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ORIGINAL INVESTIGATION

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Hormonal and temperature responses to the 5-HT_{1A} receptor agonist flesinoxan in normal volunteers

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Abstract *Rationale:* Flesinoxan is a highly potent and selective 5-HT_{1A} agonist and appears to be a potentially interesting neuroendocrine serotonergic probe. *Objectives:* We assessed hormonal (ACTH, cortisol, prolactin and growth hormone) and temperature responses to flesinoxan in normal volunteers. *Methods:* In a double-blind placebo-controlled study, single doses of 0.5 mg and 1 mg were injected over 10 min into 12 healthy male volunteers at 1-week intervals. Temperature and hormonal responses were measured at times –30, 0, 15, 30, 60, 90, and 120 min. *Results:* Flesinoxan induced a significant and dose-dependent increase in adrenocorticotropic hormone (ACTH), cortisol, prolactin (PRL), growth hormone (GH) and a decrease in body temperature. Tolerance to flesinoxan was excellent. *Conclusions:* These results showed the role of 5-HT_{1A} mechanisms in the PRL, ACTH, cortisol, GH, and temperature responses to flesinoxan. In the present study, flesinoxan appears a very promising serotonergic neuroendocrine probe.

Keywords Flesinoxan · 5-HT_{1A} receptor · Serotonin · Hypothermia · Prolactin · Growth hormone · Cortisol

Introduction

Serotonergic abnormalities have been involved in several major psychiatric disorders. In particular, 5-HT_{1A} receptors could play an important role in the pathophysiology of depression and anxiety, and in the mechanism of action of antidepressants (Naughton et al. 2000). Neuroendocrine strategy has been widely applied to assess the sensitivity of 5-HT_{1A} receptors in living conditions by using various agonists such as buspirone, ipsapirone, tandospirone, gepirone or flesinoxan. These agents are able to induce a release of some hormones such as growth hormone (GH), prolactin (PRL), adrenocorticotropin (ACTH) or cortisol, and a decrease in body temperature. Studies with the 5-HT_{1A} receptor partial agonist buspirone have reported a significant PRL release (Meltzer et al. 1983; Coccaro et al. 1990; Dinan et al. 1990; Anderson and Cowen 1992; Bridge et al. 2001), but recent data have shown the importance of dopaminergic effects of the drug in the induction of PRL release (Bridge et al. 2001). Stimulation of the hypothalamo-pituitary-adrenal axis (HPA) by the 5-HT_{1A} agonist ipsapirone has been demonstrated in several studies (Kahn et al. 1994; Meltzer and Maes 1995a; Gelfin et al. 1995; Cleare et al. 1998; Schwartz et al. 1999). Ipsapirone also stimulates the hypothalamic-GH axis (Lesch et al. 1989; Cleare et al. 1998; Newman et al. 1999; Cleare and Bond 2000), as does tandospirone (Miller et al. 1990) and gepirone (Anderson et al. 1990). However, these 5-HT_{1A} compounds are partial agonists that may have agonist or antagonist activities and most of them are metabolized into 1-phenylpiperazine (1-PP), an alpha$_2$-adrenoreceptor antagonist. These confounding factors could explain different neuroendocrine profiles. In this contex, Seletti et al. (1995) reported very interesting results by showing that flesinoxan induced a dose-dependent decrease in body temperature and an increase in GH, PRL, ACTH and cortisol plasma levels. The main interest of this study is that flesinoxan as a 5-HT_{1A} receptor probe tends to avoid several methodological problems. Flesinoxan is a potent and selective 5-HT_{1A} agonist, surpassing buspirone, gepirone and ipsapirone in receptor affinity (Olivier et al. 1991). Evidence from several functional models indicate that flesinoxan behaves as a full agonist at the 5-HT_{1A} receptor, both pre- and postsynaptically (Hadrava et al. 1995). In rats, flesinoxan increases prolactin levels at low doses and is able to induce a hypothermic response comparable to that of 8-hydroxy-2-(di-*n*-propylamino)tertralin (8-OH-DPAT) (Cryan et al. 1999). In humans, after oral intake, the distribution half-life of flesinoxan is about 2 h and its elimination half-life is about 9 h. Moreover, in contrast to most azapirones, flesinoxan is not metabolized

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into 1-phenylpiperazine (1-PP), and is available for intravenous use. This later point is particularly interesting since injectable tests appear to be much more reliable and can be performed in a much shorter time, with an associated decrease in the influence of confounding factors, such as stress, fasting, or intake of meals. To date, there have been no safety problems with flesinoxan, and the drug has been well tolerated.

In this context, the purpose of the study was to validate a "flesinoxan test" in normal volunteers by showing a reliable and dose-dependent release of different hormones and decrease of oral temperature. More specifically, our aim was to confirm the results from the study of Seletti et al. (1995).

Materials and methods

Subjects

Twelve healthy volunteers took part to the study. They were in good health, as demonstrated by history and clinical examination. They were free of depressive symptomatology, as demonstrated by scores less than 6 on the Beck, Carroll, and Hamilton rating scale for depression. They were also free of personal history of depression or alcoholism as well as in their first degree relatives. The protocol was approved by the Ethical Commitee of the University of Liège, Belgium. Subjects were fully informed of the purpose of the study and gave their written informed consent.

All normal volunteers were males aged from 22 to 34 years [mean (SD)=25.9 (3.6)], and with weight ranging from 55 to 87 kg [mean (SD)=73.8 (10.3)]. The study used a double-blind cross-over design. In three different sessions, at 1-week intervals, the subjects received intravenously flesinoxan 0.5 mg, flesinoxan 1 mg, or placebo. The drugs were diluted in saline to obtain 20 ml/70 kg and administered in 10 min.

Procedure

After an overnight fast, an indwelling catheter was inserted into a forearm vein at 8.30 a.m. The first blood sample (t –30) was collected at 9.00 a.m. and was followed by six blood samplings at t0, t+15, t30, t60, t90, t120. The beginning of the flesinoxan injection took place at t0. All samples contained 10 cc of blood. They were centrifuged within 2 h and serum was immediately frozen and kept at –18°C until analysis.

Hormone assays

GH, prolactin, cortisol, and ACTH were measured by radioimmunoassay (RIA), according to previously published methods (Franchimont 1968; Ansseau et al. 1984). In particular, intra- and inter-assay coefficients of variation were, respectively, 13.3 and 14.8% for GH (Franchimont 1968); 10.0 and 10.0% for prolactin (Franchimont 1969); 4.3 and 8.3% for cortisol (Ansseau et al. 1984). All samples were processed in duplicate within the same assay.

Clinical assessments

After each blood sampling, blood pressure, pulse rate, oral temperature (sublingual using an electronic thermistor probe), and sedative and gastro-intestinal side-effects were recorded. Subjects were also requested to complete the Profile of Mood States scale (POMS) (McNair et al. 1971). In addition, at the end of the procedure, sedative and gastro-intestinal side-effects were globally rated according to a 6-point scale. Modification in vigilance were scored as follows:0=no change; 1=very slight drowsiness; 2=slight drowsiness; 3=drowsiness; 4=significant drowsiness; 5:sleep. Digestive reactions were scored as follows:0=no reaction; 1=slight and transitory nausea; 2=nausea; 3=strong nausea without emesis; 4=emesis; 5=severe emesis.

Data analysis

Hormonal and temperature responses following flesinoxan or placebo were assessed by two different methods. First, by peak values following injection and by the areas under the curve (AUC) situated between injection and the last blood sampling. Both analyses were performed using absolute values as well as differences related to basal level (relative values). Since the results of both methods were very similar, only the area under the curve relative values (AUCR) will be reported in this paper. Our data were not normally distributed and a log-transformation did not normalize the distribution. Therefore, in order to demonstrate a dose effect, we used Kruskal-Wallis non-parametric test. The Wilcoxon test was then used for pairwise comparisons between groups. All values were expressed as means±SD.

Results

Baseline values

Baseline hormonal values were not different between placebo day, and both flesinoxan days (0.5 or 1 mg/70 kg). The 3 test days were not different in temperature values as well as in blood pressure, pulse rate and POMS scores.

Hormonal responses

ACTH

Flesinoxan injection significantly increased ACTH concentrations (Fig. 1A): AUCR (pg.min/ml), placebo –1300±3930, flesinoxan 0.5 mg 635±2550, flesinoxan 1 mg 3628±6484 (Kruskal-Wallis; $P<0.003$). Wilcoxon analysis showed a significant ACTH response after flesinoxan 0.5 mg ($P<0.05$), and after flesinoxan 1 mg ($P=0.001$).

Cortisol

Flesinoxan administration significantly increased cortisol concentrations (Fig. 1B): AUCR (μg.min/l), placebo –3178±1750, flesinoxan 0.5 mg –2255±3031, flesinoxan 1 mg 3397±4018 (Kruskal-Wallis; $P=0.0002$). Wilcoxon analysis showed a significant increase in cortisol concentrations after flesinoxan 1 mg ($P<0.0001$), but not after flesinoxan 0.5 mg ($P=0.37$).

Prolactin

Flesinoxan administration significantly altered PRL concentrations (Fig. 1C): AUCR (μIU.min/ml), placebo –

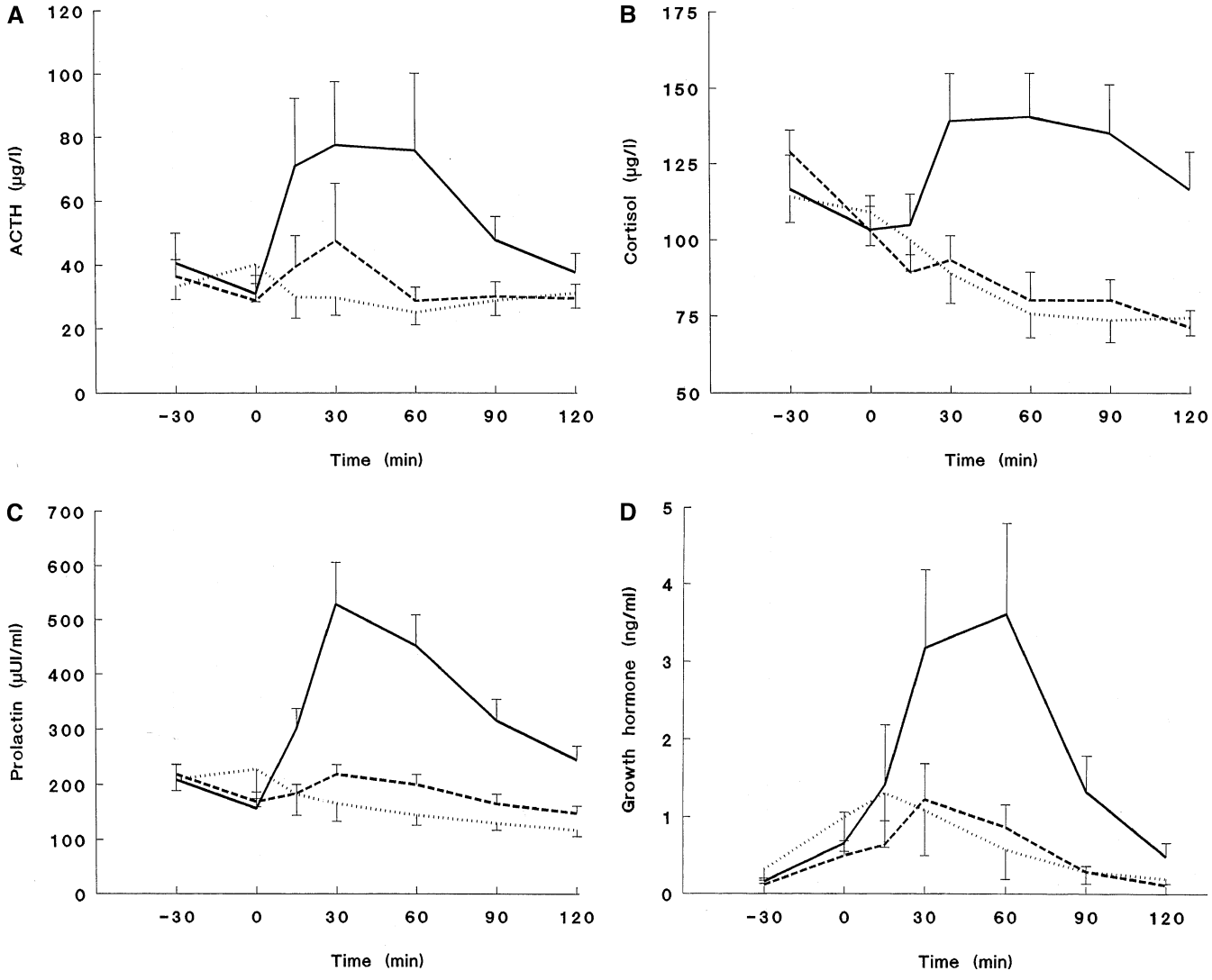

Fig. 1 Time-dependent effect of flesinoxan (0.5 mg *dashed line*; 1 mg *solid line*) and placebo (*dotted line*) on plasma ACTH (**A**), cortisol (**B**), prolactin (**C**) and growth hormone (**D**) concentrations

9104±19772, flesinoxan 0.5 mg 1940±5292, flesinoxan 1 mg 25557±17109 (Kruskal-Wallis; $P<0.0001$). Wilcoxon analysis showed a significant increase in PRL concentrations after flesinoxan 1 mg ($P<0.0001$). Injection of flesinoxan 0.5 mg already induced a slight but significant increase in PRL concentrations ($P<0.01$).

Growth hormone

Flesinoxan administration significantly increased GH concentrations (Fig. 1D): AUCR (ng.min/ml), placebo –39±64, flesinoxan 0.5 mg 18±56, flesinoxan 1 mg 175±262 (Kruskal-Wallis; $P<0.005$). Wilcoxon analysis showed a significant increase in GH concentrations after flesinoxan 1 mg ($P<0.01$), but also after flesinoxan 0.5 mg ($P<0.01$).

Temperature responses

Flesinoxan induced a dose-dependent decrease in oral temperature (Fig. 2): AUCR (min.°C), placebo 3.8±13.3, flesinoxan 0.5 mg –20.0±28.8, flesinoxan 1 mg –39.0±25.1 (Kruskal-Wallis; $P<0.0002$). Wilcoxon analysis showed a significant decrease in oral temperature after flesinoxan 0.5 mg ($P<0.003$) and after 1 mg ($P<0.0001$).

Physiological and psychological responses

The injection of flesinoxan did not induce any significant change in cardiologic parameters such as pulse, systolic and diastolic blood pressure. In contrast, flesinoxan induced a statistically significant decrease in POMS vigilance factor. However, we did not observe any statistically significant difference between placebo day and flesinoxan days for gastro-intestinal side effects. In

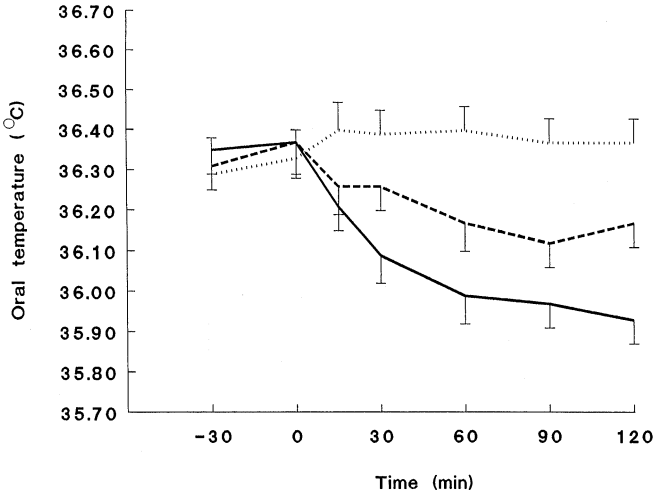

Fig. 2 Time-dependent effect of flesinoxan (0.5 mg *dashed line*; 1 mg *solid line*) and placebo (*dotted line*) on oral temperature

fact, only four patients reported slight nausea after administration of flesinoxan 1 mg.

The high dose of flesinoxan did not induce any significant effect on POMS tension, confusion, depression or anxiety factors. In contrast, flesinoxan 1 mg increased fatigue factor and decreased vigor factor scores.

Discussion

Our results demonstrated a very significant effect of flesinoxan on neuroendocrine function and body temperature in male healthy volunteers. Indeed, administration of flesinoxan induced a very significant and dose-dependent increase in ACTH, cortisol, PRL, GH and a decrease in oral temperature.

Flesinoxan 1 mg induced a very significant increase in ACTH and cortisol concentrations which is in line with several neuroendocrine studies using ipsapirone, gepirone, buspirone, fenfluramine or flesinoxan (Lesch et al. 1989; Anderson et al. 1990; Rausch et al. 1990; Maes et al. 1991; Cowen et al. 1994; Kahn et al. 1994; Meltzer and Maes 1994a, 1995a; Gelfin et al. 1995; Seletti et al. 1995; Cleare et al. 1998; Schwartz et al. 1999; Ramasubbu et al. 2000), and more specifically confirm the results of Seletti et al. (1995) who observed such an increase in plasma ACTH and cortisol levels with the high dose (1 mg) of flesinoxan. Our study is unable to state if the increase in plasma ACTH concentrations is due to the release of hypothalamic corticotropin releasing hormone (CRH) or to a direct stimulation of the ante-hypophysis. However, the identification of 5-HT_{1A} receptors at the level of several hypothalamic nucleus (Pazos et al. 1988) suggests that flesinoxan activates 5-HT_{1A} receptors at the level of the paraventricular nucleus. Moreover, serotonergic receptors of the ante-hypophysis are mainly 5-HT_2 subtypes. Concerning cortisol, a direct effect of flesinoxan on adrenal gland is not excluded (Dinan 1996). However, 5-HT receptors implicated in cortisol release at the level of the adrenal gland are 5-HT_4 receptor subtypes (Delarue et al. 1998) and it is unlikely to achieve a stimulation of 5-HT_4 receptors with flesinoxan.

The observation of PRL response to flesinoxan is in accordance with several studies performed in humans and demonstrating a significant increase in PRL secretion after administration of buspirone (Meltzer et al. 1983; Coccaro et al. 1990; Anderson and Cowen 1992) or gepirone (Anderson et al. 1990). In contrast, most studies failed to demonstrate an ipsapirone effect on PRL release which could be related to the fact that ipsapirone is a partial agonist (Lesch et al. 1989; Kahn et al. 1994). However, this effect remains controversial. Indeed, recently, in a placebo-controlled study, Clear et al. (1998) showed an increase in PRL levels after administration of ipsapirone (20 mg) in healthy men. In fact, it has been suggested that flesinoxan induced PRL response could require the integrity of both 5-HT_{1A} and 5-HT_2 receptors. Meltzer and Maes (1995b) suggested that both receptors could act on an additive or interactive mode to obtain maximal PRL effect.

The very significant increase in GH after flesinoxan completely parallels those reported by Seletti et al. (1995) and is consistent with studies using other 5-HT_{1A} agonists such as ipsapirone, gepirone or tandospirone to stimulate GH response (Lesch et al. 1989; Anderson et al. 1990; Miller et al. 1990; Cleare et al. 1998; Newman et al. 1999; Cleare and Bond 2000). This hormonal effect appears to be mediated through the stimulation of post-synaptic 5-HT_{1A} receptors (Seletti et al. 1995). Indeed, Seletti et al. (1995) reported antagonism of the GH response to flesinoxan by pindolol but not methysergide. The role of 5-HT_{1A} receptors in GH response to a 5-HT_{1A} agonist has been observed in other studies. Lesch (1991) demonstrated the blocking effect of pindolol on GH response to ipsapirone. An antagonizing action of pindolol has also been observed with buspirone (Anderson and Cowen 1992).

Flesinoxan-induced hypothermia tends to confirm results from several animal and human studies assessing the effect of different 5-HT_{1A} receptor agonists on core body temperature (Anderson et al. 1990; Lesch et al. 1990; Millan et al. 1993; Young et al. 1993; Kahn et al. 1994; Cleare et al. 1998; Cryan et al. 1999, McAllister-Williams et al. 2001). More specificaly, our results are in agreement with those of Seletti et al. (1995), who reported a dose-related decrease in body temperature after administration of flesinoxan (7 and 14 μg/kg). This hypothermic effect is probably mediated through the stimulation of 5-HT_{1A} receptors. Indeed, recently, Cryan et al. (1999) demonstrated that pretreatment with the selective 5-HT_{1A} receptor antagonist WAY 100635 blocked hypothermic response to flesinoxan in rats. Moreover, flesinoxan-induced hypothermia could be due at least in part to the stimulation of somatodendritic 5-HT_{1A} receptors (Cowen 2000). In fact, the nature of neuronal mechanisms involved in the hypothermic effect remains a subject of

controversy. In the rat, both pre- and postsynaptic receptors have been implicated (Bill et al. 1991; Millan et al. 1993; McAllister-Williams et al. 2001), and in the mouse hypothermic response is mediated via cell body 5-HT_{1A} receptors (Goodwin et al. 1987; Martin et al. 1992). However, overall, temperature response to flesinoxan could be used as a relatively direct, simple and robust measure of 5-HT_{1A} receptor sensitivity (Cryan et al. 1999).

Most pharmacological agents increasing serotonergic activity tend to induce side effects such as nausea, vomiting, dizziness or sedation. Hormonal responses after administration of a serotonergic agonist could represent artifacts due to these side effects. In the present study, flesinoxan-induced side effects were very moderate and did not explain hormonal responses.

In conclusion, the results of the present study tend to confirm the validity of flesinoxan as a serotonergic neuroendocrine probe. Indeed, ACTH, cortisol, PRL, GH and temperature responses to flesinoxan could be considered as indirect index of serotonergic activity in living human. More specifically, flesinoxan-induced hypothermia could be used as an easy and not very invasive technique to measure 5-HT_{1A} receptor sensitivity in living conditions. The use of thermal response has the advantage of being a more direct measure than anterior pituitary hormones whose release is under the control of hypothalamic factors. However, as a research tool, hormonal and temperature responses to flesinoxan are of a limited interest. First, currently, it is very difficult to obtain flesinoxan, particularly for human studies. Second, neuroendocrine responses to flesinoxan provide an indirect index of the sensitivity of 5-HT_{1A} receptors at the hypothalamic level and we do not know to what extend a hypothalamically mediated response is informative regarding the activity of 5-HT_{1A} receptors in other brain regions.

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