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# A comparison of the neuro-endocrinological and temperature effects of DU 29894, flesinoxan, sulpiride and haloperidol in normal volunteers

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**1** Nineteen healthy male volunteers participated in a double-blind, six-way, cross-over study. With a separation of 1 week between sessions, volunteers received randomly one oral dose of each of the following compounds: 3 or 10 mg of the dopamine ($DA_2$) receptor antagonist and serotonin ($5HT_{1A}$) agonist DU 29894, 1 mg flesinoxan, 400 mg sulpiride, 3 mg haloperidol or placebo.

**2** To assess the dopamine ($DA_2$) antagonistic activity of the different compounds, plasma levels of prolactin were assessed at pre-dose, 0.5, 1, 2, 3, 4, 6 and 24 h post-dose. To assess the serotonin ($5HT_{1A}$) agonistic activity, plasma levels of ACTH, cortisol and growth hormone were assessed at the same time-points as well as body temperature; the latter was also assessed 8 h post-dose. Plasma levels of DU 29894 were assessed at pre-dose and 2, 3, 4 and 24 h post-dose.

**3** Sulpiride, haloperidol and both doses of 3 mg and 10 mg DU 29894 produced statistically significant increases in prolactin levels. The increase produced by 3 mg was roughly equivalent to that produced by 3 mg haloperidol whereas the increase produced by 10 mg DU 29894 was significantly larger.

**4** Only 10 mg DU 29894 and 1 mg flesinoxan produced statistically significant increases in ACTH, cortisol and growth hormone. All compounds either showed a significant attenuation of the normal day time increase of body temperature (3 mg DU 29894, haloperidol and sulpiride) or a true significant decrease in body temperature (10 mg DU 29894 and flesinoxan).

**5** In conclusion this study clearly showed single oral doses of 3 and 10 mg DU 29894 to have both dopamine ($DA_2$) antagonistic and serotonin ($5HT_{1A}$) agonistic activity.

**Keywords** DU 29894 flesinoxan sulpiride haloperidol neuro-endocrine temperature volunteers

## Introduction

Serotonin, dopamine and their interaction are the focus of attention of many investigators in the field of schizophrenia [1]. The findings of alleviation of specifically negative symptoms in schizophrenic patients and decrease in haloperidol induced extra-pyramidal side-effects by ritanserin boosted the development of a string of mixed $5HT_2/DA_2$ receptor antagonists [2]. Other serotonergic receptors that have received attention because they either have different levels in brains of schizophrenic patients or are a preferential binding site of clinically used antipsychotics like clozapine, are the $5HT_{1A}$ and $5HT_{2C}$ receptor [3, 4]. DU 29894, 1-(7-benzofuranyl)-4-[[5-(4-fluorophenyl)-1-H-pyrrol-2yl]methyl] piperazine, is a potent dopamine receptor ($DA_2$) antagonist ($K_i$ = 0.45 nM) and serotonin ($5HT_{1A}$) agonist ($K_i$ = 1.45 nM). High affinity also exists for the $DA_3$ receptor ($K_i$ = 1.29 nM) while next highest affinities (sigma receptors, $5HT_{1c}$ receptors, verapamil type $Ca^{2+}$ channel, $5HT_2$ receptors) are at least a factor 50 less (Solvay Duphar B.V., data on file). A single rising dose tolerance study with DU 29894 showed doses between 0.5 and 15 mg to be safe and reasonably well tolerated (De Koning,

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unpublished). The pharmacokinetics of DU 29894 are linear in the oral dose range from 0.5 to 15 mg. The plasma concentration-time curve is characterized by a biphasic elimination profile, with a terminal half-life of at least 30–40 h. DU 29894 is almost completely metabolized before excretion (De Koning, manuscript in preparation). The objective of the present study was to see whether the dopamine antagonist and serotonin agonist pharmacological activities were both apparent at single oral doses of 3 and 10 mg. To this extent we compared the differential hormone/temperature responses of specific $DA_2$ receptor antagonists and a $5HT_{1A}$ agonist with that of DU 29894. The hormone alteration caused by $DA_2$ receptor antagonists, such as sulpiride and haloperidol is an increase in prolactin level. This increase occurs at relatively low doses. The profile of the increases in prolactin levels is a high peak (maximum increase over baseline can be as high as 25-fold) followed by a slow decline [5, 6]. A 5-$HT_{1A}$ agonist, like flesinoxan, can induce increases in growth hormone, cortisol/ACTH and also prolactin levels. The profile of the increase in prolactin is characterized by a relatively small and short peak (maximally a 3-fold increase over baseline) and therefore differs from that of a $DA_2$ antagonist [7]. Not all 5-$HT_{1A}$ agonists induce changes in prolactin levels [8]. 5-$HT_{1A}$ agonists like flesinoxan and ipsaperone can lower body-temperature under experimental conditions. This decline in temperature is small, about 0.4° C, but very consistent [7, 9, 10]. To our knowledge no stimulation of growth hormone, cortisol/ACTH or decrease of temperature due to $DA_2$ receptor antagonists have been reported, although chlorpromazine may induce poikilothermia [11, 12]. The oral doses used for challenge were: DU 29894, 3 and 10 mg; haloperidol, 3 mg; sulpiride, 400 mg and flesinoxan, 1 mg. A placebo dose was also used. The study had a six-way cross-over design.

## Methods

### *Ethical considerations*

The study protocol was approved by the ethics committee of the Academic Hospital in Utrecht, The Netherlands. All volunteers gave written informed consent following a verbal explanation of the study and after they had read a detailed information sheet.

### *Subjects*

Nineteen male volunteers aged 19–33 years participated in the study. One volunteer withdrew before the second session because of a cold. He was replaced from the third session onwards. All volunteers had passed a comprehensive medical examination, including clinical/neurological examination, medical history, electrocardiography, haematology, clinical chemistry, including prolactin, cortisol, growth hormone and TSH, and urinalysis. Subjects should not have participated in single dose studies of investigational drug within 30 days or in multiple dose studies within 3 months of the start of the study. Volunteers should not have used prescribed medication within 30 days or non-prescribed medication within 48 h of the start of the study. Volunteers abstained from alcohol, caffeine and strenuous physical activity for 48 h before dosing and smoking for 24 h before dosing on each study day. Special care was taken to exclude volunteers with (sub)clinical illness apparent in elevation of body temperature: 1 h before dosing, oral body temperature was measured. When the temperature was above 37° C, the volunteer was excluded from that session. A volunteer, excluded from the first two sessions, was replaced by a standby. Safety and tolerability data of both drop-out and replacement were reported. The hormone and temperature data of the replacement only were used.

### *Experimental design*

The study was conducted according to a randomised, double-blind, placebo-controlled, six-way cross-over design. Volunteers were divided in three cohorts of six volunteers using a balanced latin square of six volunters by six treatments. Each volunteer attended on six identical days of the week, each session being separated by 1 week. For each session the volunteers reported to the clinic at 08.00 h on the day of the session and remained there till 13.00 h on day 2. They returned to the clinic on day 4 for a post-dose assessment.

The following experimental procedures were carefully controlled as they are known to have an influence on either hormones or temperature. The challenge doses were administered at noon, when all hormones of interest are at their lowest level [13, 14]. Volunteers remained in a semi-recumbent position from 10.30 h till 6 h post-dose and 10.30 h on day 2 till the 24 h post-dose blood sample was collected and were prevented from falling asleep (by means of a neutral video) to prevent peaks in growth hormone upon falling asleep [14]. Only healthy male, Caucasian volunteers were included to avoid differences in response between sexes and races [15, 16]. Standardized, low protein and fat meals were provided at fixed time points [17]. Volunteers had fasted from food and beverages other than water from 22.00 h on the evening before dosing. On the day of dosing they received a light lunch at 10.00 h. An afternoon snack, evening meal and evening snack were provided at 4, 6 and 10 h post-dosing. On day 2 a breakfast was provided between 08.00 h and 09.00 h. For the first 10 h after dosing 200 ml of fluid was provided every 2 h. The same menu was given during each session. The temperature of the room in which the experiment took place was carefully controlled and kept constant at 22° C. Body temperature was measured orally in the sulcus sublingualis by means of a calibrated thermometer (to 2 decimal places) [18]. Volunteers were not allowed to drink or eat 15 min prior to the assessment and had to keep

their mouth closed during the assessment. Blood sampling for hormone determinations (prolactin, ACTH, cortisol, growth hormone) were taken via a venous catheter in a forearm vein at pre-dose, 0.5, 1, 2, 3, 4, 6, and 24 h post-dose. Blood samples for assay of DU 29894 levels were taken at pre-dose, 2, 3, 4 and 24 h post-dose. Oral body temperature was assessed at pre-dose, 0.5, 1, 2, 3, 4, 6, 8 and 24 h after dosing. Blood pressure and pulse rate were assessed at pre-dose, 2, 4, 6, 8, 24 and 72 h post-dose. ECGs were taken at pre-dose, 4, 8 and 24 h post-dose. A detailed neurological examination, assessing extrapyramidal symptoms and akathisia was performed at pre-dose, 6 and 24 h post-dose. A physical examination was performed at pre-dose, 24 h and 72 h post-dose. Adverse events were collected as spontaneously reported events, observed events or events elicited by neutral questioning. The treatments which volunteers received in random order were: DU 29894 3 mg or 10 mg, flesinoxan 1 mg, haloperidol 3 mg, sulpiride 400 mg and placebo. All medications were formulated by the pharmaceutical department of Solvay Duphar B.V. as identical capsules. Each treatment was made up of three capsules.

*Hormonal assays*

Blood samples for hormonal assays were collected in plastic EDTA tubes. Immediately after collection the tubes were stored on ice. Within 1 h of collection the samples were centrifuged at 3000 rev $min^{-1}$ at −5° C for 10 min. Immediately after centrifuging the plasma was frozen at −20° C. Cortisol was measured using a competitive enzyme-immuno-assay (Enzymum-Cortisol test, Boehringer Mannheim, FRG). Growth hormone was measured using a non-competitive radio-immuno-assay (ELSA-hGH, CIS Biointernational, France). ACTH was measured using a competitive radio-immuno-assay (reagents by IgG Corporation, Nashville, USA and CIS Biointernational, France).

*DU 29894 assay*

An h.p.l.c. method with fluorometric detection, developed by the Bioanalytical Department of Solvay Duphar B.V., was used to assay DU 29894 in plasma.

*Correlation plasma concentrations DU 29894 and prolactin*

To enable calculation of the 'population' threshold DU 29894 concentration at which prolactin levels begin to increase, the pooled individually observed prolactin plasma concentrations were plotted against the DU 29894 plasma concentration.

*Statistical analysis*

The following key variables were defined in advance. For hormones: maximum increase of plasma level of prolactin, ACTH, cortisol and growth hormone over pre-dose level at any time point, per subject, per session, per medication ($C_{max}$). The AUC of the increase of plasma level of prolactin, ACTH, cortisol and growth hormone *vs* pre-dose from 0 till 6 h post-dose. For temperature: maximum decrease of body temperature at any time point per subject per session per medication ($C_{max}$). The AUC of the decrease of body temperature *vs* pre-dose from 0 till 8 h post-dose. The AUC was calculated using the trapezoidal rule.

The basic analysis for the key variables was an analysis of variance using a within subject comparison. Special contrasts were tested using the error mean square in a Student's *t*-test at a significance level of $P < 0.05$ (two tailed) with as error the random error of the ANOVA. The following contrasts were tested. For hormones: for all treatments, difference from placebo treatment and additionally for prolactin: DU 29894 3 and 10 mg *vs* haloperidol and sulpiride; for ACTH/cortisol and growth hormone DU 29894 and 10 mg *vs* flesinoxan. For temperature: for all treatments, difference from placebo treatment and additionally DU 29894 3 and 10 mg *vs* flesinoxan. Data-entry was performed in SAS 6.06 (FSP) and the statistical analysis in SAS 6.06 (PROC GLM). Taking into account the number of 18 volunteers, the study could detect a true difference of 25% in prolactin levels at a 5% significance level (power 80%) and a true difference of 0.35° C in body temperature (power 80%).

## Results

In general the results of the statistical analysis of $C_{max}$ were identical to those of the analyses of AUC data. Therefore in the text only the results of $C_{max}$ analyses are mentioned unless relevant discrepancies with the analyses of AUC data exist. Reference will be made only to those comparisons used to assess the relative $DA_2$ and $5HT_{1A}$ pharmacological activity of DU 29894.

*Prolactin*

Sulpiride, haloperidol and both 3 mg and 10 mg of DU 29894 produced statistically significant increases in prolactin levels (see Figure 1). The increase in prolactin level produced by 10 mg DU 29894 is statistically significantly larger than following 3 mg DU 29894. The increase in prolactin levels following 400 mg sulpiride was the highest and significantly larger than following 10 mg DU 29894. The increase by 3 mg DU 29894 was not different from that following 3 mg haloperidol. In general DU 29894, haloperidol and sulpiride produced long lasting increases in prolactin. The mean maximum increase and the range of individual subject baseline and maximum prolactin levels are summarized in Table 1.

*ACTH/Cortisol*

A striking difference between the predose ACTH concentration on the 'placebo' day and on the

'active' days exists. This is due to relatively high ACTH levels of one subject during the placebo session only. Only 10 mg DU 29894 and 1 mg flesinoxan produced statistically significant increases in ACTH and cortisol levels (ACTH levels are shown in Figure 2; ACTH and cortisol levels are given in Table 2 and Table 3, respectively). In general, the increases in cortisol lagged somewhat behind those of ACTH. The increase produced by 10 mg DU 29894 was significantly larger than that following either 1 mg flesinoxan or 3 mg DU 29894.

*Growth hormone*

Only 10 mg of DU 29894 produced a statistically significant increase in growth hormone levels (see Figure 3 and Table 4). The increase produced by 1 mg of flesinoxan just failed to reach statistical significance when analyzing $C_{max}$ data, but was statistically significant from placebo when analyzing AUC data.

*Body temperature*

The mean curve of body temperature following placebo treatment shows a day time increase of about 0.3° C. All other treatments caused either a significant attenuation of the increase of body temperature (DU 29894, 3 mg; haloperidol and sulpiride) or a true decrease in body temperature (DU 29894, 10 mg and flesinoxan), see Figure 4. The difference in maximum decrease between DU 29894, 10 mg and either flesinoxan or DU 29894, 3 mg is statistically significant. In Table 5 the maximum difference in body temperature corrected for baseline and placebo is given.

*Correlation plasma concentrations DU 29894 and prolactin*

The plot of the individually observed prolactin levels in relation to DU 29894 plasma concentrations is shown in Figure 5. It can be concluded that

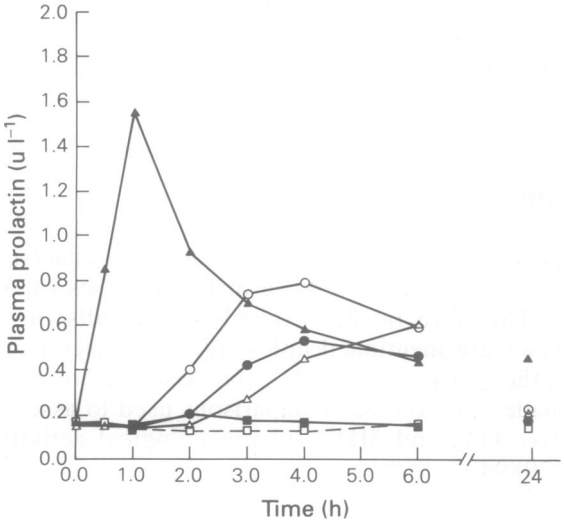


**Figure 1** Effects of placebo (–□–), DU 29894 10 mg (—○—), DU 29894 3 mg (—●—), flesinoxan 1 mg (—■—), haloperidol 3 mg (—△—) and sulpiride, 400 mg (—▲—) on plasma prolactin concentration.

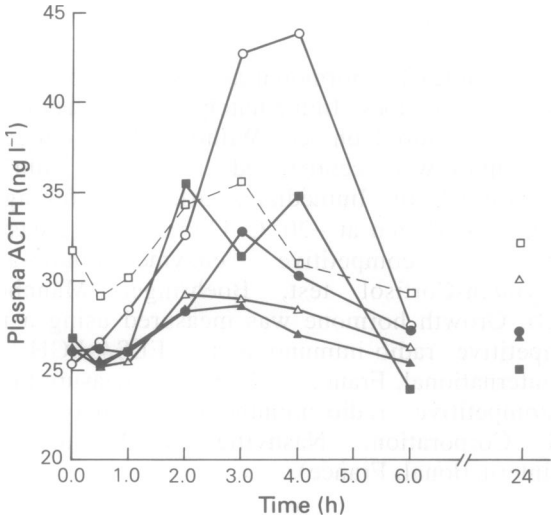


**Figure 2** Effects of placebo (–□–), DU 29894 10 mg (—○—), DU 29894 3 mg (—●—), flesinoxan 1 mg (—■—), haloperidol 3 mg (—△—) and sulpiride, 400 mg (—▲—) on plasma ACTH concentration.

**Table 1** Increase of plasma prolactin concentrations (u $l^{-1}$) over baseline

| | *Range* baseline concentrations (u $l^{-1}$)* | *Range* maximum concentrations (u $l^{-1}$)* | *Mean** increase concentrations (u $l^{-1}$)* |
|---|---|---|---|
| Placebo | 0.09–0.30 | 0.10–0.39 | 0.02 |
| DU 29894 3 mg | 0.09–0.24 | 0.23–0.81 | 0.41*** |
| DU 29894 10 mg | 0.09–0.22 | 0.64–1.25 | 0.76*** |
| Haloperidol 3 mg | 0.08–0.24 | 0.17–0.97 | 0.48*** |
| Sulpiride 400 mg | 0.08–0.25 | 0.96–2.14 | 1.44*** |
| Flesinoxan 1 mg | 0.08–0.27 | 0.16–0.41 | 0.08 |

* range of individual baseline or maximum prolactin concentrations.
** mean maximum increase of prolactin concentrations over baseline.
*** $P < 0.05$ *vs* placebo.

**Table 2** Increase of ACTH (ng $l^{-1}$) over baseline

| | *Range* baseline concentrations (ng $l^{-1}$)* | *Range* maximum concentrations (ng $l^{-1}$)* | *Mean** increase concentrations (ng $l^{-1}$)* |
|---|---|---|---|
| Placebo | 17.1–75.8 | 20.7–100 | 7.6 |
| DU 29894 3 mg | 11.9–40.2 | 19.4–59.5 | 9.4 |
| DU 29894 10 mg | 13.9–47.3 | 22.7–126 | 29.3*** |
| Haloperidol 3 mg | 12.7–39.4 | 16.8–48.7 | 6.3 |
| Sulpiride 400 mg | 14.9–35.6 | 23.9–43.8 | 7.2 |
| Flesinoxan 1 mg | 6.1–46.0 | 11.5–131 | 17.2*** |

* range of individual baseline or maximum ACTH concentrations.
** mean maximum increase of ACTH concentrations over baseline.
*** $P < 0.05$ *vs* placebo.

**Table 3** Increase of cortisol concentrations (μmol $l^{-1}$) over baseline

| | *Range* baseline concentrations (μmol $l^{-1}$)* | *Range* maximum concentrations (μmol $l^{-1}$)* | *Mean** increase concentrations (μmol $l^{-1}$)* |
|---|---|---|---|
| Placebo | 0.09–0.66 | 0.15–0.70 | 0.09 |
| DU 29894 3 mg | 0.11–0.40 | 0.18–0.51 | 0.08 |
| DU 29894 10 mg | 0.12–0.42 | 0.24–0.65 | 0.21*** |
| Haloperidol 3 mg | 0.13–0.32 | 0.14–0.41 | 0.03 |
| Sulpiride 400 mg | 0.14–0.43 | 0.18–0.46 | 0.08 |
| Flesinoxan 1 mg | 0.14–0.38 | 0.26–0.57 | 0.16*** |

* range of individual baseline or maximum cortisol concentrations.
** mean maximum increase of cortisol concentrations over baseline.
*** $P < 0.05$ *vs* placebo.

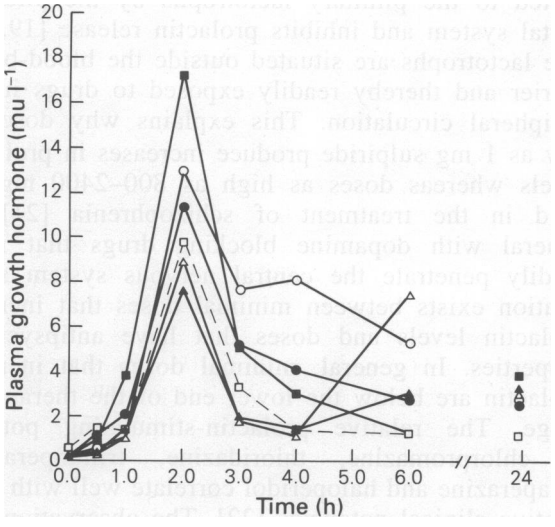


**Figure 3** Effects of placebo (–□–), DU 29894 10 mg (—○—), DU 29894 3 mg (—●—), flesinoxan 1 mg (—■—), haloperidol 3 mg (—△—) and sulpiride, 400 mg (—▲—) on plasma growth hormone concentration.

the 'population' prolactin stimulation threshold concentration is about 4–6 ng $ml^{-1}$.

*Neurological examination*

There were no noteworthy changes in neurological status. Specifically, there was no objective sign of akathisia, neither were there any reports of restlessness.

*Safety evaluations*

There were no clinically relevant changes in vital signs, ECG, clinical chemistry, haematology, urinalysis or physical examination.

## Discussion

The results of this study clearly show the presence of both dopamine ($DA_2$) antagonistic and serotonin ($5HT_{1A}$) agonistic activity in single oral doses of 3 and 10 mg DU 29894. The presence of DA antagonistic activity is suggested from the pronounced long lasting increase in prolactin levels. When plotting the prolactin plasma concentration *vs* the DU 29894 concentration no plateauing of the response was observed. From this plot the DU 29894 threshold concentration can be established, being 4–6 ng $ml^{-1}$. This corresponds to an oral dose of DU 29894 of about 2–3 mg. This value compared well with the prolactin stimulation threshold calculated from a previous single rising dose tolerance study (P. de Koning, unpublished). By comparison the mean maximum increase in prolactin following 400 mg of sulpiride was significantly higher than that produced by 10 mg DU 29894. The increase produced by 3 mg haloperidol was significantly less than that following 10 mg DU 29894 but not different from that of 3 mg DU 29894. $Dopamine_2$-receptors are located, amongst

**Table 4** Increase of growth hormone concentrations (mu $l^{-1}$) over baseline

| | *Range* baseline concentrations (mU $l^{-1}$)* | *Range* maximum concentrations (mU $l^{-1}$)* | *Mean** increase concentrations (mU $l^{-1}$)* |
|---|---|---|---|
| Placebo | 0.04–3.57 | 0.11–38.0 | 11.9 |
| DU 29894 3 mg | 0.05–1.23 | 1.13–54.8 | 17.6 |
| DU 29894 10 mg | 0.01–0.73 | 1.59–58.8 | 23.6*** |
| Haloperidol 3 mg | 0.06–0.93 | 0.58–69.3 | 14.8 |
| Sulpiride 400 mg | 0.05–0.94 | 0.11–47.0 | 10.5 |
| Flesinoxan 1 mg | 0.07–1.22 | 0.27–44.0 | 20.2 |

* range of individual baseline or maximum growth hormone concentrations.
** mean maximum increase of growth hormone concentrations over baseline.
*** $P < 0.05$ *vs* placebo.

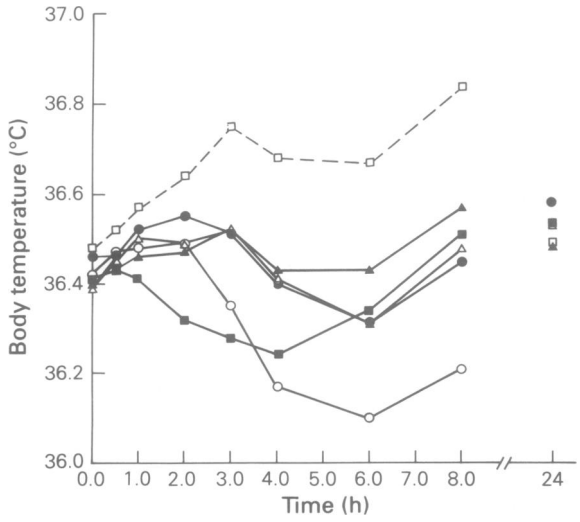


**Figure 4** Effects of placebo (–□–), DU 29894 10 mg (—○—), DU 29894 3 mg (—●—), flesinoxan 1 mg (—■—), haloperidol 3 mg (—△—) and sulpiride, 400 mg (—▲—) on body temperature.

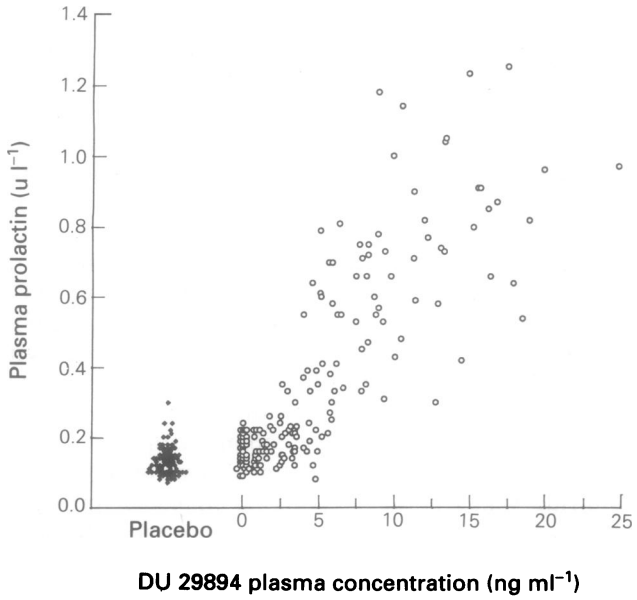


**Figure 5** DU 29894 *vs* plasma prolactin concentration.

**Table 5** Maximum difference in body temperature corrected for baseline and placebo

| | *Maximum difference (°C)* | *Range (°C)* |
|---|---|---|
| DU 29894 3 mg | –0.51 | –0.88 – –0.13 |
| DU 29894 10 mg | –0.67 | –1.14 – –0.16 |
| Haloperidol 3 mg | –0.40 | –0.93 – 0.00 |
| Sulpiride 400 mg | –0.31 | –1.09 – +0.08 |
| Flesinoxan 1 mg | –0.50 | –1.03 – –0.11 |

other places, on the lactotrophs of the anterior pituitary. Dopamine when released from the terminals of the tuberoinfundibular dopamine neurons is transported to the pituitary lactotrophs by the pituitary portal system and inhibits prolactin release [19, 20]. The lactotrophs are situated outside the blood-brain-barrier and thereby readily exposed to drugs in the peripheral circulation. This explains why doses as low as 1 mg sulpiride produce increases in prolactin levels whereas doses as high as 800–2400 mg are used in the treatment of schizophrenia [21]. In general with dopamine blocking drugs that more readily penetrate the central nervous system some relation exists between minimal doses that increase prolactin levels and doses that have antipsychotic properties. In general, minimal doses that increase prolactin are below the lower end of the therapeutic range. The relative prolactin-stimulating potency of chlorpromazine, thioridazine, trifluoperazine, butaperazine and haloperidol correlate well with their relative clinical potencies [22]. The observation that the prolactin response following 3 mg DU 29894 was in the same range as that following 3 mg haloperidol therefore gives a useful indication of doses of DU 29894 to be tested in clinical antipsychotic efficacy studies.

The presence of $5HT_{1A}$ agonistic activity in single oral doses of 3 and 10 mg DU 29894 is evident from the attenuation of increase or true decrease of body temperature as well as the significant increases in ACTH, cortisol and growth hormone. The involvement of the $5HT_{1A}$ receptor in the hypothalamic-pituitary-adrenal axis function has been clearly established by studies in which the endocrine stimulating activity of ipsaperone, a $5HT_{1A}$ agonist, could

be partially blocked by metergoline and fully blocked by (±)-pindolol but not betaxolol [23]. Similarly the elevation of growth hormone levels by flesinoxan could be blocked by pindolol [24]. Most characteristic of $5HT_{1A}$ agonist is the influence on body temperature. Whereas 3 mg DU 29894 attenuated the normal small increase in body temperature over the day, 10 mg DU 29894 like flesinoxan induced a small decrease in body temperature. The mechanism of this effect is as yet unknown but probably involves a central action [25]. The maximum decrease induced by 10 mg DU 29894 was significantly larger than that following flesinoxan which was larger (though not significantly) than that of 3 mg DU 29894. Again this comparison sheds some light on the relative $5HT_{1A}$ pharmacological activity of DU 29894 in comparison with 1 mg flexinoxan.

Of interest is the attenuation of daytime increase in temperature by both haloperidol and sulpiride. There has been much debate about the effects of dopamine antagonists on temperature, particularly in the light of the neuroleptic malignant syndrome. In the latter case the temperature increase is probably secondary to the increased muscle tone. With the exception of reports on chlorpromazine, this study is to our knowledge the first to show a clear effect of dopamine antagonists on temperature.

The time of day chosen for the challenge, noon, proved indeed correct as evidenced by the relative stability of hormone levels under placebo treatment. Of note however is the peak in growth hormone levels at 2 h post-dose under all treatments including placebo. This may be related to a variety of factors including the nutrient, particularly amino acid, composition of the midday meal.

In conclusion this study clearly showed, the feasibility of assessing different pharmacological activities present in one molecule by using appropriate selective comparative compounds. Single oral doses of DU 29894 of 3 and 10 mg proved to be safe, well tolerated and to have both dopamine ($DA_2$ antagonistic and serotonin ($5HT_{1A}$) agonistic activity. The relative potency to pure dopamine ($DA_2$) antagonists and a serotonin ($5HT_{1A}$) agonist gives useful information regarding the choice of dose ranges to be tested in clinical efficacy studies.

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