EEG profile of litoxetine after single and repeated administration in healthy volunteers

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- 1 Litoxetine is a selective serotonin reuptake inhibitor with antidepressant activity in animal models and in depressed patients.
- 2 This double-blind, cross-over, placebo-controlled study was carried out in 12 healthy young male volunteers. The aim was to assess the EEG profile of litoxetine in parallel with its pharmacokinetics after a single dose or multiple administrations for 4 days (6 doses) of two dosages (10 mg and 25 mg). Spectral analysis of four EEG leads (F4-T4, F3-T3, T4-O2 and T3-O1) was done up to 12 h post-dose.
- 3 In single or multiple doses, litoxetine induced EEG changes characterised by a dose-related increase in fast beta energies, mainly beta 2, without any changes in slow waves (delta and theta). A slight reduction in alpha activity occurred only after repeated doses.
- 4 EEG changes occurred after a single oral administration and lasted at least 12 h with litoxetine blood concentrations ranging from 4 to 10 ng ml⁻¹. With repeated administrations, the pharmacodynamic steady-state was achieved as the increase in beta 2 energies was the same before and 12 h post-dose. These effects occurred with litoxetine blood concentrations ranging from 3 to 7 ng ml⁻¹ with the 10 mg dosage and from 8 to 18 ng ml⁻¹ with the 25 mg dosage. The EEG profile did not change after 4 days of repeated administration, indicating that tolerance did not develop.
- 5 $C_{\max}$ and AUC showed proportionality between the administered dosages of 10 and 25 mg. Mean $t_{\max}$ ranged from 3 to 4 h and mean elimination half-life from 7 to 9 h independently of the dosage. Pharmacokinetic steady-state was achieved on day 4. Litoxetine did not accumulate with a twice daily regimen.
- 6 In conclusion, the EEG profile of litoxetine resembles those previously described with non-sedative antidepressants. Such EEG changes generally occur at therapeutic dosages.

Keywords litoxetine EEG serotonin reuptake inhibitor antidepressant
SSRI psychopharmacology clinical pharmacology

Introduction

Litoxetine (SL810385) is a novel, non-tricyclic, potent, selective serotonin reuptake inhibitor (SSRI). It belongs to the benzyloxypiperidine series and exhibits antidepressant activity in numerous experimental animal models [1, 2].

In tests specifically involving serotonergic neurons (i.e. 5-HTP induced head-twitches), litoxetine exhibits considerably more activity than imipramine or indalpine

(ED₁₀₀ values of 0.3, 1.5 and 2 mg kg⁻¹ i.p. respectively), for longer durations and without tachyphylaxis after repeated administration. In behavioural or electrophysiological tests (olfactory bulbectomy, tail suspension test, hopelessness test, learned helplessness, non REM sleep), litoxetine, in doses from 1 to 10 mg kg i.p., is as or more active than imipramine or other SSRIs [2]. Litoxetine also demonstrates anorectic activity [3].

Litoxetine exhibits a high selectivity for inhibiting serotonin uptake relative to noradrenaline or dopamine uptake *in vitro* in rat hypothalamic synaptosomes and human platelets (IC_{50} values of 18 and 13 nM, respectively) and as a result is three to four times more active than fluoxetine. Furthermore, it shows greater specificity. This specificity and selectivity is also demonstrated by radioligand binding studies in rat cortical membranes and by studies of effects on cerebral monoamine metabolism [1].

Litoxetine is devoid of inhibitory activity on monoamine oxidase and has no affinity for cerebral H_1 histaminergic, α_1 , α_2 and β -adrenergic, D_2 dopaminergic and benzodiazepine receptors and only weak affinity for $5HT_2$ receptors [1]. These characteristics suggest that litoxetine will exhibit none of the cardiovascular, sedative, anticholinergic and sympathomimetic effects which are often observed in humans with tricyclic antidepressants. The $5HT_3$ -antagonist properties of litoxetine may prove useful to prevent nausea and vomiting, which are common after SSRI intake [4].

The safety profile is satisfactory in healthy volunteers up to 100 mg twice daily for 14 days. Pharmacokinetic studies show that t_{max} is reached between 3 to 4 h and that the terminal elimination half-life is approximately 8 to 9 h. Pharmacokinetics appear to be linear between 5 to 100 mg, with the C_{max} and AUC increasing proportionally with the dose. Preliminary pharmacodynamic findings demonstrate that litoxetine induces a dose-related reduction in platelet serotonin uptake (50% after 5 mg to 87% after 25 mg) and is devoid of detrimental effects on psychomotor performance or cognitive ability.

The objective of this study was to investigate the EEG profile of litoxetine after single and repeated oral administration.

Pharmaco-EEG studies, which consist of the spectral analysis of EEG recorded after drug intake, have been widely used to characterise the profile of psychotropic drugs [5–8]. This technique has proved to be the most sensitive for early clinical pharmacology studies since it provides objective, quantitative, reliable, non-invasive information about the pharmacodynamic effects of a psychotropic drug on its target organ, i.e. the brain. It yields data on cerebral bioavailability of a drug by evaluating induced EEG changes vs a placebo, on the time-course of CNS activity (onset, peak and duration of the effect), and on drug-induced changes in vigilance, and can help classify the compound according to its EEG profile. Its main advantages over the assessment of psychomotor performance, which is also a useful tool to characterise psychotropic drugs [9], is that it shows no or considerably less sensitivity to motivational factors, practice and learning effects, and personality.

Methods

Study population

Twelve healthy young male volunteers aged 21 to 27 years (mean $\pm$ s.d. 23.7 ± 2.0), with a body weight of 65 to 80 kg (74.1 ± 5.4) and a height of 175 to 189 cm (181.2 ± 4.5) were included in the study. All were

screened within 15 days before dosing, by means of a medical history, a physical examination, an ECG, an EEG, routine laboratory tests (haematology, blood chemistry, urinalysis), and a urine drug screen, to ascertain that they were normal. The nature of the experiment was explained to each volunteer and all volunteers signed an informed consent form prior to participation. The protocol was approved by an Ethics Committee. All medications were prohibited from 2 weeks before the trial to completion of the trial.

Study design and study medication

In this randomised, double-blind, cross-over, placebo-controlled study, all 12 subjects completed three 4-day treatment periods separated by 1-week wash-out intervals.

During each treatment period, the subjects were given oral doses of placebo, litoxetine 10 mg, or litoxetine 25 mg, according to the following schedule: a single oral dose at 08.00 h on day 1, placebo or litoxetine 10 mg or litoxetine 25 mg twice daily (08.00 h and 20.00 h) on days 2 and 3, and finally a single oral dose on day 4 at 08.00 h.

Litoxetine and placebo were supplied in identical capsules. All drugs were given orally with 150 ml tap water in the morning at 08.00 h after an overnight fast. The sequence of drug administration was randomised according to a Latin square design.

Subjects abstained from smoking and drinking xanthine-containing beverages (coffee, tea, cola) or alcohol from 24 h before until the end of each treatment period.

Assessment criteria

EEG recording and signal processing Four EEG leads (right fronto-temporal F4-T4, left fronto-temporal F3-T3, right temporo-occipital T4-O2, left temporo-occipital T1-O3 according to the international 10–20 system) were recorded for 5 min on day 1 (single dose) and on day 4 (repeated doses after six administrations) of each treatment period, before then 30 min, 1 h, 2 h, 3 h, 4 h, 6 h and 12 h post-dose.

All the EEG recordings were performed using subcutaneous needle electrodes in a quiet, dimly lit room, with the subjects lying in a bed with their eyes closed under resting conditions. Such conditions enhance sensitivity for measuring pharmacodynamic parameters such as onset, duration, and peak activity. The reference electrode was secured to the vertex. Recordings were done simultaneously with an Alvar Junior Minidix polygraph and a Schlumberger analogue tape recorder in FM mode.

Recordings were analysed using software developed by the French Army Health Research Centre (CRESSA) and the Atomic Energy Commission (CEA). The four EEG channels were acquired by an Intertechnique IN-2 computer 12 bits after analogue-to-digital conversion at the rate of 200 Hz. The program then computed statistical parameters of the distribution, probability density, mean, moment 2nd order to 4th order with kurtosis coefficient for epochs of 5.12 s. Artifact rejections were done firstly in terms of their amplitude to eliminate artifacts due to eye or head movements and secondly from their standard deviation so as to preserve signal stationarity. Artifact-free 5.12 s epochs were submitted to spectral

analysis and Fast Fourier Transform (FFT) using Cooley Tuckey algorithm and application of Hanning ponderation. For each epoch, total energy, standard deviation, and delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta 1 (12–20 Hz) and beta 2 (20–40 Hz) relative power expressed in percentages of total energy with frequency step between 0.097 and 0.195 Hz were calculated and averaged [10].

Pharmacokinetics Blood samples were collected from a cannula inserted in a forearm vein before and then 30 min, 1 h, 2 h, 3 h, 4 h, 6 h and 12 h post-dose. The blood was immediately centrifuged (1500 g for 10 min) and the plasma was stored at -20°C until the assay. Plasma samples were assayed using high pressure liquid chromatography with spectrofluorometry detection (limit of quantification: 0.5 ng ml^{-1}).

Statistical analysis

EEG was analysed for each lead and each time point using two-way ANOVA (subject and treatment). Pair-wise comparisons were done using LSD means.

Pharmacokinetic parameters ($C_{\max}$, $C_{\min}$, $t_{\max}$, $t_{1/2,z}$, AUC) were calculated and compared using parametric ANOVA or Friedman's tests.

Results

EEG

Total energy Neither litoxetine nor placebo induced significant modifications in the total power of the EEG, regardless of the dose or EEG lead.

Fast beta activity Placebo did not change relative beta energies (20–40 Hz), which ranged from 9.7 to 12.9% in the anterior leads and from 7.2 to 8.9% in the posterior leads throughout the study. In contrast, litoxetine significantly increased these relative beta energies, both after a single oral dose and after multiple oral doses (Table 1, Figure 1). This augmentation was more marked after repeated doses (8 to 9% after 10 mg and 9 to 11% after 25 mg) than after an acute dose (4% after 10 mg

Table 1 Significant EEG changes vs the placebo in the T4-02 EEG lead ($\uparrow$ increase, $\downarrow$ decrease; 10 mg vs placebo: A = $P < 0.05$ and AA = $P < 0.01$; 25 mg vs placebo: B = $P < 0.05$ and BB = $P < 0.01$). The time-course of the significant changes in the three other EEG leads (F4-T4, F3-T3 and T3-01) is very similar

Bands (Hz)	T4-02 lead											
	Day 1				Day 4							
	H3	H4	H6	H12	H0	H0.5	H1	H2	H3	H4	H6	H12
8–12							AA $\downarrow$ BB $\downarrow$	A $\downarrow$ BB $\downarrow$	A $\downarrow$ BB $\downarrow$		A $\downarrow$ BB $\downarrow$	
20–30	B $\uparrow$	B $\uparrow$	AA $\uparrow$ B $\uparrow$	A $\uparrow$ B $\uparrow$	B $\uparrow$	BB $\uparrow$	A $\uparrow$ BB $\uparrow$	A $\uparrow$ BB $\uparrow$	AA $\uparrow$ BB $\uparrow$	AA $\uparrow$ BB $\uparrow$	A $\uparrow$ BB $\uparrow$	AA $\uparrow$ BB $\uparrow$
30–40	A $\uparrow$ B $\uparrow$	B $\uparrow$	B $\uparrow$				A $\uparrow$ BB $\uparrow$	AA $\uparrow$ BB $\uparrow$	A $\uparrow$ B $\uparrow$	A $\uparrow$ BB $\uparrow$	A $\uparrow$ BB $\uparrow$

Figure 1 Time course of the EEG changes in the relative beta activity (20–40 Hz) on T4-02 leads, after single (day 1) or repeated oral administration of placebo (—) or litoxetine 10 ($\circ$) and 25 ($\bullet$) mg. Each point is the mean value of all subjects at the corresponding time.

Figure 2 Time course of the EEG changes in the relative alpha activity (8–12 Hz) on T4-O2 leads, after single (day 1) or repeated oral administrations of placebo (—) or litoxetine 10 (○) and 25 (●) mg. Each point is the mean value of all subjects at the corresponding time.

and 6% after 25 mg). This effect was dose-related, mainly in the occipital lead, and was observed throughout the scalp. It peaked 4 to 6 h post-dose and lasted more than 12 h. On day 4, the increase in beta waves was of comparable magnitude before the dose and 12 h post-dose, suggesting that the pharmacodynamic steady-state had been reached.

Alpha activity Placebo did not change relative alpha energies (8–12 Hz), which ranged from 37.2 to 41.4% in the anterior leads and from 57.7 to 62.3% in the posterior leads. In contrast, litoxetine induced a significant decrease in relative alpha activity after repeated oral administration (Table 1, Figure 2). Alpha activity did not change significantly on day 1 after a single dose of litoxetine: the magnitude of the alpha changes observed were similar to those seen after the placebo (approximately 5%). The alpha reduction observed after multiple doses was more marked in the posterior leads (10 to 12%) than in the anterior leads (5 to 7%). It peaked 2 to 4 h post-dose and disappeared within 6 h.

Slow wave activity Neither the placebo nor litoxetine 10 to 25 mg induced significant changes in relative delta and theta activity after single or repeated doses.

In summary, spectral EEG analysis demonstrated that litoxetine induced an EEG profile characterised by a dose-related increase in fast beta energies (20–40 Hz)—mainly beta 2 (20–30 Hz)—after single or repeated doses, and by a slight reduction in alpha activity after repeated doses only, with no changes in slow activities. Litoxetine effects peaked within 3 to 4 h post-dose. These effects were long-lasting since they persisted 12 h post-dose after a single dose and before the next dose at steady-state (day 4). These EEG effects were more pronounced at steady-state than after a single oral dose.

Pharmacokinetics

Pharmacokinetic results are summarised in Table 2 and Figure 3. $t_{\max}$ occurred between 3 to 4 h irrespective of the dose. $C_{\max}$, AUC, and $C_{\min}$ (C_0 before the morning dose on day 4) showed proportionality between dose levels. There was no significant change between $C_{\min}$ and C_{12h} on day 4, indicating that steady-state was reached.

Mean elimination half-life ranged between 7 to 9 h both after a single dose and after repeated administration. AUCs from 0 to 12 h and from 0 to infinity were not

Table 2 Pharmacokinetic parameters obtained after administration of single or multiple oral doses of litoxetine in healthy young volunteers (ND: not determined; *: calculated on $n = 10$)

	Litoxetine 10 mg		Litoxetine 25 mg	
	Single dose (day 1)	Multiple doses (day 4)	Single dose (day 1)	Multiple doses (day 4)
$t_{\max}$ (h)	4.3 (0.2)	3.4 (0.2)	4.1 (0.4)	3.1 (0.2)
$C_{\max}$ (ng ml ⁻¹)	4.1 (0.2)	7.0 (0.6)	10.9 (0.4)	18.2 (1.6)
$C_{\min}$ (ng ml ⁻¹)	—	4.0 (0.4)	—	9.2 (1.0)
C (12) (ng ml ⁻¹)	—	3.2 (0.4)	—	8.1 (1.0)
$t_{1/2}$ (h)	ND	9.0 (0.6)	7.2 (0.7)*	8.3 (0.4)
AUC (ng ml ⁻¹ min)	ND	59 (5)	136 (14)*	154 (14)

Figure 3 Blood litoxetine concentrations after single (day 1) or multiple doses of 10 (○) and 25 (●) mg of litoxetine in 12 healthy young volunteers.

significantly different, indicating that litoxetine did not accumulate with a twice daily regimen.

Discussion

EEG studies carried out during the last two decades have allowed the differentiation of antidepressants from other psychotropic drugs. Two EEG patterns were identified after acute dosing: the 'desipramine-like' pattern with increased alpha activity and blunted slow and fast activities, indicating drug-induced activation, and the 'imipramine' pattern with concomitant increases in slow and fast activities and decreased alpha energy suggesting potential sedative properties which increased proportionally with slow delta waves [11].

The EEG profile of desipramine 50 mg was similar to that seen after 6 mg methamphetamine 6 mg [11]. A similar profile was seen with antidepressants whose action involves the dopamine (DA) or noradrenaline (NA) systems, such as tranylcypromine, a potent non-reversible MAO-inhibitor, or nomifensine, a DA and NA reuptake inhibitor [8, 11].

Amitriptyline, a sedative tricyclic antidepressant often used as a positive reference in clinical pharmacology trials, induced the same profile as imipramine 75 mg when given in doses ranging from 25 to 75 mg [11, 12]. Brain mapping studies indicated that the increases in slow delta and theta waves occurred mainly in the fronto-temporal areas, the reduction in the alpha range in the occipital areas, and the increase in beta activity in the fronto-central regions [13–15]. Amitriptyline induced pronounced slowing of the EEG due to its more potent sedative properties. Other sedative antidepressants, such as maprotiline or mianserin, shared

the imipramine-type EEG profile with marked slow waves [11].

The quantitative EEG profiles of SSRIs have been extensively studied and resemble those of desipramine or of imipramine, depending on the dose level, EEG recording conditions (resting EEG or vigilance-controlled EEG), area explored, and parameters analysed (absolute or relative power). The EEG profiles of SSRIs are consistent with the absence of sedative properties in therapeutic doses, with no or smaller increases in slow delta and theta activities as compared with imipramine or amitriptyline.

Zimeldine, the earliest SSRI, was not only a 5-HT reuptake inhibitor but also a potent NA reuptake inhibitor. In the 50 to 300 mg dose range, it exhibited a typical desipramine profile with a marked increase in alpha activity and, even with the highest dose, an increase in beta energies [16, 17]. These activating properties were confirmed by improvements in attention and concentration evidenced by psychometric tests [16]. Fluoxetine in doses of 30 to 60 mg induced a profile similar to that of desipramine under vigilance-controlled conditions. In contrast, a higher dose of 75 mg produced an imipramine-type EEG profile under resting conditions [18]. A single dose of fluvoxamine 75 mg produced a typical imipramine-like profile, with fewer sedative properties than imipramine used as a reference [11, 19]. This dose of 75 mg had little or no effects on psychomotor performances [11, 20]. Citalopram in doses of 10 to 50 mg demonstrated a similar profile [21, 22]. A single dose of 30 mg paroxetine also produced changes comparable with those induced by amitriptyline, with fewer sedative properties as demonstrated by the lack of detrimental effects on objective measurements of cognitive functions in humans with a single or multiple dose regimen [23, 24]. In contrast, a higher dose of 70 mg of paroxetine produced

greater EEG activation with a decrease in slow waves and an increase in beta activities [25]. A single dose of sertraline induced EEG changes consistent with alertness or vigilance-enhancing properties in a dose of 100 mg and more suggestive of sedative effects in higher doses of 200 to 400 mg [17, 26, 27]. These findings agree with the results of psychometric tests indicating a possible improvement in psychomotor performance with doses lower than 100 mg, contrasting with some degree of impairment with doses of 200 mg or more [17, 26, 28, 29].

All these SSRI-induced EEG changes are consistent with the psycho-pharmacological profile of these drugs assessed using standardised test batteries including critical flicker fusion (CFF), choice reaction time (CRT), tracking, etc. Most of these psychometric assessments demonstrated that SSRIs are essentially neutral, indistinguishable from the placebo on most of the measurements [30]. Paroxetine 30 mg, sertraline 100 mg, and zimeldine 200 mg enhanced alertness as indicated by elevated CFF thresholds without any changes in CRT.

A single dose of litoxetine also exhibited activating properties characterised by a significant increase in beta energies—mainly beta 2 waves—without any significant change either in alpha waves or in slow waves. An increase in beta 2 waves is the most typical pattern observed after antidepressant administration. In comparison with the other SSRIs, this profile indicates that litoxetine can be expected to be devoid of stimulating properties such as those seen with desipramine-type antidepressants including zimeldine or sertraline up to 100 mg. Litoxetine can also be expected to induce less sedation than imipramine-type antidepressants responsible for reductions in alpha activity and increases in slow waves. Such a profile is observed after fluvoxamine, citalopram, and some dosages of fluoxetine or paroxetine under resting conditions, although it is less marked than after imipramine or amitriptyline. Thus, EEG profile studies predict that litoxetine will induce enough activation to be clinically active as an antidepressant but will be devoid of effects on psychomotor performance and cognitive function.

This EEG effect peaked approximately at the same time as the pharmacokinetic $t_{\max}$ but was more long-lasting since it persisted for at least 12 h despite decreasing blood concentrations. After a single dose of 10 mg, the EEG effect occurred with blood concentrations lower than 4.02 ng ml^{-1} and was most marked 12 h post-dose. This effect was also more pronounced from 3 to 12 h after a single dose of 25 mg when blood concentrations ranged from 4.5 to 10.4 ng ml^{-1} (Figure 4). After multiple administrations, the pharmacodynamic steady-state in the brain was achieved as demonstrated by the fact that the beta 2 increase was similar before and 12 h post-dose. The time course of the EEG effect approxi-

Figure 4 Relation of mean blood litoxetine concentrations to mean EEG effects expressed as placebo-corrected beta energies (20–40 Hz) on the T4-02 lead after single (day 1, a) or repeated administration (day 4, b) of each litoxetine dose level. Values are expressed as the increment or decrement versus the predose baseline value. Each point is the mean for all subjects at the corresponding time. ○ 10 mg, ● 25 mg litoxetine.

mately followed the time course of blood concentrations. The EEG effect was observed throughout the assessment session on day 4, for litoxetine blood concentrations ranging from 3.18 to 6.32 ng ml^{-1} after 10 mg and from 8.14 to 9.21 ng ml^{-1} after 25 mg (Figure 4). The magnitude of this effect was comparable with both doses on the anterior leads and dose-related on the posterior leads. No tolerance or sensitisation of this EEG effect were recorded: with repeated administrations over 4 days, no blunting of the effect occurred over time. In addition, blood concentration- to-EEG effect curves did not show any hysteresis, indicating that there was no time lag between drug-induced effects and blood concentrations. The relationship seemed linear after a single dose.

In conclusion, this study confirmed that the EEG profile after repeated doses of litoxetine resembles those already described with non-sedative antidepressants. These changes occurred with doses of proven efficacy in depressed patients.

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