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ORIGINAL INVESTIGATION

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Effects of the 5-HT$_{1A}$ receptor agonist flesinoxan in panic disorder

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Abstract The effects of flesinoxan, a potent and selective 5-HT$_{1A}$ agonist, were studied in two pilot studies in panic disorder patients to explore the role of 5-HT$_{1A}$ receptors in the mechanism of action of antipanic agents. This paper reports on the results of these two studies with flesinoxan. In study I, using a single-blind crossover design, five patients were treated for 1 week with placebo, 4 weeks with flesinoxan (up to 2.4 mg per day), and 2 weeks with placebo. In study II, 15 patients were enrolled in a double-blind, three-armed study with placebo and two dosages of flesinoxan. After a single-blind placebo run-in phase of 1 week, patients were treated for 8 weeks with placebo, 0.6 or 1.2 mg/day flesinoxan. In pilot study I patients' condition worsened during the 4-week flesinoxan treatment period. Anxiety was frequently reported as an adverse event. Symptoms returned to the pre-treatment level during the 2-week placebo washout period. In pilot study II, no treatment effects in either group were observed. Anxiety as an adverse event was less prominent than in the first pilot study. A lowering of mood was seen in some patients. The sample sizes of these two pilot studies are too small to draw firm conclusions on the efficacy of flesinoxan in panic disorder, but the present data are not encouraging in this respect. The worsening of symptoms seen with the highest dose of flesinoxan is intriguing and might give a clue to the understanding of the mechanism underlying similar effects seen with antidepressants in panic disorder patients.

Key words Panic disorder · Agoraphobia · Anxiety
Flesinoxan · 5-HT$_{1A}$ agonist · Human studies

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Introduction

Several lines of pharmacological evidence, recently reviewed by Westenberg and den Boer (1994), involve serotonin (5-HT) containing neurons in the control of anxiety. Clinical support for the notion that a dysfunction of 5-HT neuronal pathways may be implicated in the pathophysiology of anxiety disorders, such as panic disorder, came initially from reports indicating antipanic efficacy of potent 5-HT uptake inhibitors, such as fluvoxamine and clomipramine (Den Boer et al. 1987; Kahn et al. 1987; Den Boer and Westenberg 1988, 1990; Johnston et al. 1988). Interestingly, most investigators have noted that the beneficial effects of these drugs were preceded by a transient worsening of symptoms. Similar anxiogenic effects have been described after single oral administration of direct- or indirect-acting 5-HT agonists such as *m*-chlorophenylpiperazine (mCPP) or fenfluramine (Kahn et al. 1988a; Targum and Marshall 1989; Klein et al. 1991). Logically, one would assume that acute administration of 5-HT uptake inhibitors would result in increased levels of synaptic 5-HT. Therefore, these findings were viewed as support for the hypothesis that anxiety equates with an increase in 5-HT function and that an enhanced sensitivity of the 5-HT system might be implicated in the pathophysiology of panic disorder (Kahn et al. 1988b). Accordingly, the beneficial effects of 5-HT uptake inhibitors in the treatment of panic disorder following chronic treatment were expected to result from adaptive changes in 5-HT function or processes beyond the 5-HT system.

There are several lines of evidence which complicate this explanation of the 'biphasic' response of 5-HT uptake inhibitors in panic disorder. The first concern is that animal research with 5-HT uptake inhibitors has revealed that acute administration of these compounds causes only modest to negligible increases in extracellular 5-HT levels in terminal regions innervated by the dorsal raphe nucleus

(Bel and Artigas 1991; Invernizzi et al. 1991). This finding may be accounted for by stimulation of the somatodendritic 5-HT_{1A} receptors, which supposedly offsets 5-HT neuronal firing by 5-HT released in the raphe region. Electrophysiological data are consistent with the above explanation, in that it has been shown that the firing rate of the dorsal raphe neurons is under inhibitory control of the 5-HT_{1A} receptors located in the raphe nuclei (Chaput et al. 1988). Second, long-term treatment with some 5-HT uptake inhibitors, such as citalopram, results in an enhanced cortical 5-HT release (Invernizzi et al. 1994) in laboratory animals as measured by microdialysis. This effect is likely to result from a desensitization of the somatodendritic 5-HT_{1A} receptors. Third, long-term treatment with the tricyclic antidepressant imipramine, which has been shown to possess beneficial effects in patients with panic disorder, enhances 5-HT synaptic transmission in animals by increasing the sensitivity of the postsynaptic 5-HT_{1A} receptors in the hippocampus (Chaput et al. 1991). Fourth, the 5-HT_2 receptor antagonist, ritanserin, which has been shown to block some of the effects of mCPP, was ineffective in patients with panic disorder (Den Boer and Westenberg 1990), suggesting that desensitization of this receptor subtype is not implicated in the mechanism of action of 5-HT uptake inhibitors in panic disorder.

The 5-HT_{1A} receptor agonists are the first practical realization of the great ferment of research during the last decade into 5-HT receptor subtypes. The advent of these 5-HT selective drugs permits further elaboration the sequence of events likely to underlie the therapeutic action of 5-HT uptake blockers in panic disorder.

Clinical studies with (partial) 5-HT_{1A} receptor agonist, such as buspirone and gepirone, have revealed an anxiolytic profile in patients with generalized anxiety disorder (Rickels et al. 1982; Harto et al. 1988; Borison et al. 1990; review: Pecknold 1994). Studies with these compounds have also been performed in panic disorder patients, but the results are either inconclusive or negative (Schweizer and Rickels 1988; Sheehan et al. 1988, 1990, 1993; Pecknold et al. 1989, 1993; Pohl et al. 1989; Robinson et al. 1989). In most studies a large placebo response may have obscured any effect. This is underscored by the negative findings with imipramine, which was used as a reference compound in some of these studies.

Flesinoxan ((+)-*N*-(2-(4-(2,3-dihydro-2-hydroxymethyl-1,4-benzodioxin-5-yl)-1-piperazinyl)ethyl)-4-fluorobenzamide hydrochloride) is a potent and selective 5-HT_{1A} agonist, surpassing buspirone and gepirone in intrinsic activity and selectivity for this receptor subtype (Schipper et al. 1991). In contrast to the azapirones, flesinoxan is probably a full agonist at the postsynaptic receptors and not metabolized to 1-(2-pyrimidinyl)-piperazine (1-PP), an α_2-adrenoreceptor antagonist, which complicates interpretation of the effects. Unlike buspirone, it has only minor affinity for the dopaminergic D_2 receptor. Therefore, flesinoxan may be a better tool to test the efficacy of 5-HT_{1A} receptor agonists in panic disorder.

Prior to initiating a large, placebo-controlled study, it was thought prudent to conduct a pilot study with flesinoxan. The aim of the pilot study was to examine immediate and short-term effects of flesinoxan in panic disorder patients. It was primarily a tolerance study looking at important side-effects and any initial exacerbation of symptoms. The second pilot study was conducted to examine the course of the initial exacerbation of symptoms seen in the first pilot study and to test whether this effect was dose-dependent.

Materials and methods

Patients

Entry criteria were that patients fulfill DSM-IIIR (APA 1987) criteria for panic disorder with or without agoraphobia, supplemented by the criterion of at least two full panic attacks during the screening period of 2 weeks. Patients who were pregnant, lactating, psychotic, suicidal, or who had a history of epilepsy, seizures, bipolar or affective disorders, or substance dependence during the past year were excluded. Patients meeting the criteria for DSM-IIIR major depressive disorder at baseline or with a Montgomery Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg 1979) score of 15 or more were considered not eligible. Patients with clinically relevant abnormalities in electrocardiographic or laboratory tests and those with multiple drug allergies were excluded. Patients taking α- or β-adrenergic blocking agents, antidepressants, antipsychotics, lithium or anxiolytics within the past 4 weeks were also not eligible. Concurrent use of psychotropic medication, other than the occasional use of oxazepam to a maximum of 40 mg per day, was not allowed. Concurrent psychotherapy or behavioural therapy was considered as an exclusion criterion. All patients gave informed consent to the protocol, which was approved by the Ethics Review Committee of the Academic Hospital Utrecht.

Design

Pilot study I had a single-blind A-B-A crossover design. After a washout period of 1 week, five patients received consecutively placebo capsules for 1 week (A), capsules containing up to 2.4 mg per day of flesinoxan for 4 weeks (B) and placebo capsules for 2 weeks (A). The dose of flesinoxan was increased from 0.6 to 2.4 mg per day in 12 days. Patients complaining of significant side effects were allowed to reduce the dose to 0.6 mg. Capsules were administered b.i.d.

Pilot study II had a parallel group, double-blind, placebo controlled design with a single-blind placebo run-in phase. After a washout period of 1 week, patients (15) were randomly assigned to receive placebo, 0.6 mg flesinoxan or 1.2 mg flesinoxan per day for 8 weeks with five patients per group. All patients received one placebo capsule per day during the 1-week placebo run-in phase. The dose of flesinoxan during the double-blind phase was escalated gradually from 0.1 mg in the first week to 0.6 mg per day in the second week. Patients allocated to the higher dose group, received 1.2 mg per day from week 5. Patients in the lower dose group received 0.6 mg per day for the remainder of the study period. The capsules were administered t.i.d.

Assessments

Patients were asked to keep a diary in which they recorded information about the panic attacks. The number of panic attacks per week was determined on the basis of this diary (Utrecht Panic Inventory; UPI). The intensity of anxiety was measured with the Hamilton Anxiety Scale (HAS; Hamilton 1959) and the Clinical Anxiety Scale (CAS; Snaith et al. 1982) and the severity of the phobic avoidance was assessed with the Fear Questionnaire (FQ; Mavissakalian 1986) on a weekly basis. The clinician also assigned a global impression score (CGI; Guy 1976) of the severity of symptoms. Adverse events were assessed by open questioning at each visit. Urine screening on benzodiazepines use was done at recruitment and at each visit thereafter.

Statistical analysis

Data were analysed using a commercially available statistical package (SPSS). To analyse the data of pilot study I, a nonparametric test was applied. Because of the cross-over design of the study, only time effects were analysed. The analyses were executed with Friedman analysis of variance, using Wilcoxon paired test as post hoc analysis.

To analyse the data of pilot study II, a multivariate analysis with repeated measures on the factor time with two or three groups was applied. In the first analysis the two flesinoxan-treated groups were taken together, in the second analysis all three groups were taken seperately.

Results

Pilot study I

Clinical variables

Five patients were enrolled; all but one were female, ages ranged from 22 to 37 years. Four patients were married or in a stable relationship. The severity of panic disorder at recruitement was severe in four patients and moderate in one patient. All subjects reported situational avoidance behaviour, with an age of onset ranging from 20 to 29 years. Patients had been suffering from panic disorder from 23 to 60 months (mean 47.7 months), and all were receiving psychotherapy at screening. None of the patients had received behavioral therapy, but all had previous drug experiences. All but one subject had had a (partial) favourable response to previous drug treatment.

In the single-blind pilot I study no changes were observed in clinical condition during the first week of treatment with placebo.

During the 4-week flesinoxan treatment period the patients' condition worsened and increased anxiety was frequently reported as an adverse event. The number of panic attacks slightly increased as rated with the UPI (mean ± SD: 1.17 ± 1.16 pretreatment to a maximum of 1.90 ± 1.21 in week 3 of flesinoxan treatment). The panic frequency showed a statistically significant time effect ($F = 18.93$; $df = 0,54$; $P = 0.008$). The severity of the attacks also increased (highest severity at a scale

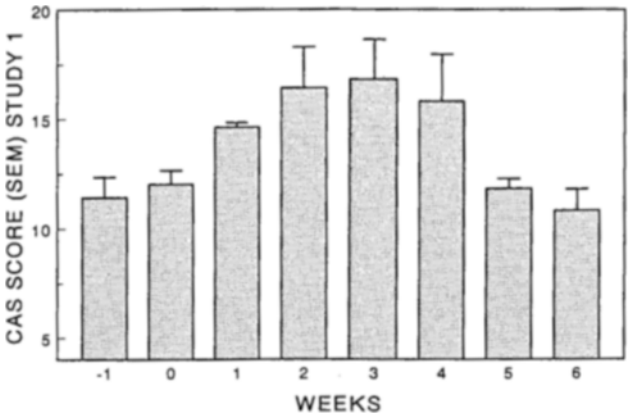

Fig. 1 The effect of flesinoxan on anxiety of panic disorder patients as assessed with the clinical anxiety scale in pilot study I. Flesinoxan increases anxiety during the flesinoxan period. 1 Week wash-out, 1 week placebo, 4 weeks flesinoxan 2.4 mg, 2 weeks placebo

from 0 to 8: mean severity 5.4 ± 2.4 pretreatment to a maximum of 7.0 ± 1.0 week 1 treatment). Both the number and frequency of panic attacks showed fluctuations during the single-blind placebo post-treatment period (mean number of panic attacks 0.29 ± 0.33 and mean severity of panic attacks 2.8 ± 3.2 in the second post-treatment placebo week). The panic frequency in the second placebo period was significantly lower than during the flesinoxan treatment period.

The core symptoms of anxiety as measured with the CAS (Fig. 1) also increased slightly during flesinoxan treatment. The CAS showed a statistically significant time effect ($F = 17.271$; $df = 0,617$; $P = 0.016$). This difference could by and large be explained by differences between baseline/run-in phase and weeks 1, 3 and 4 of the flesinoxan treatment period.

The total HAS and CAS score, reflecting general anxiety symptoms, showed a similar increase during the flesinoxan treatment period with a decrease during the post-treatment assessments. This increase was caused by higher scores on the core symptoms of anxiety.

The CGI scores (severity and improvement) showed that patients were on average "markedly ill" during the pre-treatment phase and increased to "severely ill" during the flesinoxan period, while patients reported feeling "minimally worse" to "much worse". Severity returned to pre-treatment levels during the second placebo washout phase, patients reported "no change" to "minimally improved" compared to baseline. The CGI improvement showed a significant time effect ($F = 17.125$; $df = 0,612$; $P = 0.017$), according to the Wilcoxon test, largely due to the difference between the first placebo-period and week 1 of the flesinoxan treatment period. The CGI severity score showed no statistically significant time effect.

All five patients took oxazepam occasionally throughout the study. An increased use was reported

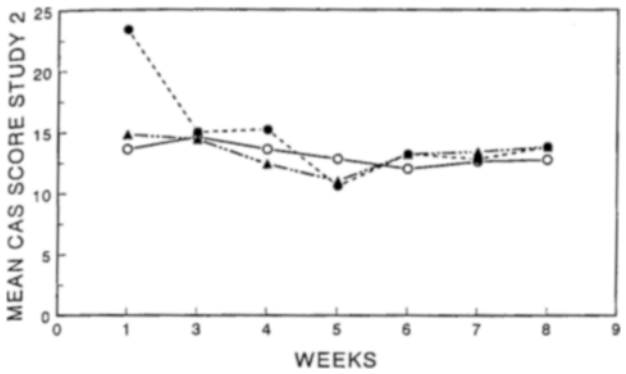

Fig. 2 The effect of flesinoxan (0.6 and 1.2 mg/day) and placebo on the anxiety in panic disorder patients as assessed with the clinical anxiety scale in pilot study II. There were no significant treatment effects. 1 Week wash-out, 1 week placebo (--●--), 8 weeks flesinoxan 0.6 mg (–○–) or 1.2 mg (–▲–) or placebo

during the flesinoxan treatment period, with a subsequent decrease during the placebo wash-out phase.

Side effects

Anxiety was reported as an adverse event by all patients, sometimes accompanied by an increased number of panic attacks and more severe avoidance behaviour. One patient reported an increase of panic with anxiety and depression during the flesinoxan treatment period. Because these symptoms did not abate after lowering the dose from 2.4 to 1.2 mg/day, this patient terminated treatment in week 5 because of depression with suicidal ideation and extreme anxiety. All these symptoms resolved in 4 days after ceasing flesinoxan to a pre treatment anxiety level. Other reported side-effects were: sleep disturbances, vivid or increased dreaming and dizziness.

Physical and biochemical results

No abnormal values were observed with regard to blood pressure and pulse frequency, before, during or after treatment. There were no consistent effects on body weight. No clinically relevant ECG abnormalities were detected. The same applies to hematological and biochemical parameters throughout the study. All urine samples for benzodiazepines were below the detection limit.

Pilot study II

Clinical variables

Fifteen patients were enrolled in this double-blind study; all but two were female, both males were in the placebo group. Ages ranged between 27 and 47 years with a mean age of 35.

Patients in the 0.6 mg flesinoxan and placebo group had fewer panic attacks at entry than those the first study. A protocol amendment which allowed fewer panic attacks at entry accounted for this. The severity of panic disorder was classified as severe for seven patients, moderate for seven patients and mild for one patient. There seemed to be a trend to a slight decrease in the number of panic attacks at week 8 in all groups but no treatment or dose effect was found. There was no consistent change in the severity of panic attacks, as rated by the patients. Treatment with both dosages of flesinoxan or placebo had no effect on total HAS and CAS score nor on panic severity as measured by the CAS (Fig. 2).

Patients remained "moderately ill" on average throughout the study. Except for a slight improvement in week 2 of treatment for the 0.6 mg flesinoxan and placebo group, there were no changes in clinical condition as measured with the CGI. Multivariate analysis showed no statistically significant time by dose effects on either of the psychometric scales. None of the patients could be classified as a responder to treatment, taking a reduction of 50% on the CAS or HAS as outcome variable.

Compared with the first pilot study, the percentage of patients using oxazepam was lower.

Side effects

One patient taking 0.6 mg/day flesinoxan terminated the study prematurely at week 6, because of increased anxiety and panic, accompanied by symptoms of depression. Reported side effects in general were: headaches, anxiety, insomnia, dizziness and depression. These side effects were more frequently observed in the flesinoxan groups.

Physical and biochemical results

No abnormal values for any of the blood pressure measures were observed, nor were there any consistent treatment effects. Likewise, there were no consistent effects on body weight, ECG and laboratory values.

Discussion

To explore the role of 5-HT_{1A} receptors in the pathophysiology of panic attacks, we studied the effects of flesinoxan, a potent and selective 5-HT_{1A} receptor agonist, in patients with DSM-III-R panic disorder. This paper reports on the results obtained with two pilot studies with this compound. The first pilot study was

planned as a prerequisite to a large placebo-controlled trial with fluvoxamine and flesinoxan. It was thought prudent to study flesinoxan initially in a single blind placebo-controlled cross-over study to asses its global effects, prior to embark on a large scale potentially pivotal efficacy study. Interestingly, all patients worsened during the flesinoxan period. Perhaps even more compelling is the attenuation of this effect during the placebo run-out phase, suggesting that this effect may be accounted for by flesinoxan. We often see in panic disorder patients on antidepressants a similar increase in anxiety (e.g., Zitrin et al. 1983; Den Boer and Westenberg 1988, 1990), but unlike antidepressants the worsening of flesinoxan did not wane but persisted for the whole treatment period of 4 weeks. The worsening was also more pronounced than seen with antidepressants, to such an extent that none of the patients could have endured the treatment any longer. Nonetheless, it may be argued that the treatment period of this pilot study was too short to observe any beneficial response. Therefore, a second pilot study with flesinoxan under double-blind conditions was conducted. In view of the worsening of symptoms in the first pilot, the dose of flesinoxan was lowered and the treatment period was lengthened to 8 weeks in order to assess if patients worsening of condition observed during the first pilot study might need a longer period prior to improvement of the condition. However, in this second pilot no consistent treatment effects in either direction were observed for any of the efficacy parameters. Panic frequency, anxiety scores and avoidance behaviour were not different from placebo, despite the very small placebo response. Unlike the first study, no worsening was noted on the anxiety scales, suggesting that the exacerbation was dose-dependent. Anxiety as an adverse event, was also less frequently reported as compared to the first pilot study. Given the small sample size of this second pilot study, no definitive conclusion can be drawn about the efficacy of flesinoxan in panic disorder, but the results from the present studies give no hint of efficacy in panic disorder. Based upon the results of the these two pilot studies, it was considered inopportune to conduct the main efficacy study.

Likewise, efficacy in panic disorder has not been demonstrated with other 5-HT_{1A} agonists. Although a case-report with buspirone suggests some efficacy in panic disorder (Frazer and Lapierre 1987), the results of placebo-controlled and double-blind studies reveal that this drug has no effect on the number and severity of panic attacks (Pohl et al. 1989; Robinson et al. 1989; Sheehan et al. 1990, 1993). Similar results have been found for ipsapirone (Keppel Hesselink, personal communication).

In contrast to panic disorder, studies with these compounds in generalized anxiety disorders are more conclusive and point at an anxiolytic profile of 5-HT_{1A} (partial) agonists in this condition (Pecknold 1994). Efficacy studies with flesinoxan in generalised anxiety disorders are also more encouraging (Bradford and Stevens 1994). In doses ranging from 0.4 to 4.0 mg, it has been shown to possess anxiolytic effects in patients with generalized anxiety disorders, with the most compelling evidence pointing to around 0.4–1.0 mg/day as the target dose for this condition. It cannot be excluded, therefore, that the dosages used in the present trials in panic disorder patients might have been too high. In contrast to the present study, no increase in anxiety symptoms was reported in patients with generalised anxiety disorders, suggesting that panic disorder patients are more sensitive to stimulation of the 5-HT_{1A} receptors. It is worth mentioning in this respect that Lesch et al. (1992) have reported a 5-HT_{1A} receptor subsensitivity in panic disorder patients. Exploring the responsivity of 5-HT_{1A} receptors in panic disorder, they found a significantly blunted thermoregulatory and neuroendocrine response to a challenge with ipsapirone.

In general, flesinoxan was well tolerated with an adverse effect profile similar to, but much less severe than, the 5-HT uptake inhibitors. In the present two pilot studies, flesinoxan did not have serious side-effects, except the occurrence of anxiety and depressive syptoms. That some panic disorder patients, who did not have these syptoms at the outset of the study, experienced a lowering of mood – one patient using 2.4 mg flesinoxan even reported suicidal ideations – is remarkable in view of the fact that flesinoxan has been found also to possess antidepressant properties (Grof et al. 1993). To the best of our knowledge, there is only one other report in the literature on the development of depressive symptoms in panic disorder patients following treatment with antidepressants (Fux et al. 1993). In this small study patients had no history of affective disorders and responded favourable to the drug with respect to their anxiety symptoms. The depressive symptoms abated when treatment was discontinued and returned when another antidepressant was administered.

The mechanism of action of 5-HT_{1A} receptor agonists in anxiety has been the focus of a number of studies, but the precise nature of the underlying effect is still controversial. In particular, the issue of whether presynaptic or postsynaptic effects account for the anxiolytic effects of these compounds is still a matter of debate (for review see De Vry 1995). In the brain, 5-HT_{1A} receptors are located postsynaptically, for example in limbic and cortical regions, and presynaptically in the raphe nuclei, where they function as autoreceptors to inhibit 5-HT firing and terminal 5-HT release (Sharp et al. 1991). Since long-term treatment with 5-HT_{1A} receptor agonists has been shown to result in an attenuation of the negative feedback regulation through the somatodendritic 5-HT_{1A} autoreceptors (De Montigny and Blier 1992), it has been proposed that the anxiolytic effects result primarily from an effect on the postsynaptic 5-HT_{1A} receptors,

which are temporarily offset by the presynaptic effects (Briley et al. 1991). Differences in sensitivity (or receptor reserve) of the postsynaptic 5-HT_{1A} receptors in specific brain regions among anxiety disorders, might account for the differential clinical effects of 5-HT_{1A} (partial) agonists. On the other hand, most preclinical evidence points toward a primary role of the presynaptic receptors in the anxiolytic effects of 5-HT_{1A} receptor agonists (De Vry 1995). A caveat to be put in here is that, these findings are, for the most part, based on acute effects in animal screens for anxiolytic drugs. Clinical studies with 5-HT_{1A} antagonists may help to dissect the complex behavioral effects of 5-HT_{1A} partial agonists in humans.

In summary, the results of the double-blind placebo controlled second pilot study give no hint of efficacy in panic disorder in the same dose range that has been found efficacious in patients with generalised anxiety disorder. Valid assessment of efficacy from this pilot study is hampered by the small sample size, but the present data are not encouraging. The data must be considered inconclusive in this respect. The efficacy and tolerance parameters of the single-blind pilot study suggests a panicogenic effect in the higher dose ranges (up to 2.4 mg/day), similar to but more pronounced than seen with antidepressants in this condition.

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