"Use of pivagabin to prepare pharmaceutical compositions"

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This invention relates to the use of pivagabin to prepare pharmaceutical compositions for treating depressive anxiety forms.

Pivagabin, or 4-(2,2-dimethylpropanol)butanoic acid, has been described in Italian patent 1 202 402 as a hydrophobic derivative of GABA which can cross the haemato-encephalic barrier and as a potential candidate for the preparation of active pharmaceutical compositions against hypertension and cerebral disturbances, such as epilepsy.

However, the experimental data reported in the said patent only refer to the preliminary tests on anti-convulsant activity in the rat and, more specifically, to tests on the inhibition of convulsions induced by pentatrazol and bicuculline.

Subsequent studies have mainly aimed to investigate the anticonvulsant activity in the animal, and various experimental results indicate that pivagabin acts in the animal as a pro-drug for the GABA [Galzigna L. et al. "Properties of two derivatives of γ-aminobutyric acid (Gaba) capable of abolishing cardiazol- and bicuculline-induced convulsion in the rat", Archives Internationales de Pharmacodynamie et de Thérapie 235: 73-85 (1978); Galzigna L. et al. "Different Action of two hydrophobic 4-amino-butyric acid derivatives on the whole animal and on isolated tissues", Aggressologie 22: 219-224, (1981); Bianchi M. et al. "Pharmacokinetics and in vitro effects of a 4-Amino butyric acid derivative with anticonvulsant action", Pharmacology 27: 237-240 (1983)]. Recently the anti-depressive and anxiolytic activity in the mouse have also been studied [de Marsanich B. et al., "Proprietà anti-depressive ed ansiolitiche della Pivagabina" in: V Convegno Nazionale - Società Italiana di Neuroscienze Pisa, 12 - 14 December (1996)].

To summarize, from the said articles it can be seen that in animals the pharmacotoxicological profile of pivagabin is as follows:

- it is substantially free of toxic effects *in vivo* in the mouse and in the rat; in fact, LD_{50} by intravenous route is of 1750 mg/kg in the mouse while no toxic effects were observed up to the dose of 1 g/kg by intraperitoneal route in the rat;
- it can pass the haemato-encephalic barrier in the rat reaching peak concentration 30 min. after sub-cutaneous administration and 10 min. after intracardiac administration;
- it releases GABA *in vitro* by hydrolysis promoted by proteolytic enzymes (amidase). This activity is particularly marked in the brain homogenate compared with other tissues;
- when administered 30 min. before the convulsant agent, it antagonises the convulsions by pentatrazol (80 mg/kg) or bicuculline (25 mg/kg) recorded as electro-myographic track;
- it shows a certain anti-depressive and anxiolytic activity in the mouse;
- when administered via intra-muscular route in the rabbit, it antagonises the alterations of electro-encephalographic record induced by strychnine.

It is also known that experimental evidence shows that, in addition to the benzodiazepines site, on $GABA_A$ receptor there is another modulatory site which links endogenous neuroactive steroids, progesterone and deoxycorticosterone metabolites [Gee K. W. et al. "A putative receptor for neurosteroids on the $Gaba_A$ receptor complex: the pharmacological properties and therapeutic potential of epalons" Crit. Rev. Neurobiol. 9: 207-277,(1995)].

For these substances (i.e. endogenous neuroactive steroids, progesterone and deoxycorticosterone metabolites), various authors have suggested anxiolytic, hypno-inducing and cognitive activation activities, and these theories are confirmed to by the activity shown on a variety of animal models [Hogskilde S et al., "Anticonvulsant properties of pregnanolone emulsion compared with althesin and thiopentone", Br. J.

Anaesth. 61: 462-467, (1988); Belelli D. et al., "Anticonvulsant profile of the progesterone metabolite 5α-pregnan-3α-ol-20-one", Eur. J. Pharmacol. 166: 325-329. (1989); Crawley J. N. et al., "Anxiolytic activity of an endogenous adrenal steroid", Brain Res. 398: 382-385, (1986); Bitran D, et al., "Anxiolytic effects of 3α-hydroxy-5α[β]-pregnan-20-one: endogenous metabolites of progesterone that are active at the $Gaba_A$ receptor", Brain Res. 561: 157-161, (1991); Wieland S. et al., "Anxiolytic activity of the progesterone metabolite 5α-pregnan-3α-ol-20-one", Brain Res. 565: 263-268, (1991); Diamond D.M. et al., "The neurosteroid dehydroepiandrosterone sulphate (DHEAS) enhances hippocampal primed burst, but not long-term, potentiation", Neurosci. Lett. 202: 204-208, (1996); Robel P. et al., "Neurosteroids: biosynthesis and function", Crit. Rev. Neurobiol. 9: 383-394, (1995); Li P.K. et al., "Reversal of scopolamine induced amnesia in rats by the steroid sulfatase inhibitor estrone-3-O-sulfamate", Brain Res. Cogn. Brain Res. 2: 251-254. (1995)].

The therapeutic use of endogenous neuro-active steroids, however, shows many disadvantages. In particular, with regard to the non-satisfactory profile of tolerability in prolonged treatments [Iizuka H. et al., "Clinical effects of cortisol synthesis inhibition on treatment-resistant depression", Nihon-Shinkei-Seishin-Yakurigaku-Zasshi 16: 33-36 (1996); Yu R. et al., "Chronic neurosteroid treatment attenuates single cell $Gaba_A$ response and its potentiation by modulators in cortical neurons", Brain Res. 706: 160-162, (1996); Calixto E. et al., "Allopregnanolone potentiates a Gaba-withdrawal syndrome in the rat cerebral cortex", Neurosci. Lett. 195: 73-76, (1995); Chen S.W. et al., "The hyperphagic effect of 3 alpha-hydroxylated pregnane steroids in male rats", Pharmacol. Biochem. Behav. 53: 777-782, (1996)] and the limited efficacy due to a rapid metabolisation [Hogenkamp D.J. et al., "Synthesis and in vitro activity of 3β-substituted-3α-hydroxypregnan-20-ones:

allosteric modulators of the $Gaba_A$ receptor", J. Med. Chem. 40: 61-72, (1997)].

It has now been found, surprisingly, that in man the pharmacological and biochemical profile of pivagabin is substantially different from that known in the animal. In fact, it is excreted in the urine in substantially unmodified form; the EEG of epileptic patients is not modified, thus indicating that it is free of anticonvulsant activity; its activity in the anxio-depressive forms is much more marked than could have been expected. Moreover, it increases the concentration of some endogenous neuro-active steroids in the animal in a statistically significant way. Thus it results the profile of a drug which is useful for the treatment of anxio-depressive forms, but which is substantially free of anticonvulsant activity that could have led to undesirable effects, and which is metabolically stable, which increases the duration of the therapeutic effect.

Therefore, it is an object of this invention the use of pivagabin to prepare a pharmaceutical composition for the treatment of anxio-depressive forms.

Typical examples of anxio-depressive forms are: mood disturbances, anxiety disorders, somatoform disorders and adjustment disorders, classified according to the diagnostic criteria of the DSM IV [American Psychiatric Association: Diagnostic and statistical manual of mental disorders. Ed. IV Washington / American Psychiatric Association (1994)].

The pharmaceutical compositions of this invention are preferably prepared in the form of suitable dosage forms comprising an effective dose of pivagabin and at least one pharmaceutically acceptable inert ingredient.

Examples of suitable dosage forms comprise tablets, capsules, coated tablets, granules, solutions and syrups for oral administration; sterile solutions for administration by injection and the slow-release forms.

The dosage forms can also contain other conventional ingredients, such as: preservative agents, stabilizers, surfactants, buffers, salts to regulate the osmotic pressure, emulsifiers, sweeteners, colourings, flavours and the like.

If required by particular therapies, the pharmaceutical composition of this invention may contain other pharmacologically active ingredients whose simultaneous administration is useful.

The quantity of pivagabin in the pharmaceutical composition of this invention may vary over a wide range depending on known factors such as for example the type of illness to be treated, the severity of the illness, the body weight of the patient, the type of dosage, the route of administration chosen and the number of doses per day. However, the optimum quantity can be determined by a person skilled in the art easily and routinely.

Typically the quantity of pivagabin in the pharmaceutical composition of this invention will be such that it ensures a level of administration of from 5 to 250 mg/kg/day. Preferably, of from 10 to 150 mg/kg/day. Even more preferably, of from 10 to 50 mg/kg/day.

The dosage forms of the pharmaceutical composition of this invention may be prepared using techniques which are well known to the pharmaceutical chemist, including mixing, granulation, compression, dissolution, sterilisation and the like.

The following experimental studies will further illustrate this invention without limiting it in any way.

1. Pharmacokinetics in Man

Pivagabin was administered orally in a single dose (900 mg) to 12 subjects (8 men and 4 women) and their urine collected in the 24 hours following the said administration.

The quantity of unmodified pivagabin in the urine collected was measured by HPLC analysis with spectrophotometric determination. The results obtained are shown in Table 1 below.

Table 1

Urinary Excretion of Unmodified pivagabin in 12 subjects		
Time	Average Quantity (mg)	Percent Quantity
0	-	-
0 ÷ 4	681	75.67
4 ÷ 8	54.9	6.10
8 ÷ 12	20.4	2.27
12 ÷ 24	23.4	2.61
Total	780	86.65

II. Biochemical Studies in the Rat

4 groups of 10 rats each were subjected to a protracted treatment (4 days) with pivagabin by intraperitoneal route at a dose of 200 mg/kg twice a day. Thus a significant and unexpected statistical increase was shown in the concentration of some neurosteroids, such as allo-tetra-hydro-deoxycorticosterone (THDOC) and allopregnanolon, in the cerebral cortex. The cerebral steroids have been determined in the homogenate of cerebral cortex with the method described by Biggio [Biggio G. et al., "Inhibition of Gabaergic transmission enhances neurosteroid concentrations in the rat brain" in The Brain: Source and Target for sex steroid hormones - Eds. Genazzani A.R., Petraglia F. and Purdy R.H. (1996)].

The results are shown in Table 2.

Moreover pivagabin, administered in the same experimental conditions, has shown that it can antagonise the reduction of the

function of the $Gaba_A$ receptors, induced in animals which are subject to acute stressogenic stimuli (footshock).

The reduction in the function of the $Gaba_A$ receptors has been measured as a significant statistical increase, in the cortex and the hippocamp, of the binding of the [^{35}S]t-butylbicyclo-phosphorotionate ([^{35}S]TBPS) (Fig. 1 and 2) [Yanli D. et al., "House fly head Gaba-gated chloride channel: four putative insecticide binding sites differentiated by [^{3}H]EBOB and [35S]TBPS", Pestic. Biochem. Physiol. 47: 98-112, (1993); Biggio G. et al., loc. cit.].

Table 2

Percentage variations compared with the control		
Allopregnanolone	+ 75%	$p < 0.01$
Corticosterone	+ 2%	n.s.
Pregnenolone	+ 15%	n.s.
Progesterone	- 8%	n.s.
THDOC	+ 55%	$p < 0.01$

III. Clinical Studies

A. Epilepsy

Preliminary studies, carried out on a non-homogenous population of 33 (14M, 19F, aged between 19 and 78) patients including 3 (1M, 2F) patients with diagnosed epilepsy have shown that pivagabin, at the dose of 450 mg by intravenous route for 15 days, did not modify the EEG of the epileptic patients.

B. Anxio-Depressive States

186 female patients with post-menopausal anxio-depressive symptoms were assigned at random to treatment with pivagabin (900 mg/day by oral route) or placebo for 90 consecutive days in conditions of double blindness. The clinical effect was evaluated with the Hamilton

Depression scale [Hamilton M. "Development of a rating scale for primary depressive illness", Br. J. Soc. Clin. Psychol. 6: 278-296 (1967)] and with the Zung self-evaluation anxiety scale [Zung W.W.K. "A rating instrument for anxiety disorders", Psychosomatics 12: 271-279, (1971)].

Thus there was a difference in the progress of the two treatment groups (pivagabin vs placebo) of points on both scales (Fig. 3 and 4).

A second study, performed on a group of 30 geriatric patients with anxio-depressive symptomatology, has confirmed the data shown above on the clinical effect of the treatment with pivagabin. The patients were assigned at random to treatment with pivagabin (900 mg/day by oral route) or placebo for 90 consecutive days in conditions of double blindness. As in the previous study, the clinical effect was evaluated with the Hamilton Depression scale and the Zung self-evaluation Anxiety scale (Fig. 5 and 6).

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CLAIMS

1. Use of pivagabin to prepare a pharmaceutical composition for the treatment of depressive anxiety forms.
2. Use of pivagabin in accordance with claim 1, characterized in that said anxio-depressive form comprises mood disturbances, anxiety disorders, somatoform disorders and adjustment disorders.
3. Use of pivagabin according to claim 1 or 2, characterized in that said pharmaceutical composition comprises a quantity of pivagabin such that it ensures a level of administration of from 5 to 250 mg/kg/day.
4. Use of pivagabin according to claim 1 or 2, characterized in that said pharmaceutical composition comprises a quantity of pivagabin such that it ensures a level of administration of from 10 to 150 mg/kg/day.
5. Use of pivagabin according to claim 1 or 2, characterized in that said pharmaceutical composition comprises a quantity of pivagabin such that it ensures a level of administration of from 10 to 50 mg/kg/day.

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