Evaluation of the α_2 -adrenoceptor blocking properties of buspirone and ipsapirone in healthy subjects. Relationship with the plasma concentration of the common metabolite 1-(2-pyrimidinyl)-piperazine

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- 1 Because the 5-HT_{1A} agonist anxiolytic azapirones have a common α_2 -adrenoceptor antagonist metabolite, 1-(2-pyrimidinyl)-piperazine (1PP), we measured central and peripheral α_2 -adrenoceptor dependent responses before and after intravenous administration of 0.15 mg clonidine when healthy subjects were taking buspirone (30 mg day⁻¹ for 4 days and 10 mg on day 5), ipsapirone (15 mg day⁻¹ for 4 days and 5 mg on day 5) or placebo.
- 2 Clonidine decreased blood pressure, heart rate, oral body temperature, salivary excretion, plasma noradrenaline, 3,4-dihydroxyphenylglycol (DHPG) concentrations, increased plasma growth hormone but did not modify plasma insulin and C-peptide concentrations. Treatments tended to modify only the effect of clonidine on growth hormone ($P = 0.07$).
- 3 The azapirones reduced clonidine induced prolongation of choice reaction time ($P = 0.015$) and tended to antagonise clonidine induced fall in critical flicker fusion frequency ($P = 0.066$).
- 4 Only buspirone reduced total reaction time and increased critical flicker fusion threshold measured 12 h after the evening dose and these effects were correlated with the residual plasma 1PP concentration which was higher on buspirone than on ipsapirone (2.76 $\mu\text{g l}^{-1}$, 95% CI: 1.3–4.22 vs 0.65 $\mu\text{g l}^{-1}$, 95% CI: 0.32–0.98, $P = 0.006$).
- 5 Mean AUC of the 1PP plasma concentrations after the last dose of treatments were 3.7 times greater with buspirone than with ipsapirone ($P = 0.0011$). The AUC ipsapirone/AUC 1PP ratio was 6.45 and the AUC buspirone/AUC 1PP ratio was 0.076.
- 6 The formation of the common metabolite 1PP is greater with buspirone than with ipsapirone. Buspirone but not ipsapirone (both given in therapeutically equivalent doses) exerted a psychostimulatory effect and this could be attributed to the higher plasma 1PP concentrations found with buspirone.
- 7 A clearcut antagonism of clonidine actions by 1PP could not be demonstrated probably because the ratio of the exogenous α_2 -adrenoceptor agonist (clonidine) to the endogenously formed α_2 -adrenoceptor antagonist (1PP) could not be controlled.

Keywords buspirone ipsapirone 1-(2-pyrimidinyl)-piperazine α_2 -adrenoceptor antagonism healthy subjects

Introduction

Benzodiazepines are the most prescribed anxiolytic drugs despite their adverse effects like sedation, motor and cognitive impairment, interaction with alcohol, the possible development of dependence, withdrawal symptoms and rebound phenomena. Azapirones are partial agonists of the 5-hydroxytryptamine-1A (5-HT_{1A}) receptor and it was hypothesised that this class of drugs would have a more advantageous adverse effect profile than benzodiazepines with similar anxiolytic action. Furthermore, 5-HT_{1A} agonists possess potential antidepressant properties [1, 2].

The azapirones buspirone, ipsapirone, gepirone and tandospirone have a common pharmacologically active metabolite the 1-(2-pyrimidinyl)-piperazine (1PP) [3–6] resulting from oxidative dealkylation of the parent compounds [7]. 1PP has α_2 -adrenoceptor antagonist activity in different animal models [4, 5, 8]. In humans plasma levels of 1PP after administration of buspirone are eightfold greater on a molar basis than that of buspirone [9]. Peak plasma concentration of 1PP after oral administration of 20 mg buspirone is attained in 30–60 min and its elimination half-life is 6.1 ± 0.3 h, twice as high as that of buspirone and varies little among subjects [3]. 1PP penetrates well into the brain [10], in rats the brain concentration of 1PP is 15 to 30 times higher than that of buspirone [9].

Ipsapirone has a high selectivity for the 5-HT_{1A} receptor [11]. After oral administration of ipsapirone to healthy subjects, time to peak plasma concentration is reached within 0.5 to 1.3 h, its elimination half-life is about 2 h. Steady state concentrations are obtained after 3 days. Ipsapirone is nearly completely metabolised by the liver and 1PP is only a minor metabolite of ipsapirone (2% of the dose given) [12].

Since α_2 -adrenoceptor blocking drugs increase self-reported anxiety in healthy subjects [13] and may trigger panic attack in patients predisposed to this condition [14] the presence of an α_2 -adrenoceptor antagonist metabolite after administration of an anxiolytic may counteract the anxiolytic effect especially in patients with panic disorder [15], and may impair the antidepressant effect of the parent drug [1].

Therefore the aim of this study was to assess whether buspirone and ipsapirone possess α_2 -adrenoceptor blocking properties in man after administration of clinically equivalent doses at steady-state condition. We measured central and peripheral α_2 -adrenoceptor dependent responses, mood and vigilance before and after administration of intravenous clonidine, a specific α_2 -adrenoceptor agonist which has been used in a number of studies to test central and peripheral α_2 -adrenoceptor responses [16–18]. Furthermore, the relationship between plasma 1PP concentration and the putative α_2 -adrenoceptor antagonism was analysed.

Methods

Subjects

Twelve healthy male subjects were selected for the study. Their age ranged from 19 to 31 years (mean

23.2), their weight from 58 to 95 kg (mean 70.2) and height from 170 to 193 cm (mean 178.7). Subjects had no previous history of cardiovascular, pulmonary, psychiatric, or other diseases, and had been free of medication for at least 1 month. Each subject had a normal 12 lead ECG and normal results following clinical, biochemical and haematological examinations before the study. All subjects had normal results on two psychological examinations (Eysenck Personality Inventory and Cattell's anxiety test). Approval was obtained from the Ethics Committee of the Pitié-Salpêtrière Hospital and each subject gave written informed consent before the study.

Study design and dosage regimen

This was a double-blind crossover study. Drugs were administered according to a balanced Latin square design. Each treatment period was separated by 1 week of wash out. Treatments were given in non-identifiable capsules. Subjects took one capsule three times per day throughout 4 days and in the morning of the 5th day which was the day of assessments. Capsules contained 5 mg ipsapirone, 10 mg buspirone or placebo. For both test drugs the administration of unit doses was chosen. The daily dose for each drug was the recommended therapeutic dose in the treatment of generalised anxiety [19–22].

Clonidine 0.15 mg in 10 ml of 0.9% saline solution was administered intravenously as a 10 min infusion [16–18].

Study outline

Subjects began to take their treatment at home. On day 2 of each treatment period they underwent a clinical examination and adverse effects or intercurrent events (if any) were reported. On day 5 in the morning subjects arrived after an overnight fast at the department. A polyethylene cannula was inserted into a forearm vein at least 30 min before the first blood sample was drawn. The contralateral arm was used for blood pressure and heart rate recording. The subjects remained in the supine position until 3 h after drug intake. They ingested their last capsule with 200 ml tap water ($t-1$ h). The intravenous clonidine was started (t_0) 1 h after the ingestion of the capsule containing the study drug. Subjects were served a standardised lunch (1200 kcal: 51% carbohydrates, 34% lipids, 15% proteins) 3 h after clonidine administration. Subjects left the department 9 h after drug intake.

Assessments

Somatic evaluations Blood pressure and heart rate were recorded on day 5 every hour until t_7 h in the supine position by an automated oscillometric heart rate and blood pressure recorder (Dinamap, Critikon). **Salivary excretion** was measured at $t-1$, t_0 , t_1 h and t_4 h. Three dental cotton tampons were used. Two were placed in the inferior gingival groove and the third sublingually. Salivary excretion was determined by weighing the tampons before and 2 min after they

had been placed in the mouth. *Oral body temperature* was measured by a high resolution thermometer (Bailey Instruments Mode Bat8) at $t-1$, $t0$, $t1$, $t3$, $t5$ and $t7$ h. The sensitivity of the thermometer was 0.1°C .

Psychometric evaluations *Critical flicker fusion frequency (CFF)* represents a measure of CNS activation. Threshold frequency was taken as the mean of three ascending and three descending readings. All measurements were carried out at a viewing distance of 1 m. *Choice reaction time (CRT)*: Total reaction time, recognition time and motor reaction time were determined. The measure given in milliseconds was the mean of 50 stimulus presentations. Both CFF and CRT were measured by the Leeds Psychomotor tester (ZAK GmbH, D-8346 Simbach/Inn, Germany) the subjects sitting in the bed. *Visual analogue rating scales (VAS)* were used to assess subjective feelings. Subjects were asked to rate their current feelings by marking the appropriate place on a 100 mm line which had a central area corresponding to a normal state. The VAS contained the following items: anxious, tired, happy, relaxed, drowsy, dizzy, clumsy, alert, energetic, sad, and depressed.

Chemical determinations *Blood glucose* was determined by a standard glucose oxidase method (inter-assay coefficient of variation 3%). *Plasma insulin* was determined by commercial kit (BioMérieux, Marcy-L'Etoile, France). Intra- and interassay coefficients of variation ranged from 3% to 6%, and from 4.5% to 6% respectively at low ($<20\ \mu\text{iu ml}^{-1}$) and high ($>100\ \mu\text{iu ml}^{-1}$) concentrations; the detection limit of the method was $2\ \mu\text{iu ml}^{-1}$. *Plasma C-peptide* was determined using CIBA-Corning kit (Cergy-Pontoise, France). Coefficients of variation of intra- and interassay were 5% and 8%, respectively; the detection limit of the method was $0.25\ \text{ng ml}^{-1}$. *Noradrenaline* and *DHPG* (3,4-dihydroxyphenylglycol) were determined by h.p.l.c. The detection limit for noradrenaline was $0.3\ \text{nmol l}^{-1}$ and for DHPG $0.6\ \text{nmol l}^{-1}$, respectively. Intraassay coefficients of variation were 6% and 7% and interassay coefficients of variation were 8.5% and 9.4% for DHPG and noradrenaline, respectively. *Growth hormone (GH)* was determined by a radio-immunologic method (BioMérieux, Marcy-L'Etoile, France). Intraassay coefficients of variation were 2% at medium and 5% at high and low concentrations. Interassay coefficients of variation were between 4% and 6%. Detection limit of the method was $0.2\ \mu\text{iu ml}^{-1}$.

Pharmacokinetics

Buspirone, ipsapirone and IPP plasma concentrations were determined [12, 23] at $t-1$ h (approximately 12 h after the evening dose of day 4), $t0$ (1 h after the last dose of the drugs and just before clonidine administration) and $t1$, $t2$, $t3$ and $t5$ h.

IPP together with 3-piperazino-benzotrifluoride as internal standard was extracted from alkalised plasma with toluene. After derivatisation with heptafluorobutyric acid anhydride the compounds were

separated from matrix components by gas chromatography on a capillary column and determined quantitatively with an electron capture detector. Buspirone was determined by a gas chromatography-mass spectrometry method [24] and ipsapirone by h.p.l.c. [12].

Adverse events These were assessed by free interview on day 2 and day 5 of each period before the clonidine infusion.

Statistical analysis

On pre-clonidine data two types of two-way ANOVA (factors: period and treatment) were performed: i) comparison of baseline values ($t-1$ h); ii) analysis of the differences $t0 - t-1$ h. Post-clonidine analysis included an ANOVA for repeated measures on the differences with respect of the $t0$ values (factors: subject, period, treatment, time = clonidine). This analysis concerned the variables CFF, CRT, VAS and biochemistry. For the variables blood pressure, heart rate, salivary excretion, temperature and blood glucose an analysis of covariance was made taking the $t0$ value as covariate. For GH, blood pressure and heart rate the post-clonidine analysis was performed also on area under the curves, maximal/minimal effect and time to maximal/minimal effect. If a significant treatment effect or treatment by clonidine interaction occurred, pairwise comparisons were realised by the t -test using the correction of Bonferroni. Quantitative data are described as means and 95% confidence interval if otherwise not indicated. Frequencies were compared by the χ^2 test. Correlations were tested by the least squares method. All statistical tests were interpreted two-sided and differences were considered significant if P values were <0.05 . The statistical analyses were performed with the statistical package BMDP (BMDP, Statistical Software, Inc., Los Angeles, California).

Results

Baseline values (12 h after the evening dose and just before the morning dose of day 5) for salivation, cardiovascular and biochemical variables were similar. No drug effect could be detected between $t-1$ h and $t0$. Clonidine significantly decreased oral body temperature, salivary excretion, systolic blood pressure and heart rate, its effect on diastolic blood pressure did not reach the level of statistical significance ($F(6,96)=1.94$, $P=0.08$) (data not shown). There was no difference between the three treatments for these actions of clonidine. As subjects were in fasting state plasma insulin and C-peptide declined significantly without difference between the treatments. Clonidine did not modify plasma insulin and C-peptide. Blood glucose increased moderately but significantly after clonidine administration ($F(5,80)=34.51$, $P<0.0001$) with a mean increase of $0.35\ \text{mmol l}^{-1}$ on placebo, $0.33\ \text{mmol l}^{-1}$ on ipsapirone and $0.37\ \text{mmol l}^{-1}$ on buspirone. Clonidine significantly decreased plasma noradrenaline ($F(3,42)=6.11$, $P=0.0015$) and plasma

Figure 1 Mean ($\pm$ s.e. mean) plasma growth hormone concentrations before (-1 and 0 h) and after intravenous administration of 0.15 mg clonidine (arrow) on day 5 after administration of placebo ($\triangle$), ipsapirone (15 mg day $^{-1}$ for 4 days and 5 mg on day 5, $\bullet$) and buspirone (30 mg day $^{-1}$ for 4 days and 10 mg on day 5, $\blacksquare$).

DHPG ($F(3,42) = 4.2$, $P = 0.01$) but this effect was not influenced by the treatments (data not shown).

The overall analysis of the GH determinations (from $t-1$ h to $t5$ h) showed a clear clonidine effect ($F(8,264) = 26.29$, $P < 0.0001$) and a treatment by clonidine interaction on the limit of significance ($F(16,264) = 1.67$, $P = 0.052$). When only post-clonidine concentrations were analysed, this treatment by clonidine interaction was also on the limit of significance ($F(6,48) = 2.12$, $P = 0.07$) (Figure 1). Post-clonidine mean area under the GH concentration curves were from $t0$ to $t1.5$ h 837 $\mu\text{iu ml}^{-1}$ (95% CI: 249 – 1425) on placebo, 597 $\mu\text{iu ml}^{-1}$ (95% CI: 293 – 901) on ipsapirone and 266 $\mu\text{iu ml}^{-1}$ (95% CI: -32 – 564) on buspirone (difference not significant). No difference occurred for peak or time to peak GH concentrations.

Neither clonidine nor the azapirones influenced visual analogue rating scales items evaluating mood (anxious, happy, relaxed, sad and depressed). However, items exploring vigilance and attention (tired, drowsy, energetic, clumsy, alert and confused) were significantly modified by clonidine but buspirone and ipsapirone did not interfere with these effects.

Before drug administration on day 5 ($t-1$ h) after 4 days of treatment, CFF showed significant differences ($F(2,20) = 6.37$, $P = 0.007$) (Figure 2): CFF threshold on buspirone was higher than on placebo, there was no difference between ipsapirone and placebo. After clonidine administration CFF threshold fell ($F(1,16) = 5.04$, $P = 0.04$) and the treatment by clonidine interaction was on the limit of significance ($F(1,16) = 3.24$, $P = 0.066$).

Total reaction time and recognition time were also different on day 5 before the morning dose ($F(2,20) = 3.98$, $P = 0.035$ and $F(2,20) = 5.09$, $P = 0.02$, respectively). Pairwise comparisons showed that total reaction time ($P = 0.015$) and recognition time ($P = 0.007$) were shorter when the subjects were taking buspirone than when they were on placebo (Figure 2). No difference was found between ipsapirone and placebo. Clonidine prolonged total reaction time, recognition time and motor reaction time. There was a significant

Figure 2 Critical flicker fusion frequency (CFF), recognition time (CRT-R) and total choice reaction time (CRT-T) before and after administration of clonidine (0.15 mg) (arrow) when subjects were on placebo, ipsapirone or buspirone (mean $\pm$ s.e. mean, symbols as in Figure 1). Buspirone vs placebo a) $P = 0.015$, b) $P = 0.007$.

treatment by clonidine interaction for total reaction time ($F(2,16) = 5.53$, $P = 0.015$) and recognition time ($F(2,16) = 4.31$, $P = 0.03$) but pairwise time by time analysis did not show significant differences between buspirone and placebo ($0.05 < P < 0.1$).

The mean residual plasma concentration of 1PP (day 5, $t-1$ h) was four times higher on buspirone than on ipsapirone (2.76 $\mu\text{g l}^{-1}$, 95% CI: 1.3 – 4.22 vs 0.65 $\mu\text{g l}^{-1}$, 95% CI: 0.32 – 0.98 , $F(1,11) = 11.75$, $P = 0.006$). The rise in plasma 1PP 1 h after the last dose was also different ($F(1,11) = 16.24$, $P = 0.002$). Peak plasma concentration of 1PP was higher on buspirone (6.8 $\mu\text{g l}^{-1}$, 95% CI: 4.06 – 9.54) than on ipsapirone (2 $\mu\text{g l}^{-1}$, 95% CI: 1.2 – 2.8 , $F(1,11) = 17.99$, $P = 0.0014$). Time to maximal plasma 1PP concentration was similar with buspirone and ipsapirone (1.17 h, 95% CI: 0.95 – 1.39 and 1.75 h, 95% CI: 1.15 – 1.35 , respectively). Areas under the 1PP concentration curves

Figure 3 Mean ($\pm$ s.e. mean) plasma 1-(2-pyrimidinyl)-piperazine (1PP) concentrations after 4 days of treatment by ipsapirone (15 mg day⁻¹ and 5 mg on day 5 at 0 h), buspirone (30 mg day⁻¹ for 4 days and 10 mg on day 5 at 0 h) and placebo in healthy subjects. (Symbols as in Figure 1).

Figure 4 Buspirone – placebo (■) and ipsapirone-placebo (○) differences in critical flicker fusion frequency (CFF) and total reaction time (CRT-T) as a function of plasma 1PP concentrations. (All measured at $t-1$ h (before the morning dose of day 5).)

were greater with buspirone (30.6 $\mu\text{g l}^{-1}$ h, 95% CI: 17.6–43.6) than with ipsapirone (8.2 $\mu\text{g l}^{-1}$ h, 95% CI: 4.6–11.8, $F(1,11) = 19.36$, $P = 0.001$) (Figure 3).

After 4 days of ipsapirone administration 15 mg day⁻¹, the mean residual plasma concentration was 2.02 $\mu\text{g l}^{-1}$ (95% CI: 0.95–3.09). After the 5 mg dose of day 5 the mean C_{max} was 20.14 $\mu\text{g l}^{-1}$ (95% CI: 15.92–24.36) and the AUC ipsapirone/AUC 1PP ratio was 6.45.

The mean residual plasma concentration of buspirone after 4 days of 30 mg day⁻¹ was 0.14 $\mu\text{g l}^{-1}$ (95% CI: 0.1–0.18), the mean C_{max} was 0.93 $\mu\text{g l}^{-1}$

Table 1 Adverse effects reported during the study (number of subjects)

	Placebo	Ipsapirone	Buspirone
Dizziness	1	6	5
Weakness	1	2	3
Nausea	0	1	2
Headache	1	2	0
Lightheadedness	0	2	1
Feeling of malaise	0	1	1
Fatigue	0	1	1
Drowsiness	0	1	1
Heat flush	0	2	0
Sweating	1	1	1
Sensation of cold	0	0	1
Concentration difficulty	0	1	0
Sensation of inebriation	0	0	1
Blurred ideas	0	1	0
Diarrhoea	1	0	0
Abdominal pain	0	1	0
Slowing down	0	1	0

(95% CI: 0.44–1.43) and AUC 2.334 $\mu\text{g l}^{-1}$ h (95% CI: 1.2–3.46). The ratio of AUC buspirone/AUC 1PP was 0.076.

There was a significant linear correlation between plasma 1PP concentrations and difference in CFF ($r = 0.67$, $P = 0.018$) and difference in total reaction time ($r = -0.65$, $P = 0.023$) with respect to placebo before administration of the morning dose of day 5 while subjects were taking buspirone but not while they were taking ipsapirone (Figure 4).

Table 1 shows the adverse effects reported by the subjects. Eleven subjects had adverse effects when taking ipsapirone, eight when taking buspirone and four when taking placebo ($\chi^2 = 8.889$, $P < 0.01$). More subjects reported dizziness with ipsapirone and buspirone than with placebo. More adverse effects occurred during the first 2 days of treatment than later. Twenty adverse effects were reported with ipsapirone on day 1 and 2 and only 11 on day 3, 4 and 5. On buspirone 15 adverse effects were experienced on day 1 and 2 and only 8 on day 3 through 5. The adverse effects on placebo were reported on day 1 and 2 ($n = 4$).

Discussion

The main question of this study was whether buspirone and ipsapirone possess, in healthy humans, central and/or peripheral α_2 -adrenoceptor antagonist properties. Previous studies have shown that azapirones have a common pharmacologically active α_2 -adrenoceptor antagonist metabolite, 1PP [3–6] which has anxiogenic-like effects [25], seems to counteract the antidepressive properties of buspirone [26], and antagonises the effect of clonidine in different animal models [4, 5]. Formation of 1PP after ipsapirone has been found to be smaller than with buspirone [12] although no direct comparison has been made.

To evaluate α_2 -adrenoceptor antagonism several central and peripheral responses were chosen. All of

them have been found to be modified by the α_2 -adrenoceptor agonist clonidine [16–18]. Therefore we used the intravenous clonidine test [16–18] to try to demonstrate a potential antagonism of clonidine actions and answer the question whether this antagonism may be related to the presence of 1PP.

We observed the known effects of clonidine: decrease in blood pressure, heart rate, salivation, body temperature, plasma noradrenaline and DHPG, vigilance, and increase in plasma GH concentration, moderate increase in blood glucose. None of the peripheral effects of clonidine was antagonised in the presence of the azapirones.

Clonidine induced GH elevation was somewhat modified by the active treatments although this did not reach the predetermined level of significance probably because the power of the study was insufficient to detect statistically significant antagonism.

Clonidine prolonged choice reaction time and decreased CFF threshold corresponding to its well known sedative effect. Treatments interacted with this decrease of vigilance but between treatment difference could not be shown. These results suggest that in man azapirones modify mainly central α_2 -adrenoceptor dependent functions whereas in rat both central and peripheral effects of clonidine have been found to be suppressed [4]. This is, however, in agreement with the finding that 1PP accumulates in the brain [9, 10].

Clear between treatment differences were seen before clonidine administration when evaluations were made 12 h after the evening dose and before the next, morning dose. At this time point, buspirone showed a psychostimulatory effect (increase in CFF threshold, shortening of choice reaction time) and this action correlated with the higher residual plasma 1PP concentrations. This is in agreement with the finding that the α_2 -adrenoceptor antagonist yohimbine shortens choice reaction time [27].

Patients with several types of anxiety show increased α_2 -adrenoceptor sensitivity. Patients with panic anxiety produce greater increases in nervousness, palpitations, restlessness, tremors and have greater increase in sitting blood pressure and greater plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) responses to yohimbine than healthy controls [14]. Similarly, the effect of clonidine in decreasing plasma MHPG, sitting and standing blood pressure is greater in patients with agoraphobia and panic disorder [28]. Since patients with anxiety disorders may have increased noradrenergic sensitivity, it is likely that the anxiolytic buspirone may trigger symptoms of anxiety or panic attacks in certain susceptible patients.

It has been shown that in man buspirone after single dose administration increases plasma prolactin and GH levels [29–31]. Buspirone [30] and ipsapirone [32] lower body temperature, increase plasma ACTH and cortisol concentration [33]. Further, in animal studies increases in blood glucose, plasma adrenaline and noradrenaline have been demonstrated [34]. In the present study after 4 days of azapirone administration to healthy subjects baseline body temperature, plasma noradrenaline, DHPG, blood glucose, insulin, C-peptide, and GH levels did not differ from those observed after placebo suggesting that neuroendocrine effects of azapirones do not undergo tolerance after repeated administration [35]. In conclusion, this study shows that buspirone has psychostimulatory effect in healthy subjects and this may be attributed to the α_2 -adrenoceptor antagonist metabolite 1PP whose formation, after administration of therapeutically equivalent doses, was substantially higher when subjects were taking buspirone than when they were taking ipsapirone. Further studies in patients with anxiety disorders are needed to determine whether the high plasma 1PP concentration observed with buspirone has clinical consequences or not.

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