*Pharmacology Biochemistry & Behavior*, Vol. 23, pp. 653–659, 1985. © Ankho International Inc. Printed in the U.S.A. 0091-3057/85 $3.00 + .00

# Pharmacological and Clinical Studies of Cyclopyrrolones: Zopiclone and Suriclone

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Received 4 March 1985

JULOU, L., J. C. BLANCHARD AND J. F. DREYFUS. *Pharmacological and clinical studies of cyclopyrrolones: Zopiclone and suriclone.* PHARMACOL BIOCHEM BEHAV 23(4) 653–659, 1985. —Among the non-benzodiazepine compounds which have been found to interact with the "GABA receptor-BZ receptor-chloride channel complex," the very chemically original cyclopyrrolone family has a special place. This has been demonstrated using selected pharmacological, biochemical and clinical data obtained with two cyclopyrrolones, zopiclone and suriclone, which, in addition to their capacity of displacing BZ from their sites, simultaneously possess the main pharmacological properties of BZ and well established therapeutic activities, as hypnotic and anxiolytic, respectively. However, although cyclopyrrolones recognize BZ receptor sites, their mechanism of action might not exactly fit with that of BZ. Indeed, using tritiated zopiclone and suriclone, it has been shown that they could act on sites distinct from those of BZ or could induce receptor conformational changes different from those induced by BZ.

Cyclopyrrolones Zopiclone Suriclone

SINCE the discovery in 1977 [19,24] of high affinity benzodiazepine (BZ) binding sites in rat and human brain, which was a major step in the understanding of the mechanism of action of this class of "minor tranquilizers," the search for potential non-BZ anxiolytics interacting with the BZ receptors or the "BZ receptor-GABA receptor-chloride channel complex" has become very active and fruitful, as will appear from this symposium.

However, among the non-BZ compounds which have been found to interact with the BZ receptor, those of the cyclopyrrolone family seem to have a special place.

Firstly, the potential interest of this original and first non-BZ family as a source of "minor tranquilizers" of the BZ type was indeed established between 1970 and 1976 [16], before the discovery of BZ binding sites in brain, thanks to the use of a battery of "classical psychopharmacological techniques," which were considered as characterizing the pharmacological spectrum of BZ. Moreover, for primary screening, among these techniques, a paramount importance was given to the pentylenetetrazole-induced convulsions test.

Secondly, starting from the discovery of the chemical lead of this family (RP 24 361), which had a complete spectrum of activities but a low potency and a narrow safety margin, about 500 compounds were synthesized in our laboratories [16] and a general formula of the cyclopyrrolone family can at present be proposed (Fig. 1). It consists of a pyrrolone-2 condensed in positions 3–4 with a cycle (a benzene nucleus or a heterocycle), with a heterocycle in position 1 and in position 5 an alcohol function esterified by a carbamic acid.

Thirdly, although chemically very different from BZ such as nitrazepam and diazepam, zopiclone (RP 27 267) and suriclone (RP 31 264) (Fig. 2), the two most thoroughly studied compounds of the cyclopyrrolone family, are, to our knowledge, up to now, the first non-BZ compounds which possess simultaneously the following properties: (1) the main types of activities characterizing the pharmacological profile of hypnotics or anxiolytics of the BZ family which we presented as early as 1978 in the case of zopiclone [1], with an extended paper published later [15]; (2) the capacity of displacing BZ from their sites which we published as early as 1979 in the case of zopiclone [3,4]; (3) a well established therapeutic activity as an hypnotic (zopiclone) [20] or anxiolytic (suriclone) [2,14].

Our paper, which is focused on zopiclone and suriclone, and bears upon selected data from many available results, will be divided into four parts: Method, Pharmacological Actions, Mechanism of Action, Clinical Results.

## METHOD

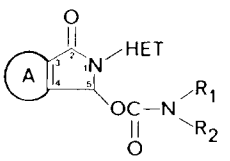
### *Animals*

The mice (18–25 g weight) were $CD_1$ (COBS) or $OF_1$ (IOPS) strain from Charles River (France) and IFFA-CREDO (France); the rats (150–250 g weight) were CD (COBS) strain from Charles River (France). Cats were mongrels (3–4 kg weight).

### *Drugs*

For pharmacological experiments, drugs were administered orally, generally as a suspension in an aqueous solution of gum arabic (volumes administered: 25 or 50 ml/kg PO in the mouse, 5 ml/kg PO in the rat, 1 ml/kg PO in the cat).

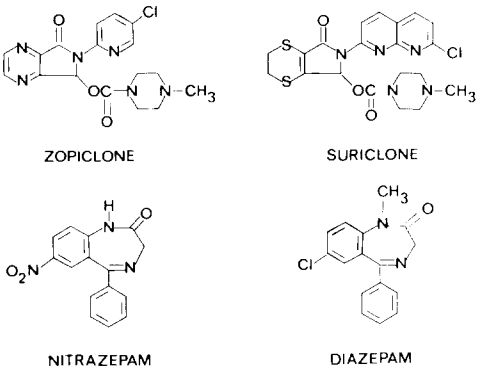
For binding studies the unlabelled drugs were dissolved in the buffer (Tris-HCl, 50 mM, pH 7.4) or, if necessary, in 50% (v/v) dimethylformamide-buffer at a concentration of $1.2\ 10^{-4}$ M. The maximal concentration of dimethylformamide in the incubation medium was 0.25% (v/v).



CYCLOPYRROLONES

| A ( examples ) | HET ( examples ) |
|---|---|
| BENZENE | PYRIDINE |
| PYRIDINE | PYRIDAZINE |
| PYRAZINE | QUINOLINE |
| DIHYDRODITHIINE | NAPHTHYRIDINE |

FIG. 1. General chemical structure of cyclopyrrolones.



ZOPICLONE SURICLONE NITRAZEPAM DIAZEPAM

FIG. 2. Chemical structure of two cyclopyrrolones (zopiclone and suriclone) and two benzodiazepines (nitrazepam and diazepam).

*Pharmacological Studies*

Most of the techniques used for the determination of the pharmacological profile of drugs are well known and it is not necessary to describe here the detailed protocols. We shall, however, give occasionally in the tables or in the figures some information on the experimental conditions and the reference of one of our previous publications [15].

*Biochemical and Electrophysiological Studies*

We shall give in the tables the references of our previous papers where the description of the techniques that we have used will be found.

*Clinical Studies*

The methodology and study conditions can be found in the papers referred to in this article and mentioned in the reference section.

## PHARMACOLOGICAL ACTIONS

Using various experimental models, we have shown that zopiclone and suriclone exert the 5 main types of activities—anticonvulsant, myorelaxant, anti-aggressive, sedative-hypnotic and anticonflict (or anxiolytic)—which characterize more or less specifically the pharmacological profile of BZ.

In Table 1, we present some data which we obtained with zopiclone, suriclone, nitrazepam and diazepam.

Against pentylenetetrazole-induced convulsions, a test considered as specially useful for predicting clinical potency of BZ—this was pointed out by Zbinden and Randall in 1967 [29] and again, in 1981, by Haefely *et al.* [13]—zopiclone and suriclone were found to be very active. At least in rats, their potencies were in the same range as those of nitrazepam and diazepam.

Moreover, as shown in the bottom of Table 1, as an example, in rats the safety margins of zopiclone and suriclone are very high, at least as high as those of BZ.

Although we do not present here the corresponding data, it is worth mentioning that we have shown [15,16] in mice that zopiclone and suriclone are very active (but 5 to 15 times less than diazepam) against many other convulsants which are known to interfere with the "GABA ionophore receptor complex," directly such as picrotoxin and bicuculline, or with the synthesis of GABA such as isoniazid, allylglycine and 3-mercaptopropionic acid.

Zopiclone and suriclone are also active against electrically-induced convulsions such as maximal electroshock [15,16]. But it is especially worth considering their activities against amygdalar kindling seizures in the rat, which, as indicated in Table 1, are close to those of nitrazepam and diazepam, respectively. Indeed, in this epilepsy model, daily electrical stimulations of amygdala induce a progressive increase of epileptic afterdischarge duration, accompanied by more and more evident epileptic behavioral symptoms, leading, after about 2 weeks, to a generalized convulsive crisis. Neuronal pathways in the kindled brain apparently become sensitized to a previously ineffective stimulus and the sensitization persists for several weeks: in 1982, Braestrup and Nielsen [9] proposed the hypothesis of the existence of some analogy between this phenomenon and the mechanism of induction of an anxiety state in man after repeated stresses.

Concerning myorelaxant activity, zopiclone and suriclone were found in mice, rats and cats to be less active than nitrazepam and diazepam.

A similar situation was found when considering the anti-aggressive and sedative-hypnotic activities in mice and rats. It can, however, be mentioned that, in this latter species, in the confinement motor activity test, suriclone was found to be about two times less active than zopiclone and nitrazepam and very close to diazepam.

The "anxiolytic effects" of zopiclone and suriclone were compared with those of diazepam in the conflict test as described in 1973 by Cook and Davidson [10]. Both cyclopyrrolones were found to be active and similar to diazepam.

It appears that zopiclone alleviates, over a dose range of 2.5 to 20 mg/kg PO the suppressant effects of punishments, while significantly decreasing the unpunished responses only from 20 mg/kg PO (Fig. 3 and Table 1). This demonstrates a clear anticonflict activity of zopiclone which has also been confirmed by other authors [23, 26, 28]. The minimal effective dose of diazepam and the dose inducing a significant decrease of unpunished responses are similar to those of zopiclone. Suriclone also possesses a clear anti-conflict activity which does not noticeably differ from that of diazepam (Fig. 3 and Table 1). It alleviates over a dose range of 2.5 to 20 mg/kg PO the suppressant effects of punishments.

We have obtained similar results with suriclone in a rapid conflict method using a continuous reinforcement (CRF) schedule in water deprived rats, with 3 test periods of 5 minutes each, the intermediate period being simultaneously rewarded and punished, while the other two are only rewarded [25].

TABLE 1

PHARMACOLOGICAL ACTIVITIES OF CYCLOPYRROLONES (ZOPICLONE AND SURICLONE) IN COMPARISON TO THOSE OF BENZODIAZEPINES (NITRAZEPAM AND DIAZEPAM)

| Activity/Test*† M=Mice, R=Rats, C=Cats | | $ED_{50}$ or MED‡ (mg/kg PO) Zopiclone | Suriclone | Nitrazepam | Diazepam |
|---|---|---|---|---|---|
| Anticonvulsant | | | | | |
| Pentylenetetrazole (150 mg/kg SC) | M | 5.4 | 2.7 | 0.2 | 0.4 |
| | R | 1.2 | 2.4 (1 hr) | 0.8 | 7.9 |
| Amygdalar kindling seizures | R | ~ 0.6 (0.30 hr) | ~ 2.4 | ~0.4 | ~ 1.3 |
| Myorelaxant | | | | | |
| Traction grasping | M | 14.5 | 7.0 | 1.2 | 2.4 |
| Inclined screen | R | 42 | 50 | 1.0 | 12 |
| Limpness of hind legs | C | ~15 | ~12 (1 hr) | ~0.5 | ~ 1.0 |
| Anti-Aggressive and Sedative-Hypnotic | | | | | |
| Fighting behavior (electrically induced) | M | 12 | 12.5 | 0.3 | 2.3 |
| Righting reflex after chlorpromazine (5 mg/kg SC) | M | 32 | 6.0 | 0.4 | 2.0 |
| Confinement motor activity | R | 5.2 | 11.6 | 4.1 | 13.8 |
| Anxiolytic (Cook's Conflict) | | | | | |
| Punished behavior/unpunished behavior‡ | R | 2.5/20 | 2.5/20 | — | 2.5/40 |
| Safety Margin | | | | | |
| $LD_{50}/ED_{50}$ (pentylenetetrazole) | R | ~1900 (2310/1.2) | ~1900 (4500/2.4) | ~2700 (2200/0.8) | ~300 (2425/7.9) |

*For technical details, see [15].

†Tests were performed 1 hr (zopiclone, nitrazepam, diazepam) or 1 hr 30 min (suriclone) after drug administration or otherwise precised under the $ED_{50}$.

‡MED: minimal effective dose.

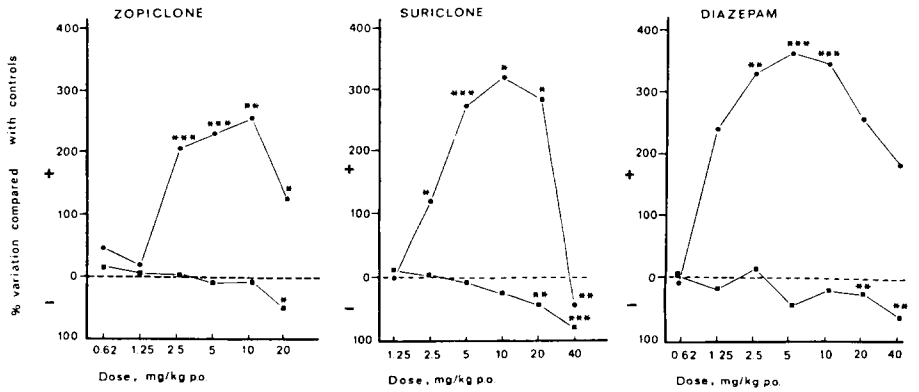



FIG. 3. Anxiolytic activity of zopiclone, suriclone and diazepam in the conflict conditioning test in rats. Drugs were administered by oral route 1 hr (zopiclone and diazepam) or 1 hr 30 min (suriclone) before the test. $FR_{10}$, punished schedule component (●); $VI_{30}$s, non-punished schedule component (■). $*p \leq 0.1$; $**p \leq 0.01$; $***p \leq 0.001$.

## MECHANISM OF ACTION

Following the discovery in 1977 by Squires and Braestrup, and Möhler and Okada of high affinity BZ binding sites in rat and human brain, we first published, in 1979 in the case of zopiclone [3] and in 1983 in the case of suriclone [5], the high affinity of these two cyclopyrrolones for BZ binding sites in rat brain.

We present in Table 2 some selected data demonstrating: (1) the high affinities, in the nanomolar range, of zopiclone and suriclone for central BZ receptors in rat hippocampus and cerebellum; zopiclone affinity (36 nM) is in the same range as those of nitrazepam and diazepam, while that of suriclone (0.8 nM) is clearly stronger; as in the case of both BZ, the affinities of zopiclone and suriclone are practically the same in the two brain regions; (2) the absence of affinity

TABLE 2

COMPARISON OF CYCLOPYRROLONE AND BENZODIAZEPINE AFFINITIES

| Activity/Test* (Rat) | | Zopiclone | Suriclone | Nitrazepam | Diazepam |
|---|---|---|---|---|---|
| Affinity for Central Benzodiazepine Receptors | | | | | |
| [$^3$H] Flunitrazepam $K_i$ (nM) | Hippocampus | 36 | 0.82 | 9.5 | 14 |
| | Cerebellum | 22.5 | 0.87 | 15.5 | 13 |
| Affinity for Peripheral Benzodiazepine Sites | | | | | |
| [$^3$H] Flunitrazepam $IC_{50}$ (nM) | Kidney | >1,000 | >1,000 | >1,000 | 30 |
| [$^3$H] Ro 5-4864 $IC_{50}$ (nM) | Cerebellum | >100,000 | >100,000 | — | 62 |
| Affinity for Other Brain Receptors | | | | | |
| Serotonin, GABA, Norepinephrine $\alpha_1$–$\alpha_2$ Dopamine, Acetylcholine | | None (10 $\mu$M) | None (10 $\mu$M) | None (literature) | None (literature) |

*For technical details see [3, 4, 5].

TABLE 3

MAIN CHARACTERISTICS OF CYCLOPYRROLONE BINDING SITES

| Activity/Test* (Rat) | | [$^3$H] Zopiclone | [$^3$H] Suriclone | [$^3$H] Flunitrazepam |
|---|---|---|---|---|
| Specific Binding Characteristics | | | | |
| Hippocampus | $K_D$ (nM) | 16 ± 3.5 | 0.52 ± 0.12 | 1.65 ± 0.1 |
| | $B_{max}$ (fmol/mg protein) | 663 ± 133 | 1790 ± 394 | 1539 ± 307 |
| Cerebellum | $K_D$ (nM) | 16 ± 4.4 | 0.65 ± 0.16 | 2.6 ± 1.29 |
| | $B_{max}$ (fmol/mg protein) | 1100 ± 155 | 1524 ± 554 | 1327 ± 334 |
| Displacement Studies ($K_i$ nM) | | | | |
| Hippocampus | Flunitrazepam | 3.4 | 4 | 2.3 |
| | Diazepam | 19 | 19.5 | 14.5 |
| | Nitrazepam | 18 | 14.5 | 9.5 |
| | Ro 15-1788 | 0.8 | 1.05 | — |
| | CL 218 872 | 124 | 641 | 699 |
| | PK 8165 | 175 | 147 | 77 |

*For technical details see [4,5].

of zopiclone and suriclone for peripheral BZ sites (in the kidney and the cerebellum), similar to nitrazepam, in contrast to diazepam; (3) the absence of affinity of both cyclopyrrolones and both BZ for other brain receptors, which indicates a similar specificity of both types of compounds for BZ receptors.

Thanks to the availability of [$^3$H] zopiclone (30 Ci/mmol) and [$^3$H] suriclone (33 Ci/mmol), we have also been able to demonstrate specific binding of both cyclopyrrolones to rat brain membranes.

In Table 3, we present, in comparison with flunitrazepam, the binding characteristics of zopiclone and suriclone. These results confirm the high affinity of both cyclopyrrolones, comparable in hippocampus and cerebellum, previously shown by displacement studies. It can be mentioned that the affinity of suriclone is slightly stronger than that of flunitrazepam and that the number of sites labelled by both compounds is very similar.

Moreover, displacement studies have shown that BZ such as flunitrazepam, diazepam, nitrazepam, Ro 15-1788, as well as non-BZ compounds such as the triazolopyridazine derivative CL 218 872 and the quinoline derivative PK 8165, which are known to possess affinity for BZ receptors, are also able to compete for sites labelled by [$^3$H] zopiclone and [$^3$H] suriclone. In addition, it can be seen that the relative $K_i$ potencies of these different compounds are similar when using either the cyclopyrrolones (except with zopiclone for CL 218 872) or flunitrazepam as ligands.

We have however found some differences between cyclopyrrolones and BZ in their binding modifications induced by various agents.

Indeed, as shown in Table 4, in contrast to BZ, such as nitrazepam and diazepam, the affinities of zopiclone and suriclone are only slightly decreased after flunitrazepam photolabelling: $IC_{50}$ ratios higher than 15 in the case of both BZ, while between 1.5 and 2.5 for both cyclopyrrolones. These results indicate that zopiclone and suriclone, which behave pharmacologically and clinically as agonists of BZ receptors, are much less sensitive than either agonist of the BZ family to the receptor sites changes induced by photolabelling [6].

Table 4 also shows the absence of modulation by GABA

TABLE 4

DIFFERENCES BETWEEN CYCLOPYRROLONE (ZOPICLONE AND SURICLONE) AND BENZODIAZEPINE BINDING

| Activity/Test* | | Zopiclone | Suriclone | Nitrazepam | Diazepam |
|---|---|---|---|---|---|
| Photolabelling by Flunitrazepam Photoshift: $IC_{50}$ Ratio | | | | | |
| Hippocampus (Rat) | [$^3$H] Suriclone | 1.4 | 1.8 | 16 | 71 |
| | [$^3$H] Ro 15-1788 | 2.6 | 1.3 | — | — |
| Influence of GABA in Rat Hippocampus: | | | [$^3$H] Zopiclone (15 nM) | [$^3$H] Suriclone (0.4 nM) | [$^3$H] Flunitrazepam (1 nM) |
| On Binding Variation (%) (0°C—GABA 100 $\mu$M): | | | + 6 | − 6 | +45 |
| On Thermal Inactivation (60°C): Delay (min) for 50% Binding Decrease | without GABA | | 7 | 18 | 24 |
| | with GABA (10 $\mu$M) | | 19 | 68 | 79 |

*For technical details see [4, 5, 6].

TABLE 5

BIOCHEMICAL AND ELECTROPHYSIOLOGICAL EVIDENCES OF A LINK BETWEEN CYCLOPYRROLONES AND GABAERGIC SYSTEM

| Activity/Test* | Zopiclone | Suriclone | Nitrazepam | Diazepam |
|---|---|---|---|---|
| cGMP Decrease—Cerebellum (Rat) | | | | |
| Minimal Effective Dose (mg/kg PO) | ~ 2.5 | ~ 1 | ~ 2.5 | ~10 |
| Time (hours) | 0.30 | 2.30 | 0.30 | 2.30 |
| Decrease (%) | ~35 | ~35 | ~35 | ~40 |
| Dorsal Root Potential (Cat) | | | | |
| Dose (mg/kg IV) | 1.0 | 0.5 | — | 0.5 |
| Time (hours) | | 0.30 | — | 0.30 |
| Increase (%) | Active† | ~60 | — | ~60 |

*For technical details see [4,8].
†Results obtained by Polc *et al.* [22].

of cyclopyrrolones binding. This is another difference between the two chemical families.

However, as it appears also in Table 4, the adjunction of GABA, at the concentration of 10 $\mu$M during the incubation time, clearly increases the delay required to reduce by 50% the binding of zopiclone and suriclone by thermal inactivation, as in the case of flunitrazepam.

From most of the previous *in vitro* binding studies, we can hypothesize that, although zopiclone and suriclone specifically displace BZ from their receptors with high affinity, they could act on sites distinct from those of BZ or could induce receptor conformational changes different from those induced by BZ. This hypothesis is reinforced by other data that we have presented in another symposium [7]; these data will be published more extensively later.

However the fact that GABA protects zopiclone and suriclone binding, like flunitrazepam binding, from heat inactivation, indicates that, in the case of both cyclopyrrolones, there could exist a link between their binding sites and GABA receptors as for BZ receptor sites [4,8].

The *in vivo* results presented in Table 5 confirm the validity of this statement. Indeed, after oral administration to the rat, zopiclone and suriclone are able, like the two BZ, to decrease the cGMP content in the cerebellum, an effect which is now considered to be a consequence of an activation of GABAergic system. Moreover, as also shown in this table, after intravenous injection, similar to BZ, zopiclone and suriclone enhance the dorsal root potentials of the cat, an effect which reflects the increase in the presynaptic GABAergic inhibition of monosynaptic excitation of spinal cord motoneurones.

In another type of biochemical experiment [8], we have shown that suriclone is capable, similar to diazepam, of inhibiting, at high doses (50 mg/kg PO) in the rat striatum, the homovanillic acid (HVA) increase induced by a neuroleptic agent (thioproperazine: 0.5 mg/kg SC), an effect which, according to Keller *et al.* [17], reflects an activation of the striato-nigral GABAergic system.

We must, of course, also recall the importance of the protecting activities of zopiclone and suriclone against convulsants interfering with the GABAergic function such as bicuculline, isoniazid, allylglycine and 3-mercaptopropionic

acid. It must, however, be recalled that both cyclopyrrolones are devoid of any direct effect on GABA receptor ($^3$H-muscimol binding) [4,8].

## CLINICAL RESULTS

Both cyclopyrrolones have been studied in man, especially zopiclone, the results on which have been published in numerous papers, the first of them in 1979 [11], and particularly in the International Symposium "Zopiclone, a third generation of hypnotics" [20]. Initial results on suriclone are also available [2,14].

It is worth mentioning that another compound of this series, suproclone, is undergoing international development [12, 18, 21].

Zopiclone has been developed as an hypnotic but it also possesses some mild anxiolytic properties. In man, zopiclone is rapidly and completely absorbed; peak plasma levels are obtained in about 1 hour; the distribution half-life is about 1.5 hours and the plasma elimination half-life is about 4.5 hours.

Sleep laboratory studies and clinical trials in chronic and situational insomnia, both in adult and in elderly patients, showed that clinically significant hypnotic effects could be obtained with doses as low as 5 mg but that the dose leading to the best balance between hypnotic properties, effects on performances and adverse reactions was 7.5 mg.

Sleep laboratory studies showed this dose of zopiclone to be as effective as flurazepam 30 mg or nitrazepam 5 mg. Clinical studies showed it to be at least as effective as flunitrazepam 1 mg, triazolam 0.5 mg or temazepam 20 mg.

Zopiclone has been shown to retain its effectiveness over prolonged periods of time (up to 1 year). Long-term administration, on the other hand, did not lead to significant adverse effects on clinical tolerance or biological parameters.

In healthy volunteers, sleep stage changes were limited and became significant only with doses larger than 7.5 mg. Usually, stage 2 is increased and REM is delayed, intra-night compensation leading to a globally unchanged proportion of the latter. Zopiclone is almost devoid of effects on SWS, which if anything is slightly increased.

Since zopiclone has short distribution and elimination half-lives, residual effects in the morning are generally insignificant. Psychometric tests in healthy volunteers (both young and aged) showed the product to be almost devoid of side-effects at doses of up to 7.5 mg. When residual effects are present, however, they are not detected for more than 12 hours after drug intake.

Three features seem to distinguish zopiclone from benzodiazepines: (1) with doses of up to 7.5 mg, there is almost no interaction with alcohol which can be detected by the usual psychometric tests; (2) respiratory depression is almost absent with doses of up to 7.5 mg; (3) dependence potential could not be shown in polydrug abusers. Obviously, if these findings are confirmed in actual practice, zopiclone will represent a significant advance in the field of hypnotics.

Suriclone appears to be an anxiolytic with limited effects on vigilance. Quantitative EEG studies showed that with doses of 0.5 mg and higher a typical anxiolytic EEG profile was obtained with a slower onset but a longer duration of effect than diazepam.

In generalized anxiety disorders, an anxiolytic effect could be detected with doses as low as 1 mg/day. Controlled dose-response studies showed the best balance between effectiveness and tolerance to be achieved in the dose range of 1.2 to 1.8 mg/day.

Controlled clinical studies in the same indication have shown suriclone 1.5 mg/day to be at least as effective as lorazepam 5 mg/day or diazepam 20 mg/day.

The profile of somatic complaints following drug administration clearly differs from that of benzodiazepines; drowsiness is less frequent but dizziness appears to be more frequent with suriclone.

No significant changes both from a clinical point of view and on biological parameters were noted in long-term (up to 1 year) administration studies in man.

In patients with somatic symptoms of anxiety, some effect was seen with doses as low as 0.3 mg/day. In such patients the optimal dose ranges between 0.4 and 0.6 mg/day.

Preliminary results on performance and alcohol interaction have been obtained with these low doses. The effect on performance is similar to that of benzodiazepines whereas suriclone appeared to reverse the alcohol-induced impairment of performances.

Initial results of the studies on dependence potential showed that the "linking" of suriclone by polydrug abusers was low, at most equal to that of benzodiazepines.

Thus, the results obtained up to now with suriclone confirm the potential therapeutic usefulness of this drug against anxiety.

## CONCLUSION

Among the non-BZD compounds which have been found to interact with the "so-called BZ receptors," the very chemically original cyclopyrrolone family, illustrated in this paper by zopiclone and suriclone, seems to have a special place. They possess the 5 main types of activities (anticonvulsant, myorelaxant, anti-aggressive, sedative-hypnotic and anti-conflict) which are considered as characterizing the pharmacological profile of minor tranquilizers of the BZ type. Moreover their safety margins are very high, at least as high as those of BZ. They have a high and specific affinity for BZ receptors, but could, however, act on sites distinct from those of BZ or could induce receptor conformational changes different from those induced by BZ. As suggested by R. R. Trifiletti and S. H. Snyder [27], cyclopyrrolones could act on "a site on the BZ receptor complex, allosteric to the recognition site for BZ."

Whatever the precise meaning of those latter differences between the two families, *in vivo* biochemical and electrophysiological studies suggest that the GABAergic system is also involved in the mechanism of action of zopiclone and suriclone.

Studies on more than 2000 volunteers and/or patients confirmed the clinical usefulness of cyclopyrrolones, as an hypnotic for zopiclone and as a somewhat atypical anxiolytic for suriclone.

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