RESUMEN

Tele-acogida : suficiencia ei insuficiencia de los medios. El punto de vista neuropsiquiátrico.

El Real Decreto del 20 de juilio de 1973 ha precisado el modo de funcionamiento de los centros de Tele-acogida. El mismo los situa en las fronteras de la neuropsiquiatría. Parece ser que el psiquiatra esta poco concernido por esta ayuda por teléfono. Algunos benevolos, formados según los criterios del Real Decreto, recogen las llamadas telefonicas de los casos de crisis e intentan hacerles frente como pueden. El motivo de estas llamadas se situa en más de una tercera parte, en problemas socio-psiquiátricos. Sería de desear que en adelante, como lo desea el Estado belga, la sociedad psiquiátrica se interesara por esta forma de actividad paramédica.

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Pilot study of a specific serotonergic antagonist, pirenperone, in the treatment of anxiety disorders*

by M. ANSSEAU**, A. DOUMONT**, D. THIRY** and Y. GELDERS***

ABSTRACT

Pirenperone (R 47465) is the prototype of a new class of psychotropic drugs, selective serotonin 5-HT$_2$ receptor blocking agents. In an open pilot study, the anxiolytic properties of pirenperone were evaluated in a sample of five anxious inpatients who met Research Diagnostic Criteria for current Generalized Anxiety Disorder and who had a score of at least 25 on the Hamilton Anxiety Scale (HAS). Three dosage levels were tested : 15, 30 and 60 mg/a day in 3 divided doses. Each dosage period lasted at least 5 days, at the end of which patients were reassessed by HAS, Clinical Global Impression and a side-effects check-list.

Results suggested a modest anxiolytic activity, without a clear dose-response relationship and with good tolerance. Subsequent treatment by lorazepam (7.5 mg/d) seemed to result in more specific improvement [Acta psychiat. belg., 83, *517-524 (1983)*].

Key words : pirenperone, tranquillizing agents, serotonin antagonists, anxiety disorders.

Introduction

Among biochemical models of anxiety, the serotonergic theory holds the current belief that the anxiolytic action of benzodiazepines may depend ultimately on an inhibition of serotonergic transmission. This theory is substanciated by the following lines of evidence (for review, see Guidotti, 1978).

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The most characteristic action of benzodiazepine anxiolytics in the animal is a « behavioral disinhibition », i.e. a normalization of behavioral responses that are suppressed by punishment or the absence of reward. This effect of benzodiazepines is mimicked by serotonin antagonists (e.g. methysergide, cinanserin, bromolysergic acid), by serotonin synthesis inhibitors (e.g. parachlorophenylalanine), and by drugs that damage serotonin nerve terminals (e.g. dihydroxytryptamine). In the same animal model, the intraventricular administration of serotonin or the stimulation of dorsal raphe nuclei decrease the behavioral responses, an action that

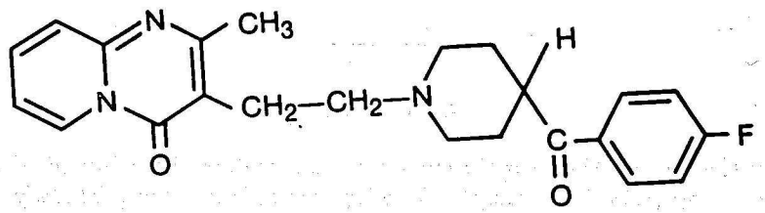


FIG. 1. — Structural formula of pirenperone (R 47465).

is antagonized by systemic administration of benzodiazepines. Finally, the decrease of brain serotonin turnover rate induced by benzodiazepines is directly correlated with their anticonvulsant and antianxiety properties.

In this context, the synthesis of a new class of psychotropic drugs, selective serotonin 5-HT_2 receptor blocking agents, of which pirenperone (fig. 1) is the prototype, has opened a new potential class of anxiolytic agents (Janssen, 1983). Indeed, central serotonergic (5-HT) receptors have been divided into two types : 5-HT_1, selectively labelled by serotonin, and 5-HT_2, selectively labelled by spiperone or ketanserin (Peroutka and Snyder, 1979). The physiological role of 5-HT_1 sites remains unclear, whereas 5-HT_2 sites were shown to mediate the antagonism of various serotonergic effects measured *in vivo,* e.g. tryptamine-induced clonic seizures (Leysen *et al.,* 1978) and 5-hydroxy-tryptophan-induced head twitches (Peroutka *et al.,* 1981).

Pirenperone possesses a receptor binding profile of a pure 5-HT_2 antagonist, lacking significant binding to 5-HT_1-receptors. Its profile is compared to that of several reference compounds in Table (Janssen Pharmaceutica, 1981). It resembles closely that of ketanserin, except for pirenperone's binding to dopamine receptors which is intermediate between ketanserin and the potent dopamine antagonists haloperidol and domperidone, what suggests that significant dopamine antagonism can be expected *in vivo.*

TABLE

In vitro receptor binding profiles of pirenperone and of reference compounds

Affinities (Ki-values) in nanomolar concentration

Compound	Serotonin		Histamine	Norepine-phrine	Dopamine
	5-HT_2	5-HT_1	H_1	α_1	DA
Pirenperone	2.0	1000	14	6.8	16
Ketanserin	2.1	1000	10	10	220
Domperidone	330	1000	5530	91	0.9
Haloperidol	48	1000	1000	8.0	1.2
Cyproheptadine*	6.5	700	2.7	100	31
Methysergide	12	99	1000	2300	200

*Active also on muscarinic receptors (Ki = 19).

Pirenperone demonstrated pronounced behavioral anxiolytic effects in the old world monkey after injection of 25 µg/kg (Colpaert *et al.,* 1981). It has been given to volunteers without untoward effects (Scheijgrond *et al.,* 1981). Accordingly, the purpose of this pilot study was to assess the anxiolytic properties of pirenperone in a preliminary sample of anxious inpatients.

Material and method

1. Subjects.

The study was performed in 5 inpatients at the Psychopharmacology Unit of the University Hospital « de Bavière », Liège, Belgium. They met Research Diagnostic Criteria for « Generalized Anxiety Disorder » (Spitzer *et al.,* 1978) and had a score of 25 or more on the Hamilton Anxiety Scale (Hamilton, 1959) at the end of a wash-out period of at least 4 days on placebo. All these patients were adjudged clinically suitable for anxiolytic drug treatment with benzodiazepines, and all gave informed consent.

2. Procedure.

The initial dose of pirenperone was 15 mg (5 mg TID) and could be increased to 30 or 60 mg daily according to clinical status. Each dosage level was administered for at least 5 days.

Patients were assessed before treatment and at the end of each phase by Hamilton Anxiety Scale, Clinical Global Impression (Guy, 1976) and a side-effects checklist.

No other psychotropic medications were given, except PRN flunitrazepam at a maximal dose of 2 mg HS in two cases of marked insomnia (# 3 and 5).

At the end of the study, the patients showing some improvement (i.e. a score on the Hamilton Anxiety Scale of less than 20) were given a placebo test (single blind condition) in order to verify partially the relationship of improvement to the active pharmacological treatment. Patients with none or little improvement were treated by lorazepam (2.5 mg TID) in order to determine the relative efficacy of pirenperone in comparison to a classical anxiolytic drug.

Blood samples were collected before treatment and 2 hours after each change of dose in order to determine the plasma level of pirenperone.

Results

All 5 patients admitted to the study completed it. They were 4 females and 1 male, with an age range from 24 to 62 (mean = 50.2). Individual case reports follow (fig. 2).

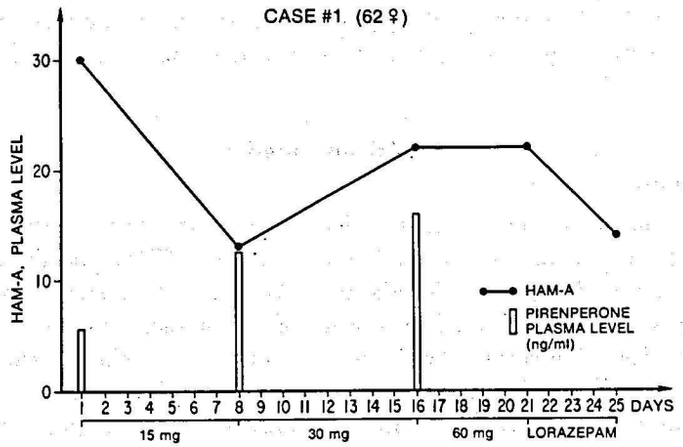
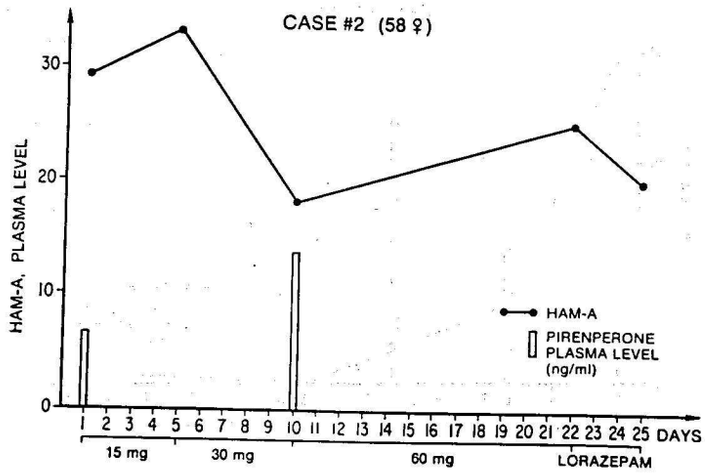


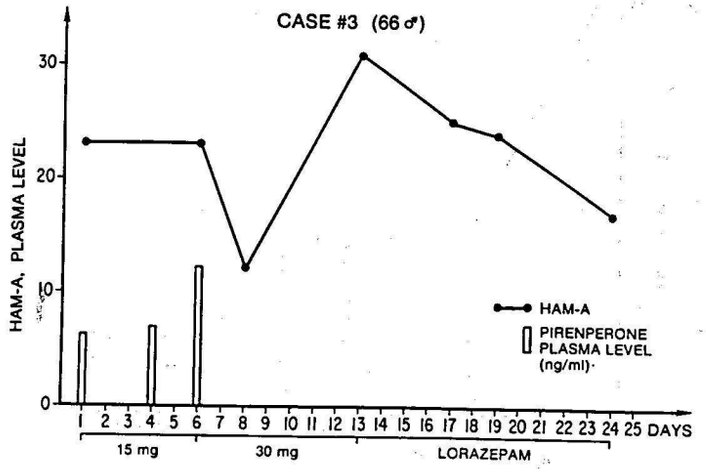
FIG. 2. — Hamilton Anxiety Scale (HAM-A) changes over time for 5 patients during treatment with pirenperone (15, 30, or 60 mg/d), lorazepam (7,5 mg/d), or placebo. Plasma levels of pirenperone (ng/ml).

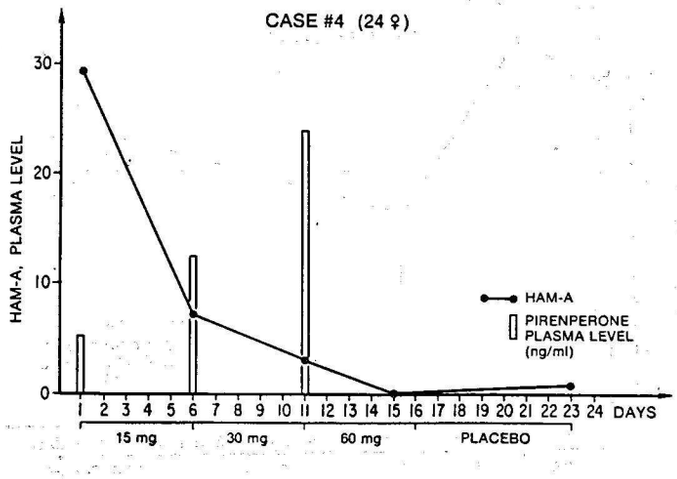
Case 1 (62 ♀). — Marked improvement in symptomatology with 15 mg dose but partial relapse with increase of dose to 30 and 60 mg a day. No side-effects. With lorazepam, slightly more pronounced anxiolytic effect.

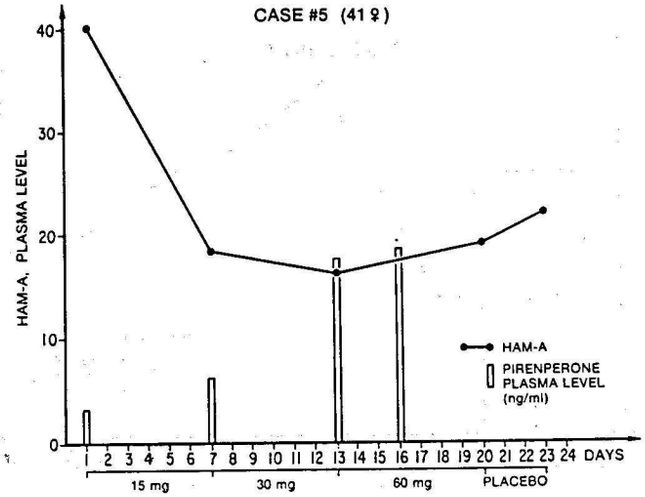
Case 2 (58 ♀). — With 15 mg a day, worsening of the clinical picture; with 30 mg, marked improvement but new worsening of the symptomatology in spite of the increase of dose to 60 mg a day. Frequent sweating. With lorazepam, slight improvement but marked sedation.

Case 3 (66 ♂). — No change with 15 mg dose; with 30 mg, transitory improvement, then relapse and deterioration of the clinical picture. Flunitra-









zepam 2 mg was prescribed for marked insomnia while the patient was receiving 30 mg of pirenperone. A subsequent increase of pirenperone dosage was impossible due to the severity of the clinical picture. No side-effects. With lorazepam, more potent anxiolytic effect.

Case 4 (24 ♀). — Very marked improvement with 15 mg and 30 mg and clinical remission with 60 mg. After 7 days on placebo, no change in the clinical picture. No side-effects.

Case 5 (41 ♀). — Marked improvement with 15 mg ; no further change on 30 and 60 mg. Flunitrazepam 2 mg for marked insomnia was added when the patient received 30 mg of pirenperone. No side-effects. Slight deterioration after 3 days on placebo.

Plasma levels of pirenperone.

The plasma levels of pirenperone (fig. 2) were correlated significantly with dosage (Pearson $r = .91$; $p < 0.001$).

Discussion and conclusion

The data from this open trial suggest that pirenperone may possess modest anxiolytic properties, although a clear dose-response relationship is not evident and possible placebo effects have not been controlled. In our sample, pirenperone appears devoid of any antidepressant or hypnotic activity (as measured by the specific items of the Hamilton Anxiety Scale). Neither does it appear to increase sleep disturbance : the two patients who needed a hypnotic exhibited the same level of insomnia before pirenperone. Patients appear to tolerate pirenperone well, without sedative, extrapyramidal or anticholinergic side-effects.

In comparison with lorazepam, pirenperone appears to be less specifically anxiolytic and less efficacious in promoting general well being. At the same time, it may also be less sedative.

In conclusion, these results suggest that a serotonin 5-HT_2-antagonist like pirenperone may possess anxiolytic properties. Whether these are sufficient to find direct clinical application awaits further double-blind, placebo controlled testing. Moreover, pirenperone is the first drug from a new chemical family of 5-HT_2 antagonists : in its succession are more potent and more specific compounds (Janssen, 1983) that might be successfully tested in the pharmacological treatment of anxiety disorders.

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RESUME

Etude pilote d'un antagoniste sérotoninergique spécifique, la pirenpérone, dans le traitement de l'anxiété.

La pirenpérone (R 47465) est le prototype d'une nouvelle classe de psychotropes qui bloquent de façon sélective les récepteurs sérotoninergiques 5-HT_2. Dans une étude pilote ouverte, les propriétés anxiolytiques de la pirenpérone ont été évaluées chez un échantillon de cinq patients hospitalisés qui remplissaient les critères de « trouble anxieux généralisé » des « Research Diagnostic Criteria » et avaient une note minimum de 25 à l'échelle d'anxiété de Hamilton. Trois posologies ont été successivement administrées : 15, 30 et 60 mg/jour en 3 prises. A la fin de chaque période, qui durait au moins 5 jours, les patients étaient évalués par l'échelle de Hamilton, l'Impression Clinique Globale et une liste d'effets indésirables.

Les résultats mettent en évidence une activité anxiolytique modeste, sans une claire relation dose-effet, et une bonne tolérance. Cependant, le traitement ultérieur par lorazepam (7.5 mg/jour) a apporté une amélioration plus spécifique.

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Treatment of depressive anxiety states associated with psychosomatic symptoms

A double-blind multicentre clinical study : mianserin versus melitracen-flupentixol

by M. VAN MOFFAERT (1), M. DIERICK (2), Fr. DE MEULEMEESTER (2) and A. VEREECKEN (3)

ABSTRACT

A four-week randomized multicentre study comparing mianserin and melitracen-flupentixol was conducted in 90 outpatients suffering from depressive anxiety states with a predominantly psychosomatic symptomatology.

Both patient groups showed a favourable clinical response to treatment as well as a good tolerance. No significant differences were observed in the drop-out rates or in the incidence of side-effects, although drowsiness tended to develop more frequently during the first days of mianserin treatment.

The improvement scores of the groups showed that mianserin has significant advantages when depressed mood, sleep disturbances and autonomic disregulations predominate the depressive anxiety state. [Acta psychiat., belg., 83, *525-539 (1983)*].

Key words : *mianserin, melitracen-flupentixol, depressive anxiety state, psychosomatic complaints, double-blind study, therapeutic effects, side-effects.*

Introduction

Clinical pictures characterized by a complex of mental and somatic symptoms constitute a diagnostic and therapeutic problem.

The diagnosis is hampered by the vicious circle which develops between the mental and somatic elements. On the one hand the patients somatizes

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