The psychomotor and cognitive effects of litoxetine in young and middle aged volunteers

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- 1 The effects of a range of doses of litoxetine (twice daily for 4 days), a novel specific serotonin re-uptake inhibitor, were evaluated in young and middle aged volunteers.
- 2 Psychometric testing was carried out at various time points on days 1 and 4 of each treatment period. The test battery consisted of critical flicker fusion (CFF), choice reaction time (CRT), compensatory tracking (CTT), Stroop and Sternberg memory scanning tests. Subjective feelings of sleep and sedation were measured by the Leeds Sleep Evaluation Questionnaire (LSEQ) and line analogue rating scales (LARS).
- 3 Pharmacokinetic profiles were determined from analyses of blood samples taken after the final dose on day 5.
- 4 Overall, there were few changes in any of the psychometric tests and although the higher doses of litoxetine improved CFF, these effects were weak in that differences could only be detected when the results were pooled against time.
- 5 The pharmacokinetic profile of litoxetine was very similar in both the young and middle aged subjects, and there was no difference regarding tolerability.
- 6 There is little evidence from this study to suggest that litoxetine has any intrinsic sedative activity which is likely to interfere with the performance of activities of everyday life.

Keywords antidepressant litoxetine psychomotor performance cognitive function pharmacokinetics healthy volunteers

Introduction

It is generally accepted that there is little to choose between antidepressants today in terms of efficacy. The treatments available however, are diverse in terms of their pharmacology and in particular, the occurrence of side effects. Although the tricyclic antidepressants (TCAs) are the most widely used antidepressants, they are associated with major disadvantages, for example, anticholinergic side effects, characterised as dry mouth, blurred vision, constipation and sedation. In addition, many of the TCAs have been shown to impair performance on tests of psychomotor and cognitive function [1–3]. Furthermore, as the majority of mentally ill patients prescribed psychoactive drugs are ambulant out-patients [4] who may be involved in a variety of

situations, ranging from highly skilled activities to the simpler tasks of everyday life, it is important to maintain the integrity of psychomotor and intellectual functions. An antidepressant, or indeed any psychoactive drug, which disrupts those abilities will put the patient and anyone who comes into contact with that patient at increased risk of accident due to drug induced sedation.

Increased appreciation of the role of serotonin in depression has led to the development of highly selective inhibitors of serotonin re-uptake (SSRIs). These compounds have little influence on noradrenaline and dopamine systems, and by enhancing serotonergic transmission, provide effective antidepressant activity without the sedating, anticholinergic

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or cardiotoxic reactions characteristic of older antidepressant drugs.

This class of compounds includes, amongst others, paroxetine, sertraline, fluoxetine, zimeldine and litoxetine, the most recent member of the SSRIs. The non-sedating properties of these SSRIs represent a significant benefit over the older tricyclic antidepressants [1–3,5] in the context of daytime functioning, the risk of accidents and the quality of life.

Litoxetine is a novel benzyloxypiperidine derivative, and is a potent and selective inhibitor of brain serotonin re-uptake [6–7]. It is practically devoid of activity at dopaminergic, adrenergic (α_1 , α_2 and β), muscarinic, histaminergic and central benzodiazepine receptors and has only weak affinity for serotonin receptors of the 5-HT₂ subtype. Litoxetine also possesses 5-HT₃ antagonistic properties giving this compound an original pharmacological profile in that it may, unlike other SSRIs, be devoid of emetic effects [8].

Litoxetine appears to be a novel antidepressant with few or no effects on biological parameters and which is well tolerated. This SSRI may also prove to be advantageous for the otherwise ambulant depressive; therefore it was proposed to study the psychomotor and cognitive effects of litoxetine using a standard, validated psychometric test battery and to assess pharmacokinetic parameters following single and multiple dosing.

Methods

Subjects

Nineteen drug-free (excluding oral contraceptives) healthy female volunteers, aged between 18–35 years or 40–65 years, were admitted to the study. Two age groups were included to investigate whether there were any age-dependent effects on any of the measures. All subjects were in good physical and mental health and had no history of significant disease or mental illness.

Subjects provided written informed consent and the study was approved by the Ethics Committee of the Isle of Wight Area Health Authority.

Design

The study was a double-blind, randomised, placebo controlled, 5-way cross-over study. The treatment sequence was balanced for residual effects using a 5 × 5 Latin square design where each subject acted as her own control. Nineteen subjects were enrolled onto the study to allow for the completion of 15 subjects to balance the Latin square. During each treatment period subjects received either litoxetine 2.5 mg, 5 mg, 10 mg, 25 mg or placebo twice daily on days 1–4 and once on day 5. Each treatment period was separated by a 9 day washout interval. Drugs and placebo were packaged in identical capsules.

Procedure

Prior to the investigation subjects received training and familiarisation with the battery of psychomotor tests until they reached a performance plateau. In addition, subjects were medically examined and blood and urine samples were analysed.

On day 1, subjects attended the test centre early in the morning where a standardised breakfast was given. Baseline sampling and psychometric testing were performed pre-dose, then at 2, 4, 6, 8 and 12 h post-dose. A second dose was administered at 12 h post-dose and subjects remained at the test centre overnight. On awakening the next morning (day 2), subjects completed the Leeds Sleep Evaluation Questionnaire (LSEQ), following which medication was administered at $t + 24$ h. Vital signs were also monitored at all of the above time points. Subjects were then taken home where they were required to self administer treatments twice a day. They returned to the test centre on day 4 and the procedure for day 1 was repeated, with subjects staying overnight. After completing the LSEQ on the morning of day 5, the last dose was given.

Compliance was verified by the investigator who observed capsule ingestion on study days and by the study monitor who checked the returned capsules. An additional measure of compliance was the plasma level of litoxetine as revealed by the pharmacokinetic profile.

Pharmacokinetics and quantitative determination of litoxetine

Blood samples (8 ml) were taken on day 5 pre-dose and at 1, 2, 3, 4, 5, 6, 8, 10 and 12 h post-dose via a heparinised in-dwelling cannula in the non-dominant forearm. Aliquots (3 ml) were transferred into a polycarbonate lithium heparinised bottle and 5 ml were centrifuged at 3000 rev min⁻¹ for 10 min. From the latter the plasma was decanted into a plain polycarbonated bottle. Both the whole blood and plasma samples were stored at –20° C.

Vital signs were also measured at these time points. After removal of the cannula subjects were taken home and returned on the morning of day 6 where vital signs were assessed and blood samples taken at 23 and 24 h post-dose.

Quantitative determination of litoxetine was performed by h.p.l.c. with fluorescence detection. It involved a liquid-liquid interaction of the drug and its internal standard from alkalised blood samples (pH 11.7) by a mixture of *N*-hexane-ethyl ether and a re-extraction of the organic phase with an aqueous phosphate buffer (pH 2.3). This buffer (200 µl) was then injected on to a column packed with Spherisorb C18 5 µm, eluted with a mixture of acetonitrile/phosphate buffer 0.05 M pH 2.3 containing 0.2% triethylamine, at a flow rate of 1.5 ml min⁻¹.

The fluorescence detector was set at an excitation wavelength of 283 nm and an emission wavelength of 340 nm. The method showed linearity in the range of 2–100 ng ml⁻¹ of litoxetine. The limit of

quantification of this method was approximately 1.5 ng ml⁻¹ when 200 µl of aqueous buffer were injected into the column.

The pharmacokinetic parameters calculated during this study were $C_{\max}$ (maximum blood concentration), $t_{\max}$ (time to maximum concentration), $C(0)$ (trough concentration pre-final dosing on day 5), $C(12)$ (day 5 concentration at 12 h post-dose), AUC(0,12 h) (area under the concentration-time curve) and $t_{1/2}$ (elimination half-life). The blood concentration-time profiles of litoxetine were fitted with a one-compartment open model using Siphar 3.1, allowing the evaluation of $t_{1/2}$. In addition, blood:plasma ratios were calculated for each individual subject at every dose and sampling time.

Assessments

The test battery consisted of objective and subjective tasks which have previously been shown to be valid and reliable measures of the effects of psychoactive drugs [5, 9–11].

Critical flicker fusion threshold (CFF)

CFF [9, 11] was used as a means of measuring the ability to distinguish discrete sensory data. The test device was composed of four light emitting diodes held in foveal fixation at 1 m from the subject. The lights flickered on and off at a constantly increasing or decreasing rate and subjects were required to discriminate flicker from fusion. Individual thresholds were determined by the psychophysical method of limits on three ascending and three descending scales [12]. The mean of these values was then recorded.

Choice reaction time (CRT)

CRT was used as a sensitive measure of drug-induced changes in sensorimotor performance [5, 13]. From a central starting position subjects were required to extinguish one of the six red lights, illuminated at random, by touching the appropriate response button. Using this arrangement it was possible to measure three components of reaction time: the total reaction time (TRT) from stimulus onset to completion of response; the movement time (MRT) between the start and response buttons and the processing or recognition time (RRT), obtained from subtracting MRT from TRT. The mean reaction time for 20 stimulus presentations was recorded.

Sternberg memory scanning task

High speed scanning and retrieval from short term memory were assessed using a reaction time technique pioneered by Sternberg [14]. Subjects were required to memorise a series of 1–4 digits (the stimulus set) presented sequentially. They were then presented with a series of individual probe digits and were required to respond to the probes by using a two button yes/no choice response box. Twenty-four such presentations were made during each assessment.

Accuracy and response times were measured, with stimulus presentation and data capture facilitated by a BBC Microcomputer.

Compensatory tracking test (CTT)

This interactive task of psychomotor function entailed tracking a moving arrow on a VDU screen using a joystick [1]. The response measure (RMS) was the mean deviation from the track program over the 1 min trial period, with lower scores indicative of more accurate tracking. A peripheral awareness task (PRT) was included in which the subject responded to a stimulus presented in the periphery of vision, while simultaneously attending to the track test. The mean reaction time to 10 of these stimuli over the trial period was taken as the response measure for this component of the divided attention task.

Stroop test

A computerised version of the Stroop test was used as a measure of selective information processing ability [15]. Subjects were required to respond to the presentation of colour names which may be presented in a congruent or discrepant colour, by pressing the appropriate button on a choice response box. The 'yes' button is pressed when the colour name matches the colour of the 'ink' (matched response), and the 'no' button when the two do not match (unmatched response). The response time (ms) was multiplied by np/nc (where np = number of presentations and nc = number of correct responses) with the result that reaction times were increased as errors were made. Finally, the log of each new reaction time was taken to counter the skew introduced by the transformation.

Subjective sedation

Subjective ratings of drug effects were obtained from a series of 10 cm line analogue rating scales (LARS). The mean scores of ratings of 'tiredness', 'drowsiness', and 'alertness' (which were included amongst a number of distractor scales) were taken as a measurement of perceived sedation [16].

Leeds Sleep Evaluation Questionnaire

The LSEQ was designed to measure four aspects of subjective assessment of sleep: getting to sleep (GTS), quality of sleep (QOS), awakening from sleep (AFS), and behaviour following waking (BFW), using a series of 10 cm line analogue rating scales [17]. These questionnaires were completed on the morning following the day of medication and subjects are required to rate each of these aspects in relation to their normal (non-drug) performance.

Adverse events

Any adverse events spontaneously reported by the subject or observed by the clinician were recorded in the case record forms.

Statistical analysis

The psychometric data were analysed as a two-factor randomised block (repeated measures) analysis of variance. Comparisons between means were performed using two-tailed 95% confidence intervals [18–19].

For pharmacokinetic data, individual $t_{\max}$ values were compared using a non-parametric Friedman test. $C_{\max}$, $C(0)$, $C(12)$ and AUC values were compared in middle aged subjects by a two way ANOVA and in young subjects with the non-parametric Friedman's test. Blood:plasma concentration ratios were compared by ANOVA.

Results

Psychometrics

Analysis (described above) of psychometric data was performed for those 10 subjects (seven middle aged and three young) who completed all five treatment periods. Treatment was discontinued for three subjects following the dispensing of incorrect test medication. Four subjects were withdrawn following adverse events (see later) and a further two withdrew for reasons unrelated to the medication. A summary of the results of the psychometric tests is presented in Table 1.

For CFF (Figure 1), litoxetine 5 mg, 10 mg, and 25 mg scores were significantly better than placebo. The significant drug effect was evident in the time-averaged (pooled data) treatment term and the differences were in ascending order. No dose of litoxetine decreased CFF. Differences were apparent in the baseline data but these were not significant.

In the RRT component of the CRT there were no significant differences from placebo in the time-averaged results. Although there were no differences from placebo, at 4 h post-dosing on day 1 litoxetine 5 mg produced a lower RRT than 25 mg, however the latter also had a high standard deviation and at this time point 25 mg was also higher than baseline, 4 h and 12 h on day 4. A similar pattern was observed in TRT

and there were no differences in MRT. The time-averaged results are presented in Table 2.

In the short term memory task a main effect for treatment was revealed where a slight improvement in performance was obtained with litoxetine 5 mg in comparison with placebo (Figure 2). The higher doses of litoxetine (10 mg and 25 mg) produced similar results to placebo. These effects, however, were not evident at any individual time point.

The time-averaged effects for tracker peripheral reaction time (PRT) showed that litoxetine 2.5 mg impaired reaction time compared with placebo (Figure 3). However this effect was only evident at 1 time point (day 4, 2 h). Litoxetine 25 mg was significantly faster than all other treatments in the time-averaged data. In the RMS component tracking was less accurate with the litoxetine 5 mg group in comparison with placebo and 10 mg litoxetine.

No significant differences from placebo were detected in the unmatched Stroop results, however litoxetine 5 mg scores were lower (i.e. better) than 10 and 25 mg. The time-averaged matched result for litoxetine 5 mg was lower than all other treatments (Figure 4).

There were no significant results on any of the variables of the LSEQ, although all active treatments produced poorer sleep induction scores than placebo and also poorer QOS ratings (Table 3). No differences were evident on the AFS score. There were no

Figure 1 The overall effects of litoxetine $\pm$ s.d.) on CFF (data pooled over days 1 and 4). P = placebo; L = litoxetine; * $P < 0.05$ vs placebo.

Table 1 Summary of the effects of litoxetine on the psychometric test battery

	Day 1	Day 4	Pooled data
Critical flicker fusion (Hz)	L 10 mg > Plb: 4 h, 8 h L 25 mg > Plb: 4 h, 12 h	NS	L 5, L 10, L 25 mg > Plb
Choice reaction time (ms)	NS	NS	NS
Short term memory (ms)	NS	NS	Plb > L 5 mg
Compensatory tracking			
RMS (units)	NS	L 5 mg > Plb: 12 h	L 5 mg > Plb
PRT (ms)	NS	L 2.5 mg > Plb: 2 h	L 2.5 mg > Plb Plb > 25 mg
Stroop			
matched (ms)	NS	NS	Plb > L 5 mg
unmatched (ms)	NS	NS	NS

Plb = placebo; L = litoxetine; NS = not significant.

Table 2 The effects of litoxetine on all components of CRT (ms $\pm$ s.d.)

	Placebo	Litoxetine 2.5 mg	Litoxetine 5 mg	Litoxetine 10 mg	Litoxetine 25 mg
RRT	413 $\pm$ 61	415 $\pm$ 79	400 $\pm$ 53	415 $\pm$ 61	414 $\pm$ 65
MRT	242 $\pm$ 52	241 $\pm$ 48	242 $\pm$ 49	243 $\pm$ 50	247 $\pm$ 51
TRT	656 $\pm$ 82	656 $\pm$ 106	642 $\pm$ 82	658 $\pm$ 85	661 $\pm$ 94

Figure 2 The overall effects of litoxetine ($\pm$ s.d.) on STM reaction time (data pooled over days 1 and 4). P = placebo; L = litoxetine; * $P < 0.05$ vs placebo. **Figure 3** The overall effects of litoxetine ($\pm$ s.d.) on CTT reaction time (data pooled over days 1 and 4). P = placebo; L = litoxetine; * $P < 0.05$ vs placebo. **Figure 4** The effects of litoxetine ($\pm$ s.d.) on matched Stroop reaction time (data pooled over days 1 and 4). P = placebo; L = litoxetine; * $P < 0.05$ vs placebo.

differences between treatments in the subjective sedation scores (LARS) (Figure 5).

Pharmacokinetics

The pharmacokinetic results are given in Table 4, where mean values for each dose of litoxetine (5, 10 and 25 mg) are split into age groups. Following the 2.5 mg dose, blood concentrations were close to the quantitation limit of the analytical method (1.5 ng ml⁻¹) therefore no pharmacokinetic parameters could be calculated. Due to the small number of young subjects ($n = 3$) no valid statistical comparisons could be made between the age groups.

In middle aged subjects 5 mg litoxetine blood concentrations could not be followed for long enough to calculate reliably the elimination half-life. Following 10 and 25 mg mean elimination $t_{1/2}$ were 9.1 ± 0.7 and 7.7 ± 0.3 h respectively and these values were not significantly different. In addition, no differences were observed in t_{max} . There were no significant differences between $t_{1/2}$ or t_{max} values for young subjects. These results suggest that $t_{1/2}$ and t_{max} were independent of the administered dose.

C_{max} values increased proportionally with drug dose in both young (3.4, 8.3, 22.3 ng ml⁻¹) and middle aged (3.4, 8.3, 19.1 ng ml⁻¹) subjects. $C(0)$, $C(12)$ and AUC were also augmented with increasing dose in both groups. Although no statistical comparison could be made between young and middle aged subjects, the parameters C_{max}/dose and AUC/dose were similar for both groups, suggesting that the pharmacokinetic profile of litoxetine was the same in the young and middle aged.

Plasma concentrations of litoxetine 5 mg in young subjects were close to the quantitation limit of the analytical method (1.5 ng ml⁻¹). For blood:plasma concentration ratios, comparisons of each subject for all doses did not show any significant differences between sampling times in both groups of subjects. It appears, therefore, that the blood:plasma concentration ratio was constant with time for a given dose. Combining all doses the ratios were 1.62 ± 0.07 in middle aged subjects and 1.73 ± 0.04 for young subjects (Table 4).

Adverse events

Of the 19 assessable subjects, 13 received placebo of whom nine experienced adverse events. Thirteen subjects received litoxetine 2.5 mg twice daily and 13

Table 3 The effects of litoxetine on LSEQ scores (mm $\pm$ s.d.)

	Placebo	Litoxetine 2.5 mg	Litoxetine 5 mg	Litoxetine 10 mg	Litoxetine 25 mg
GTS	49 $\pm$ 9	45 $\pm$ 11	45 $\pm$ 8	43 $\pm$ 15	46 $\pm$ 9
QOS	51 $\pm$ 9	46 $\pm$ 13	50 $\pm$ 9	46 $\pm$ 13	45 $\pm$ 12
AFS	50 $\pm$ 5	47 $\pm$ 11	48 $\pm$ 7	49 $\pm$ 13	46 $\pm$ 9
BFW	50 $\pm$ 9	50 $\pm$ 9	51 $\pm$ 8	50 $\pm$ 12	48 $\pm$ 9

Figure 5 The effects of litoxetine ($\pm$ s.d.) on subjective sedation (LARS) (data pooled over days 1 and 4). P = placebo; L = litoxetine.

received 5 mg twice daily, of which nine and 10 experienced adverse events respectively. Eleven of the 14 subjects who received 10 mg and nine of 11 subjects receiving 25 mg litoxetine reported adverse events. The number of subjects reporting at least one event, and the total number of events reported, were not significantly different between treatments.

The events leading to withdrawal from the study were varying combinations of headache, dizziness, syncope, somnolence, nausea and vomiting. These events occurred in four subjects receiving litoxetine (one subject in each dose category). No subjects withdrew due to intolerance whilst receiving placebo and no major (life-threatening) events were recorded.

Discussion

In addition to being clinically effective and well tolerated, it is essential that antidepressants should not cause sedation or impair psychomotor and cognitive function. Compounds which induce these detrimental effects will increase the risk of drug-related accident in otherwise ambulant patients.

The present study investigated the effects of a range of doses of litoxetine in healthy young and middle aged volunteers. The tests used here have been shown elsewhere to be sensitive to the effects of drugs which alter psychomotor and cognitive function [1–3, 5, 9, 10, 11, 13, 16–17]. Overall, the effects upon cognition, as measured by CFF, revealed significant improvements following litoxetine 5, 10 and 25 mg. In addition, performance in the short term memory test was slightly improved by litoxetine 5 mg and this dose also improved the matched Stroop

Table 4 Mean ($\pm$ s.e. mean) blood pharmacokinetic parameters of litoxetine after 5 days of repeated twice daily dosing in young and middle aged subjects

Subjects	Dose (mg)	t_{max} (h)	C_{max} (ng ml $^{-1}$)	$C(0)$ (ng ml $^{-1}$)	$C(12)$ (ng ml $^{-1}$)	$t_{1/2}$ (h)	AUC (ng ml $^{-1}$ h)	$C_{max}/dose$ (ng ml $^{-1}$ mg)	AUC/Dose (ng ml $^{-1}$ h (mg))	Blood:plasma concentration ratio
Middle aged (n = 7)	5	4.4 $\pm$ 0.6	3.4 $\pm$ 0.2	2.2 $\pm$ 0.2	2.3 $\pm$ 0.3	—	28 $\pm$ 11	0.68 $\pm$ 0.04	5.6 $\pm$ 0.8	1.43 $\pm$ 0.10
	10	3.6 $\pm$ 0.5	8.3 $\pm$ 0.9	4.6 $\pm$ 0.7	3.5 $\pm$ 0.6	9.1 $\pm$ 0.7	66 $\pm$ 7	0.83 $\pm$ 0.09	6.6 $\pm$ 0.7	1.75 $\pm$ 0.09
	25	4.1 $\pm$ 0.6	19.1 $\pm$ 1.6	8.9 $\pm$ 0.8	7.3 $\pm$ 0.7	7.7 $\pm$ 0.3	152 $\pm$ 15	0.77 $\pm$ 0.06	6.1 $\pm$ 0.6	1.61 $\pm$ 0.12
Healthy young (n = 3)	5	2.3 $\pm$ 0.3	3.4 $\pm$ 0.3	2.1 $\pm$ 0.4	1.9 $\pm$ 0.2	8.8 $\pm$ 1.6	28 $\pm$ 4	0.63 $\pm$ 0.06	5.6 $\pm$ 0.8	—
	10	4.3 $\pm$ 0.7	8.3 $\pm$ 0.1	4.3 $\pm$ 0.3	3.7 $\pm$ 0.5	7.9 $\pm$ 1.7	69 $\pm$ 4	0.83 $\pm$ 0.01	6.9 $\pm$ 0.4	1.74 $\pm$ 0.04
	25	2.0 $\pm$ 0.0	22.3 $\pm$ 1.1	11.2 $\pm$ 0.4	8.6 $\pm$ 1.6	8.0 $\pm$ 0.8	174 $\pm$ 13	0.89 $\pm$ 0.04	7.0 $\pm$ 0.9	1.71 $\pm$ 0.08

results. The highest dose of litoxetine improved tracker RT whereas the lowest dose impaired performance on this task. Measurement of CRT did not reveal any differences between litoxetine and placebo. In addition to objective tests of performance and sedation, it is important that a subjective assessment is obtained, i.e. a patient's reaction as to how they feel. In the present study, no subjective sedative effects were recorded and litoxetine did not appear to affect sleep significantly. From these results, it can be seen that the psychological effects of litoxetine were relatively small and that in all of the tests drug effects were weak. This may be due to the relatively small group size, however other evidence suggests that litoxetine possesses a similar profile to non-sedating antidepressants [20].

Pharmacokinetic analysis revealed that $t_{\max}$ and $t_{1/2}$ were independent of the administered dose whereas $C_{\max}$, AUC, $C(0)$ and $C(12)$ increased proportionally with the dose. Blood:plasma concentrations were independent of both dose and sampling time, these values being 1.62 and 1.73 for middle aged and

young subjects respectively. Although statistical comparisons of the pharmacokinetic parameters between groups were not relevant due to the small number of young subjects, the values appear to be similar (see Table 4). These values correspond with data reported elsewhere [20]. There was also no age related effect in the tolerability profile of litoxetine. The predominant adverse effects were headache, somnolence, fatigue and nausea and the incidences of these events did not significantly differ between treatments.

Like some of the other SSRIs, e.g. sertraline, paroxetine, fluoxetine and fluvoxamine [21] there is no evidence from this study to suggest that litoxetine has any intrinsic sedative activity likely to interfere with the performance of the activities of every day living. Antidepressants without sedative side effects are essential for maintaining a maximal therapeutic response. Newer drugs such as litoxetine, which reduce depression without disrupting the integrity of the patient's cognitive processes, will have an important role to play in the pharmacotherapy of depressive disorders.

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