dog, three phases of elimination are measured, respectively 1.3, 10.8 and 185 h. Pirlindole and its metabolites are excreted both in urine (50–70%) and faeces (25–45%). Pirlindole is largely bound (95%) to plasma proteins in rats, dogs and men which explains its relatively long terminal elimination half-life. Chronic administration of pirlindole by the oral route to dogs at several different doses during 1 year shows that the amplitude of blood level is strictly dose-dependent and that there is no risk of accumulation. The pattern of distribution of pirlindole in the body is independent of the route of administration. Maximal concentrations are reached in most organs after 1–3 h (1.5 h in the brain). Pirlindole is extensively metabolized and unchanged and is only found in trace amounts in the urine. The

rat eliminated mainly unconjugated products while the dog and the man eliminate mostly conjugated products.

Acute and chronic animal toxicological studies have not revealed potentially dangerous effects of the drug at usual doses. The doses considered as toxic in animals far exceed those recommended in patients (150–300 mg day^{-1} p.o. equal to 2.1–4.3 mg kg^{-1} p.o. for a mean weight of 70 kg). Reproduction mechanisms have not been shown to be significantly modified by the drug. Pirlindole does not present measurable mutagenic, clastogenic or carcinogenic properties. Findings from pharmacodynamic, pharmacokinetic and toxicologic studies lead to the exclusion of toxicity from accumulation, tolerance, dependence or withdrawal syndrome.

In conclusion, pirlindole shows pharmacological, pharmacokinetic and toxicological properties which make it suitable for the management of depression.

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