ORIGINAL ARTICLE

Psychomotor and cognitive effects of piribedil, a dopamine agonist, in young healthy volunteers

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ABSTRACT

Piribedil is a dopamine agonist acting on D_2 and D_3 central nervous system dopamine receptors. This drug has been administered to 12 young healthy male volunteers (age 22 ± 2 years) according to a single center randomized, double-blind, two ways cross-over, placebo controlled trial, including a washout period of one week. Placebo and piribedil were administered by a single intravenous infusion over 2 h (3 mg). Psychomotor performance and cognitive functions were assessed through a standardized and computerized psychometric tests battery and a continuous electroencephalogram (EEG) mapping. Piribedil improved simple reaction time ($P = 0.02$), immediate ($P = 0.045$ and 0.004), and delayed free recall ($P = 0.05$), dual coding test ($P = 0.02$) and increased theta and fast beta waves on the EEG ($P < 0.05$ and 0.001, respectively). No deleterious effect was observed on the tests exploring attention and concentration via the other procedures. It is concluded that a single intravenous perfusion of piribedil 3 mg improves alertness and the information processing speed within the central nervous system, in healthy volunteers.

INTRODUCTION

A large amount of neurochemical and clinical studies contributed to demonstrate that dopamine (DA) is a neurotransmitter not only involved in the motor disturbances of Parkinson's disease but also in the ageing process, either in animal or in human brain [1–3]. Dopamine is particularly vulnerable to the effects of age, notably in the prefrontal cortex (PFC) [4]. Neurochemical and behavioural changes suggest that DA loss may contribute to PFC age-related cognitive decline, particularly as DA is vital to proper PFC function [5,6]. In that respect, DA or its precursor levodopa, and more recently DA agonists, appear as potential candidates to treat age-related cognitive disorders [7] or mild cognitive impairment (MCI), as recently demonstrated by Nagaraja and Jayashree [8] in a randomized double-blind study.

Piribedil [9] is a synthetic DA receptor agonist acting directly on D_2 ($Ki = 1.3 \times 10^{-7}$ mol/L) and D_3 ($Ki = 2.4 \times 10^{-7}$ mol/L) central nervous system (CNS) receptors as well as on D_1 through its main active metabolite S584 [10,11]. Any affinity for the serotonergic, histaminergic or cholinergic receptors have been described but Millan *et al.* [12] have shown that piribedil displays antagonist properties at α_2-adrenoceptors. This receptor binding profile explains the potential benefit that could be obtained by the use of piribedil not only as a symptomatic pharmacological agent in Parkinson's disease [13,14] but also in age-related cognitive disorders, the daily dosage varying according to the main indication of this drug: 100–250 mg/day in Parkinson's disease;

50–150 mg/day in cognitively impaired elderly individuals [15,16]. Many, mainly ancient studies, definitively demonstrated the possibility to restore cognitive functions (memory, reaction times, speed of information processing and so on) through the use, in humans, of DA agonists, either direct like lisuride, ropirinole or pergolide or indirect like levodopa and amantadine [17,18]. Recent developments in the pharmacology of cognition [19] justify a reappraisal of the problem through experimental designs focused on the impact of drugs on the main cognitive functions. This approach may be highlighted by recently-raised questions such as the possibility of deterioration of vigilance by DA agonists [20], the clear-cut involvement of cognitive and memory disturbances in Parkinson's disease [21], as well as the rapid development of the pharmacology of cognition during the recent years [22].

The present study was designed to assess the effect of a single intravenous infusion of piribedil, 3 mg, over 2 h, on psychomotor and cognitive functions and performance, and electroencephalogram (EEG), in young healthy volunteers, compared to placebo, according to standardized phase I studies.

MATERIALS AND METHODS

Study design

This study was a single centre, randomized, double blind, two-way cross-over, placebo-controlled design, with a wash-out interval of one week. The study protocol was approved by the Ethics Committee of Brest (France).

Subjects

Twelve young healthy male volunteers (age 22 ± 2 years; weight 69 ± 6 kg; height 177 ± 5 cm) were included after a selection visit. The volunteers were male Caucasians with ages ranging from 18 to 35 years. Clinical examination, including blood pressure, pulse rate, electrocardiogram and biological data (haematology, biochemistry, urinalysis) had to be within normal ranges. Written informed consent had to be obtained from each subject. Alcohol intake or smoking were considered as exclusion criteria as well as caffeine or any drug intake during the study.

Study medication

Placebo and piribedil (3 mg) were randomly administered by single intravenous infusion over 2 h. Piribedil was given intravenously (one vial of 1 mL) in order to avoid the large first pass-effect encountered after oral administration and consequently to obtain less variability in plasma drug concentrations. The duration of the infusion and the dosage of piribedil were chosen according to the usual and well known adverse drug reactions of DA agonists, notably in healthy volunteers.

Assessment criteria

Psychomotor performance and memory

A battery of tests was used to regularly and continuously assess psychomotor performance and cognition. These tests, which have been extensively used for this type of investigations [23,24], are shortly described below.

Simple Reaction Time (SRT). This test explores the alertness and fatigue by the speed of reaction to a simple visual stimulus. The score is the mean reaction time to 21 randomly presented stimuli.

Tapping Test (TAP). This procedure evaluates motor activity by measuring the subject's ability to make fast movements of the wrist and fingers. The subject had to tap a plate with the spike of a stylus, as quickly as possible for 30 s. The score is the mean number of hits per seconds.

Arithmetic Calculation Test (PAULI). This test assesses attention and concentration. The subject had to add together the two digits of numbers during three minutes. Final outcome is the number of correct answers.

Digit Symbol Substitution Test (DSST). This procedure evaluates attention and information processing [25]. The subject had to associate as quickly as possible digit to symbol according to an example. Final outcome is the number of correct associations.

Body Sway (BS). Posturography is an objective method used to detect the effects of sedative drugs on body balance and attention [26]. This technique is designed for measuring and recording involuntary postural oscillations of a subject placed on a calibrate force platform. Foot position are marked on the platform so the subject's feet could be exactly positioned on a repeated basis. Subjects were asked to stand erect and motionless, staring at a plumbline placed in front of them. Recording time is 2 min (1 min with eyes open and 1 min with eyes closed). The signals emitted by the platform are analysed by a computer and the parameters retained for analysis are the total displacement distance of the gravity center (eyes open and eyes closed) and the surface corresponding to this displacement (eyes open and eyes closed).

Dual Coding Test (DCT). This test simultaneously measures immediate free recall of words and pictures.

Previous studies [27,28] have emphasised that picture memorization involves a dual coding, in a visual and a verbal coding, respectively. This verbal coding needs 500 ms in young subjects and 1 s in elderly subjects to appear (breakpoint of dual coding). Five sets of eight pictures and eight words are shown to the subject, with presentation times that decrease from 1920 ms to 120 ms (1920 ms, 960 ms, 480 ms, 240 ms and 120 ms). Outcomes are the dual coding breakpoint as well as the difference between pictures recall and words recall at time 1920 ms (with dual coding) and 120 ms (without dual coding) [29].

Digit span under divided attention (WMT). Attentional capacity in working memory (attentional cost) is assessed via WMT. The first period corresponds to the digit span forward; the second period corresponds to the digit span computed from a series of digits derived from the second element of an addition. The subject is presented with an addition and a result; the subject has to state whether the sum is correct or incorrect (push button) and to memorise the sum. He, then, had to perform a digit span on the sum. The trial starts with a series of two additions. The number of additions increases according to the subject's successful performance. Measurement is the difference between the digit span forward and the computed digit span using the addition results (attentional cost). Its principle is to measure the attentional working memory under divided attention.

Learning Memory Test (LMT). This test explores declarative memory (short and long-term memory), i.e. immediate and delayed free recall of words. Twenty-one items (simple words) are presented to the subject on a video screen with a frequency of one word every 500 ms. The subject is subjected to four trials with a different order of presentation at each trial. At the end of each presentation, the subject has to recall as many words as possible. Following these trials, the subject has to perform a distraction task during 3 min and then to recall the words after 1.5 min. The score is the number of correct words recalled.

Electroencephalogram

Electroencephalogram recording was performed before dosing, all along the infusion and post infusion. Subcutaneous needle electrodes were used, in a quiet, dimly lit room, with the subjects in supine position, eyes closed, under resting conditions. Measurement was a spectral analysis of four EEG leads (F4T4, right fronto-temporal; F3T3, left fronto-temporal; T4O2, right parieto-occipital; T3O1, left parieto-occipital). Total energy and its repartition in the different frequency bands of the EEG: delta (0–4 Hz); theta (4–8 Hz); alpha (8–12 Hz); beta 1 (12–16 Hz); beta 2 (16–20 Hz); beta 3 (20–30 Hz); beta 4 (30–40 Hz) and beta 5 (40–50 Hz) were recorded using software developed by the French Army Health Research Center (CRESSA) and the Atomic Energy Center (CEA). EEG was recorded during 5 min at T0 + 0.25 hours, T0 + 0.5 h, T0 + 1 h, T0 + 1.25 hours, T0 + 1.5 h, T0 + 1.75 hours, T0 + 2 h and T0 + 4 h.

Subjective evaluation

Alertness, contentedness and calmness under treatment were assessed using horizontal visual analog scales of 100 mm (VAS) [30]. The subject had to self-evaluate the sensation he experienced by drawing a vertical bar on the scales that opposed two items (i.e. awake – sleepy).

Safety

Adverse events were collected, whether spontaneously reported by the subjects or observed by the investigator, for the duration of hospitalization and during the end of study visit.

The safety assessments were also based on the results of routine physical examinations, vital signs (blood pressure and heart rate), 12-lead electrocardiograms and routine laboratory safety tests.

Experimental design

The order in which the tests were carried out was determined according to the duration of the task and the possible interaction between the tasks. Treatment was administered at T0 (infusion onset, 30 min after breakfast). The schedule was drawn up according to the pharmacokinetic steady-state of piribedil [31]. The washout period between two consecutive sessions was 1 week. All tests were performed before dosing and at T0 + 2.25 hours, T0 + 3.5 h and T0 + 5 h for SRT, TAP, PAULI, BS and WMT, at T0 + 2.5 h and T0 + 5 h for DSST and LMT, at T0 + 2 h and T0 + 6 h for VAS and at T0 + 3.5 h for DCT.

Statistical analysis

The statistical analysis was performed with SAS 6.05 software (SAS Institute Inc, Cary, NC, USA). The statistical analysis threshold was set at 0.05. Values of $P < 0.10$ were considered as a trend. For pharmacodynamic parameters, homogeneity at the baseline was analyzed by a three-way ANOVA (subject, treatment, period). Treatment effects during the course of the study were assessed using a three-way ANOVA (subject, treatment, period)

when appropriate on raw data or on area under the curve (AUC) for parameters with repeated time measurements. For EEG parameters, treatment effects were assessed using a two-way ANOVA (subject, treatment) for each derivation and each evaluation time. Pairwise comparisons were performed using the Student-Newman-Keul's test. The population sample size was based upon previous studies that showed statistically significant effects of psychotropics on cognitive functions and memory tests similar to those used in the present study [32–34]. In the same way, studies with EEG spectral analysis were performed on a similar population sample size [35].

RESULTS

Psychomotor performance and memory

The 12 subjects completed the study. No differences at baseline and no period effect were found for the SRT, TAP, PAULI's and BS tests. For the SRT test, a significant treatment effect was found between T0 + 3.5 h and T0 + 5 h: reaction times are the shortest for subjects receiving the active compound (– 5.8%, $P = 0.02$); a trend to a significant difference was found for the TAP test between T0 + 3.5 h and T0 + 5 h: indeed, the number of hits by second was more important with piribedil than with placebo ($P = 0.08$). No treatment effect was found for the PAULI's test and for the DSST (*Table I*). When considering the BS test, some statistically significant differences were observed (*Table II*): the total length of change of gravity center position with eyes open was more important with piribedil than with placebo between T0 and T0 + 02.25 hours ($P = 0.02$) and inversely between T0 + 3.5 h and T0 + 5 h ($P = 0.05$). The analysis of the same parameter with closed eyes shows significant increase with piribedil between T0 and T0 + 02.25 h ($P = 0.01$) and between

Table I Psychomotor performance and attention results.

	Simple Reaction Time			Tapping Test			Arithmetic Calculation Test			Digit Symbol Substitution Test		
	Mean	SD	*P*-value	Mean	SD	*P*-value	Mean	SD	*P*-value	Mean	SD	*P*-value
Piribedil	374.8	26.64	0.02	10.45	0.91	0.08	141.2	33.03	0.31	203.5	30.43	0.24
Placebo	397.8	39.11		10.14	1.04		146.8	27.67		209.3	42.26	

Simple Reaction Time (msec) (mean AUC and SD with *P*-value) with piribedil and placebo between 3.5 and 5 h after dosing; Tapping Test (tap/sec) (mean AUC and SD with *P*-value) with piribedil and placebo between 3.5 and 5 h after dosing; Arithmetic Calculation Test (PAULI), number of correct responses (mean AUC and SD with *P*-value) with piribedil and placebo between 3.5 5 h after dosing; Digit Symbol Substitution Test, number of items correctly associated (mean AUC and SD with *P*-value) with piribedil and placebo between 2.5 and 5 h after dosing.
SD, Standard deviation.

Table II Body sway results.

	Piribedil		Placebo		
	Mean	SD	Mean	SD	*P*-value
Total length					
Open eyes					
H 0.25–H 2.25	872.16	173.76	799.5	177.94	0.02
H 3.5–H 5	606.19	126.38	684.69	198.17	0.05
Closed eyes					
H 0.25–H 2.25	1387.69	355.98	1251.47	331.05	0.01
H 2.25–H 3.5	794.32	215.06	717.08	166.11	0.03
Area					
Open eyes					
H 2.25 – H3.5	257.29	91.49	328.91	191.49	0.08
H 3.5–H 5	302.75	97.09	464.94	309.28	0.05
Closed eyes					
H 0.25–H 2.25	956.03	610.04	786.94	575.81	0.16
H 2.25–H 3.5	610.36	402.34	501.77	306.17	0.22

Body Sway total length (mm) or area (mm^2), eyes open or closed, (mean AUC and SD with *P*-value) with piribedil and placebo.
SD, standard deviation; h, hour postdose.

T0 + 02.25 h and T0 + 3.5 h ($P = 0.03$). Regarding the second analyzed parameter, the surface, with open eyes, a trend to decrease with piribedil was found between T0 + 02.25 h and T0 + 3.5 h ($P = 0.08$), whereas a significant decrease was found between T0 + 3.5 h and T0 + 5 h ($P = 0.05$); for the surface with closed eyes, no treatment effect was observed.

The analysis of the DCT showed no treatment effect regarding the number of words or pictures recalled either with piribedil or placebo. With a presentation time set at 120 ms, a treatment effect was found on the difference between pictures and words recall: more pictures than words are recalled with placebo ($P = 0.02$). The dual coding breakpoint during the piribedil period appears between 120 and 240 ms ($P = 0.03$) and between 240 and 480 ms during the placebo period ($P = 0.03$). The WMT test shows no significant differences between piribedil and placebo. The LMT test reveals striking differences (*Table III*) for immediate recall at the first trial (short-term), for delayed recall after 4 trials and for recall after the distraction task. In all of these three situations, words recall was improved by piribedil compared with placebo but these differences were only statistically significant for immediate free recall at the first trial (+ 12.9%, $P = 0.045$) and for recall after four trials (+ 10.3%, $P = 0.004$), while a trend to significance was noted with the delayed free recall (+ 11.2%, $P = 0.05$); the observed period effect ($P = 0.037$) was probably due to a learning effect, between the two periods of investigations.

Electroencephalogram

Piribedil produced EEG changes indicative of an increase of vigilance: decrease in alpha waves (8–12 Hz) and increase in theta (4–8 Hz) and particularly fast beta (20–30 Hz) activities. Such an effect is statistically significant ($P < 0.01$ to $P < 0.001$) at T0 + 0.25 h, T0 + 0.5 h and is still present at T0 + 4 h (*Figure 1*). A decrease in 12–16 Hz and 16–20 Hz ($P < 0.05$ and $P < 0.001$, respectively) was noted but it appears to be due to a spectrum reorganization rather than a specific effect of piribedil.

Subjective evaluation

The analyzed parameters were alertness, contentedness and calmness. No statistically significant difference was found before and after treatment administration.

Safety

Following piribedil administrations, seven subjects presented adverse drug reactions at one time: drowsiness at T0 + 6 h for five subjects, vomiting at T0 + 1.75 h for one subject, disorientation at T0 + 8 h for another unique subject. Among the 10 adverse drug reactions observed, seven were classified as mild and three as moderate. These adverse drug reactions spontaneously and rapidly resolved. After placebo, three subjects complained about adverse drug reactions: drowsiness for two subjects at T0 + 6 h and T0 + 6.5 h and headache for one subject at T0 + 6 h. Among the five adverse drug reactions observed, four were classified as mild and one as moderate No serious vital clinical, ECG or biological signs were notified or observed. No sign of treatment-induced dysautonomia was observed.

DISCUSSION

The present study aimed at assessing the potential positive effects of piribedil compared with placebo on psychomotor performance and cognition, in young healthy volunteers. As is usual in phase I clinical trials, a single dose administration is a prerequisite, authorizing a clear definition of the impacts of the drug on the different components of cognition and psychomotor responses. The procedure and experimental design used in this study conform with the admitted technique to obtain the cognitive mapping of CNS compounds. The dosage of piribedil had to take into account the high risk of dopaminergic adverse drug reactions in this healthy

Table III Learning memory test results.

	Immediate free recall			After 4 trials			Delayed free recall		
	Mean	SD	*P*	Mean	SD	*P*	Mean	SD	*P*
Piribedil	30.42	7.30	0.045	10.5	1.37		53.96	11.70	0.05
Placebo	26.88	5.95		9.42	1.62	0.004	47.92	10.38	

Mean Learning Memory Test (mean AUC and SD with *P*-value) with piribedil and placebo between 2.5 and 5 h after dosing.
SD, Standard deviation.

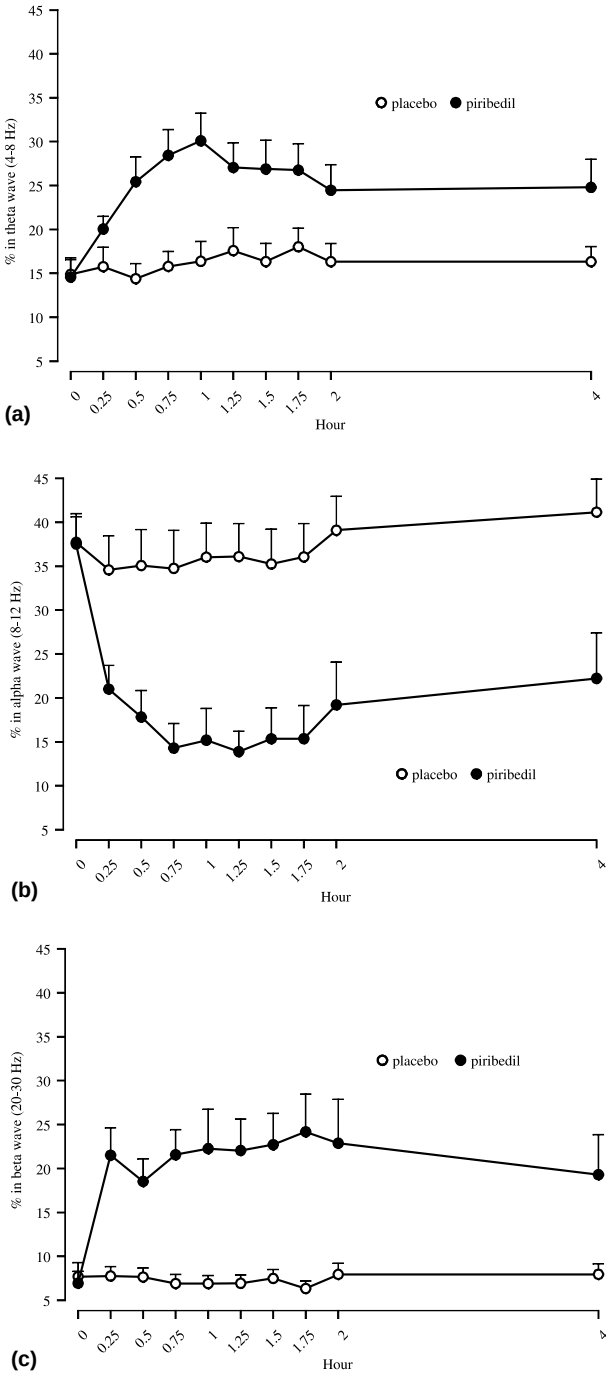

Figure 1 EEG results. (a) Time course of theta activity (4–8 Hz) before 0 and after (0.25–4 hours) IV infusion of piribedil 3 mg vs. placebo (mean ± SD); (b) Time course of alpha activity (8–12 Hz) before 0 and after (0.25–4 hours) IV infusion of piribedil 3 mg vs. placebo (mean ± SD); (c) Time course of beta activity (20–30 Hz) before 0 and after (0.25–4 hours) IV infusion of piribedil 3 mg vs. placebo (mean ± SD).

population. Higher dosage systematically induces nausea and vomiting incompatible with the comfort of the volunteers and with the performing of psychometric tests. To avoid potential drug interactions, we prefer not to associate an antiemetic drug, hence the dosage of 3 mg IV was just below the maximum admitted tolerated dose in healthy subjects. In the present study, mean plasma concentrations of piribedil were 10 ng/mL at the end of the perfusion (results not shown), weak but active concentrations [36]. The present results show that a single administration of piribedil (3 mg IV over 2 h) is devoid of any deleterious effects on cognitive and psychomotor functions, notably speed of reaction (SRT), motor activity (TAP), attention, alertness and information processing (DSST, PAULI's test). This absence of negative effects is corroborated by the subjective assessments through the different VAS assessing alertness, contentedness and calmness; the scores (in mm) during the two treatment periods (piribedil/placebo) were strictly similar.

Conversely, when compared with placebo and despite the fact that cognition and psychomotor performance were at their best at the baseline in this specific healthy group of individuals, piribedil positively improved memory performance assessed by LMT (immediate and delayed free recall) and the DCT, schematically exploring information processing speed within the brain. This effect may be considered as specific for memory components as far as working memory, attention and concentration, assessed on WM, DSST and PAULI's test respectively, are not modified by the active compound in comparison with placebo. The positive effect observed on the TAP is in favour of an objective improvement of alertness and speed of information processing within the brain. This assertion is corroborated by the clear-cut modification of the EEG spectrum obtained after piribedil infusion; in fact, to our knowledge, the CNS drugs increasing theta and beta (20–30 Hz) activities while decreasing alpha waves can be considered as alerting compounds and certainly not sedative [37,38]. The absence of coherence when observing the results obtained on the BS makes difficult any interpretation on the impact of piribedil on the subscores and at different times. The present study performed with a DA agonist appears as very coherent and symmetric when confronting the published results obtained with the same experimental design, with antipsychotics [33,34] which share the pharmacological property to antagonize the brain D_2 dopaminergic receptors [11,39]. Our results are also relevant when compared to the recent study of

Nagaraja and Jayashree [8] who demonstrated, after a randomized, double-blind clinical trial that piribedil (50 mg/day) improves global cognitive function in patients with MCI. As piribedil stimulates three dopaminergic receptors subtypes (D_1, D_2, D_3), and antagonizes α_2-adrenoceptors, it is difficult to try to relate one of these receptors to a specific task or psychomotor activity; however, several experiments carried out in animals, mainly monkeys, clearly demonstrated that postsynaptic dopaminergic stimulation enhances delayed response performance (D_2 receptors), working memory (D_1 receptors), and more globally influence higher cognitive function [39]. In human healthy volunteers, Servan-Schreiber et al. [40] demonstrated the pro-cognitive effect of dopaminergic stimulation and the improvement of attention by D-amphetamine (speeding of reaction time; accuracy in a 'conflict' condition at fast reaction times). Few clinical studies are devoted to the analysis of EEG modifications induced by dopaminergic agents except the study by Luthringer et al. [41] who showed, while using apomorphine (D_1, D_2 agonist), an overall increase in beta activity, in both absolute and relative energy at time 0.5 h postdosing. The results obtained with piribedil in the present study are more clear-cut, more comprehensive and still persist 2 h after infusion stop. This EEG alerting effect should be discussed in relation to the recent publication by Frucht et al. [20], which reports sudden irreversible attacks of sleep induced by two DA agonists, pramipexole (D_2, D_3 agonist) and ropinirole (D_2 agonist); In the present study, a single dose administration of piribedil does not induce deleterious effects on vigilance and alertness. When considering the present, although non exhaustive, cognitive mapping of piribedil, it appears that the improvement of implicit memory, alertness and speeding of information observed in healthy volunteers could be of interest in patients suffering from disorders in this field of psychomotor and cognitive activities, mainly elderly and parkinsonian patients [42–44]. In those situations, the question of dosage will have to be taken into account, knowing that in the present study, the potential adverse drug reactions, and particularly psychostimulation, and the ceiling effect on several components of cognition were a serious limitation to test a superior dosage or to obtain dose-effect relationships curves. Our results are in favour of an absence of deleterious impact of piridebil on psychomotor performance, vigilance, attention or sleep/wakefulness rhythm [45].

CONCLUSION

Piribedil, 3 mg IV infused over 2 h in young volunteers is devoid of any detrimental effects on psychomotor and cognitive performance. The observed and reversible adverse drug reactions, mainly nausea and vomiting may be attributed to the stimulation of DA receptors in the *area postrema*. The improvement of memory is associated with an increase of fast beta waves activity at the EEG and with a positive effect on the TAP. These results confirm both an alerting effect and a speeding information process within the brain, after IV infusion of 3 mg of piribedil. Such studies in healthy volunteers appear as of great interest for research focused on the role of DA on cognition and intelligence [46]. The extrapolation of such phase I results to elderly and parkinsonian patients is hazardous because of the known modifications of central dopaminergic receptors sensitivity in both these conditions; in the same way, dosages and duration of administration considerably vary according to the experimental setting. However, more and more data are in favour of the predictive value of such phase I studies vs. results obtained with patients [47]. Complementary studies should be conducted to confirm these results after repeated administration and to demonstrate a potential therapeutical benefit in elderly and in parkinsonian patients.

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