Alterations in the Pituitary-Thyroid and Pituitary-Adrenal Axes—Consequences of Long-Term Mifepristone Treatment

Oskari Heikinheimo, Sirpa Ranta, Steven Grunberg, Pekka Lähteenmäki, and Irving M. Spitz

The effects of short-term administration of the antiprogestin and antiglucocorticoid, mifepristone, have been well characterized. However, little is known about the effects of prolonged administration of mifepristone. We analyzed hormonal parameters in four female and three male patients with unresectable meningioma who were treated with mifepristone (200 mg/d) for 20 to 40 months. Serum samples were collected at monthly intervals approximately 24 hours following mifepristone ingestion. Serum thyrotropin (TSH), thyroxine (T_4), free T_4 (fT_4), 3,5,3-triiodothyronine (T_3), prolactin, and cortisol were analyzed by fluoroimmunoassay, and androstenedione by radioimmunoassay (RIA). Levels of mifepristone and its three most proximal metabolites were measured by high-performance liquid chromatography. TSH values increased significantly ($P < .005$, one-way ANOVA), with the most pronounced increase evident during the first 3 months of mifepristone treatment. Despite these changes, concentrations of TSH remained within the normal range throughout the treatment period. There were no significant changes in serum T_4, fT_4, T_3 or prolactin; however, a transient decrease in serum T_4 was noted at 2 to 3 months. Cortisol and androstenedione values increased significantly and in parallel ($P < .05$), suggesting an adrenal origin also for androstenedione. As during short-term administration, levels of mifepristone and its metabolites remained stable in the micromolar range. Individual levels of mifepristone were significantly correlated with those of TSH and cortisol. This suggests that the alterations in the pituitary-thyroid and -adrenal axes occurred in a concentration-dependent manner. It is concluded that long-term mifepristone treatment results in resetting of the pituitary-thyroid balance. As in the case with cortisol and androstenedione, it is likely that the alterations in serum TSH are due to the antiglucocorticoid properties of mifepristone. The clinical significance of these biochemical alterations in thyroid homeostasis remains to be determined. However, monitoring thyroid function during long-term mifepristone treatment appears to be warranted.

LONG-TERM ANTIPROGESTIN administration has been proposed as a new treatment modality for various hormone-dependent conditions. Of the antiprogesterone compounds, mifepristone (RU486) is by far the best characterized. It is being currently investigated in the treatment of uterine fibroids,[1] endometriosis,[2] breast cancer,[3] and meningioma,[4] all requiring long-term administration. Besides binding to the progesterone receptor, mifepristone also has a high affinity for the glucocorticoid receptor, and antagonizes glucocorticoid actions in several model systems. As a consequence, mifepristone has been proposed as a possible alternative treatment for Cushing's syndrome due to extrapituitary corticotropin (ACTH)-producing tumors, or adrenal carcinoma.[5-6]

Short-term endocrine effects of mifepristone are well characterized, and reflect both the antiprogestin and antiglucocorticoid properties of the compound. Mifepristone induces uterine bleeding by a direct action on the progesterone-primed endometrium, and the combination of mifepristone followed by prostaglandin is being used successfully to terminate early human pregnancy.[7-8]

Within the dose range of 20 to 400 mg/d, the antiprogesterone activity, as evidenced by complete pregnancy terminations, of mifepristone is not dose-dependent.[9-10] In contrast, mifepristone activates the hypothalamic-pituitary-adrenal (HPA) axis in a dose-dependent manner,[11-12] as evidenced by increases in serum concentrations of pro-opiomelanocortin-derived peptides such as ACTH or β-endorphin, as well as cortisol.[11-12] In addition, mifepristone transiently increases serum prolactin in a dose-dependent manner.[13] These dose-dependent effects of mifepristone are seen at single doses of approximately 200 to 400 mg and greater.[11,13] Activation of the pituitary-adrenal axis is also seen during long-term daily administration of 200 mg mifepristone.[14]

In the present study, we characterized the endocrine effects of long-term mifepristone administration in a group of patients with unresectable meningioma who received 200 mg mifepristone daily for a minimum of 20 months. We specifically focused on the pituitary-thyroid and -adrenal axes and the relationship of these endocrine responses to the pharmacokinetics of mifepristone.

SUBJECTS AND METHODS

Patients

A total of four women (one postmenopausal and three premenopausal) and three men with unresectable meningioma were studied. The clinical characteristics and outcomes of these same patients have been reported previously.[15-16] All subjects received a daily oral dose of mifepristone (200 mg) for a minimum of 20 months. During the first 14 days of mifepristone therapy, dexamethasone (1 mg) was also administered.[15] The patients received no additional hormonal therapy. Blood samples were collected before initiation of mifepristone, monthly during the first year, and thereafter at 3-month intervals. Samples were

From the Steroid Research Laboratory, Department of Medical Chemistry, University of Helsinki, Helsinki, Finland; the Vermont Cancer Center, University of Vermont, Fletcher Allen Health Care, Burlington, VT; and the Center for Biomedical Research, The Population Council, New York, NY.

Submitted July 8, 1996; accepted August 27, 1996.

Supported in part by the Contraceptive Development Program of the International Committee for Contraception Research of The Population Council, New York, a grant supplement to National Institutes of Health Grant No. 2U10CA32102-13, and a fellowship grant (to O.H.) from the Sigrid Jusélius Foundation (Helsinki, Finland).

Presented in part at The Clinical Research Meeting of the American Society for Clinical Investigation, Baltimore, MD, April 29 to May 2, 1994.

Address reprint requests to Oskari Heikinheimo, MD, Steroid Research Laboratory, Department of Medical Chemistry, University of Helsinki, PO Box 8, SF-00014, Helsinki, Finland.

0026-0495/97/4603-0011$03.00/0

drawn between 8 and 10 AM approximately 24 hours following mifepristone ingestion. Mifepristone tablets (200 mg) were supplied by Roussel-Uclaf (Romainville, France).

Assays

Serum thyrotropin (TSH), thyroxine (T_4), free T_4 (fT_4), 3,5,3'-triiodothyronine (T_3), prolactin, and cortisol were determined by an immunofluorometric assay system (Delfia; Wallac-Pharmacia, Turku, Finland) using assay kits purchased from the manufacturer. Serum androstenedione level was measured by radioimmunoassay (RIA) using reagents supplied by the World Health Organization. All samples from an individual patient were analyzed in the same assay.

Normal ranges for TSH, T_4, fT_4, T_3, prolactin, and cortisol with the Delfia system are 0.3 to 3.8 mU/L, 69 to 141 nmol/L, 8.5 to 19 pmol/L, 1.3 to 2.5 nmol/L, 83 to 523 mU/L, and 200 to 850 nmol/L (morning values), respectively. Intraassay and interassay coefficients of variation were 4% to 5% and 6% to 7%, 3% to 6% and 5% to 7%, 4% to 8% and 6% to 10%, 3% to 4% and 5% to 7%, 4% and 5% to 6%, 5% to 7% and 4% to 7%, and 3% to 5% and 6% to 10% for TSH, T_4, fT_4, T_3, prolactin, cortisol, and androstenedione assays, respectively.

Serum levels of mifepristone and those of its three most proximal metabolites (monodemethylated, didemethylated, and hydroxylated[17]) were measured by high-performance liquid chromatography preceded by column chromatography as previously described.[18-19]

Serum alpha-1-acid glycoprotein (AAG), T_4-binding globulin, and thyroid antibodies (thyroglobulin and thyroid peroxidase) were analyzed in two samples collected from each patient at 2 to 3 months and at 8 to 12 months. These assays were performed by a commercial laboratory (Medix, Kauniainen, Finland) using immunoturbidometric, immunofluorometric, RIA, and agglutination methods with assay kits supplied by Orion Diagnostica (Espoo, Finland), Wallac-Pharmacia, Fujirebio (Tokyo, Japan), and Sorin Biomedica (Saluggia, Italy), respectively.

Data Analysis

Statistical analyses of TSH, T_4, fT_4, T_3, prolactin, androstenedione, and cortisol were made using one- and two-way ANOVA. Further comparison of the individual values at different time points was made using paired *t* tests. In certain instances, linear regression was used. A *P* value of .05 or less was considered significant.

RESULTS

Figure 1 shows the concentrations of TSH, T_4, fT_4, and T_3 during long-term mifepristone administration. Concentrations of TSH increased during the first 3 months of mifepristone treatment ($P = .001$, one-way ANOVA). Similarly, when analyzed for the first 15 months of mifepristone treatment, one-way ANOVA indicated a significant increase in TSH levels ($P = .002$). From 4 months onward, TSH levels remained stable, as also indicated by the nonsignificant variation in TSH from 4 to 15 months of mifepristone treatment ($P = .74$, one-way ANOVA). When analyzed separately for women and men, the kinetics of serum TSH were indistinguishable between the two sexes ($P = .8$, two-way ANOVA; data not shown).

The alterations in serum T_4 were in part opposite to those of TSH. There was an initial decrease, which reached a nadir at 3 months. Thereafter, T_4 levels returned to the pretreatment range. When analyzed by one-way ANOVA, the variation in serum T_4 levels was not statistically significant during either the first 4 or 15 months ($P = .46$ and .92, respectively).

Serum levels of fT_4 and T_3 paralleled those of T_4, with correlation coefficients of .93 and .48, respectively ($P < .001$).

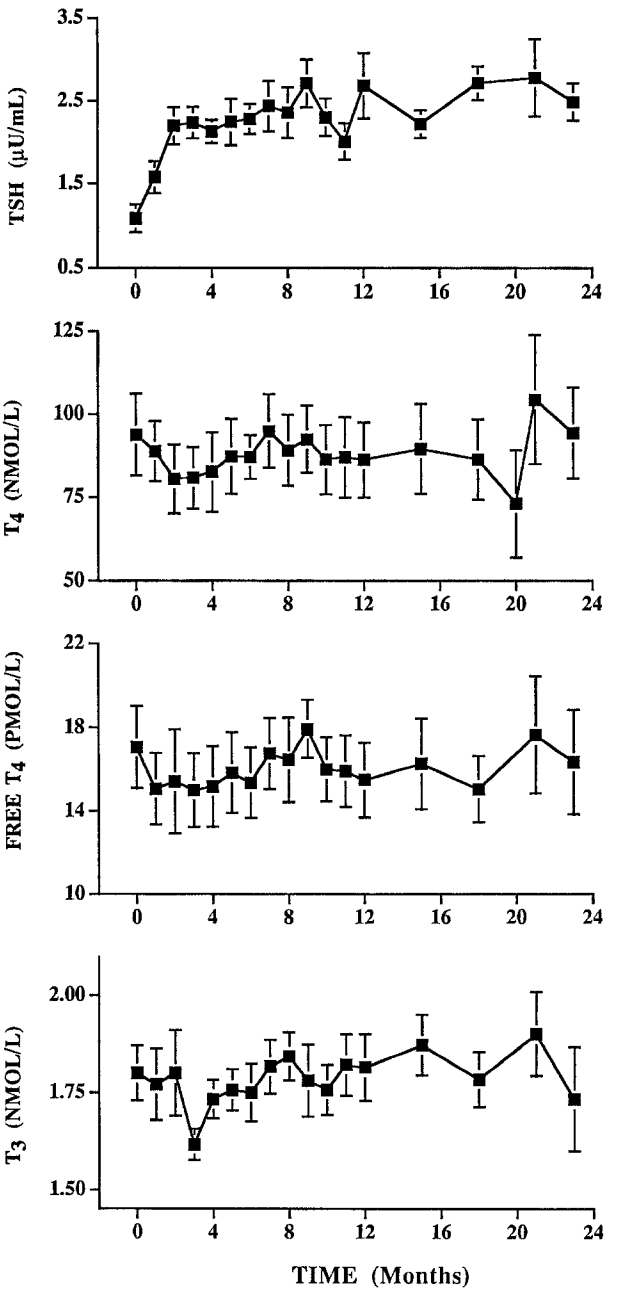

Fig 1. TSH, T_4, fT_4, and T_3 levels (mean ± SEM) during daily administration of mifepristone (200 mg) to patients with unresectable meningioma. One-way ANOVA showed a significant increase in TSH levels ($P = .002$), whereas only nonsignificant alterations were seen for T_4, fT_4, and T_3. When analyzed separately for both sexes, the kinetics of serum TSH were indistinguishable (data not shown). Normal ranges for TSH, T_4, fT_4, and T_3 with the Delfia system are 0.3 to 3.8 mU/L, 69 to 141 nmol/L, 8.5 to 19 pmol/L, and 1.3 to 2.5 nmol/L, respectively.

The lowest levels of both fT_4 and T_3 were measured at 3 months. However, when analyzed by one-way ANOVA, no statistically significant variation was noted in serum fT_4 or T_3 during the first 15 months of mifepristone treatment.

None of the patients had measurable levels of thyroglobulin or thyroid peroxidase antibodies.

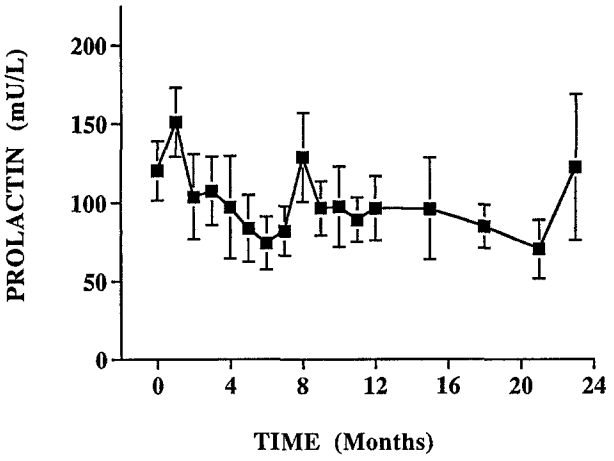

Fig 2. Serum prolactin concentrations (mean ± SEM). In contrast to TSH, prolactin levels were unaltered during mifepristone administration. Normal serum prolactin levels range from 90 to 523 mU/L in women and from 83 to 414 mU/L in men.

The levels (mean ± SEM) of prolactin are shown Fig 2. No statistically significant alterations were seen in serum prolactin over the first 3 or 20 months of mifepristone treatment ($P = .1$ and .8, respectively, one-way ANOVA).

Serum cortisol and androstenedione concentrations are shown in Fig 3. Mean cortisol levels were increased during mifepristone administration. Androstenedione levels also increased significantly and were correlated with those of cortisol ($r = .53$, $P < .001$). In individual patients, serum levels of cortisol or androstenedione were not significantly correlated with those of TSH or T_4.

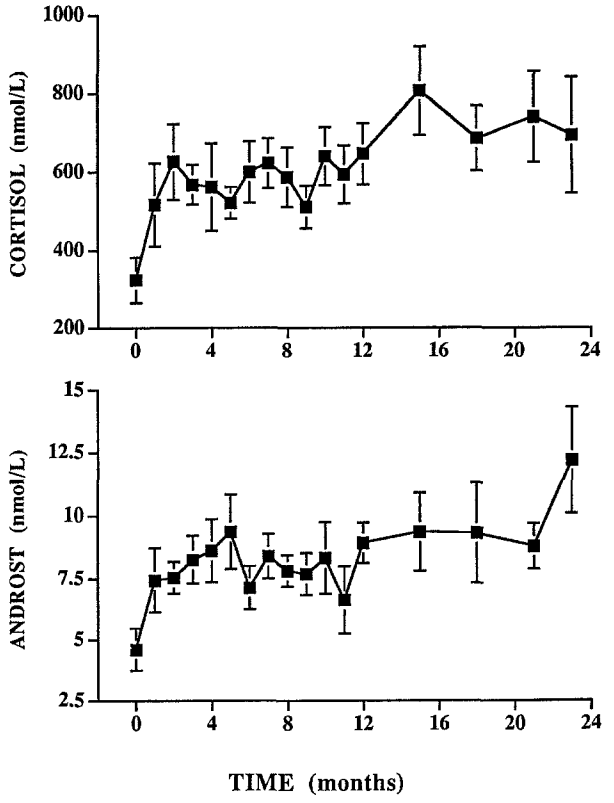

Fig 3. Cortisol and androstenedione (ANDROST) concentrations (mean ± SEM) increased significantly during mifepristone administration ($P < .05$, one-way ANOVA).

In individual subjects, mifepristone levels remained in the micromolar range throughout the study period, and varied from 0.7 to 4.9 μmol/L (Fig 4). The mean of individual mifepristone concentrations was 2.9 μmol/L. Levels of three of its most proximal metabolites were also present in steady, micromolar concentrations throughout the period of mifepristone administration (Fig 4).

T_4-binding globulin levels (mean ± SD) were 18.9 ± 2.7 and 18.1 ± 3.0 mg/L in samples collected at 2 to 3 and 8 to 12 months, respectively. Similarly, there were no alterations in AAG levels measured in samples collected at 2 to 3 and 8 to 12 months. Levels were 0.53 ± 0.15 and 0.56 ± 0.13 g/L in the two samples, respectively. AAG levels correlated significantly with mifepristone concentrations measured in these same samples ($r = .6$, $P < .02$).

DISCUSSION

Glucocorticoids influence thyroid hormone homeostasis at several levels. The glucocorticoid deficiency of Addison's disease is associated with increased levels of TSH,[20] whereas administration of exogenous glucocorticoids or the hypercortisolemia of Cushing's disease result in suppressed basal and TSH-releasing hormone–stimulated levels of TSH.[21-22] In addition, glucocorticoids abolish the nocturnal surge of TSH secretion.[23-24] Thus, glucocorticoids appear to have a permissive role in the regulation of TSH secretion. Exogenous glucocorti-

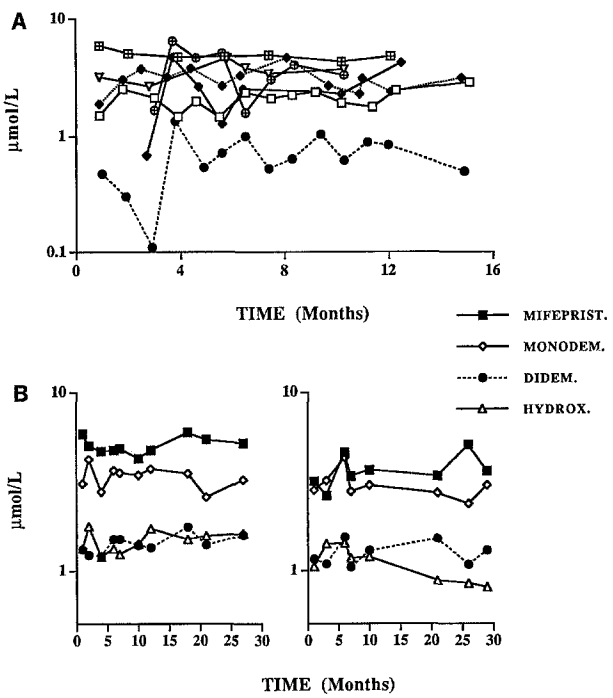

Fig 4. (A) Individual concentrations of mifepristone in 7 subjects. (B) Individual concentrations of mifepristone (■) and its monodemethylated (◇), didemethylated (●), and hydroxylated (△) metabolites in 2 patients.

coids also suppress serum T_3,[21,25-26] an effect most likely mediated via downregulation of the 5′-deiodinase enzyme system converting T_4 to T_3.[27] In addition, a recent study by Takiyama et al[28] showed that glucocorticoids increased iodine uptake and the release of organified iodine by porcine thyroid cells in vitro, suggesting direct effects on the thyroid gland.

In the present study, long-term administration of the antiprogestin and antiglucocorticoid, mifepristone, was associated with increases in serum cortisol and androstenedione and alterations in thyroid homeostasis. Basal levels of TSH increased progressively for 2 to 3 months, and thereafter remained elevated throughout the duration of the study. Yet these changes were not accompanied by statistically significant alterations in serum T_4, fT_4, or T_3. However, a transient decline in serum T_4 was seen at 2 to 3 months. The effect of mifepristone administration on the pituitary-thyroid axis has been previously addressed following daily administration of 50 or 100 mg mifepristone for 3 months. However, in these studies, only nonsignificant increases in serum levels of TSH were noted.[1-2] The discrepancy between the results of these studies and the present study might be related to differences in the dose and length of mifepristone administration and/or to the increased sensitivity of the immunofluorometric assay system in comparison to conventional RIA methods.[29-30]

However, it must be stressed that although the alterations in serum TSH were statistically significant, these changes occurred within the normal range of TSH concentrations. Moreover, thyroid antibodies were not detectable in any of the patients in the present study. Previously, Chrousos et al[6] reported the acute development of Hashimoto's thyroiditis in one of 11 patients treated with high-dose mifepristone for Cushing's disease. Thus, the clinical implications of the present findings remain to be determined.

Although the thyroid hormone receptor (TR) belongs to the same nuclear receptor superfamily as progesterone and glucocorticoid receptors, neither mifepristone nor its proximal metabolites bind to TR in vitro (W. Chin, personal communication, April 1994). Even though the activations of the HPA and pituitary-thyroid axis were associated, they were not significantly correlated in individual patients, suggesting that the activations of the pituitary-thyroid and -adrenal axes are likely to involve different mechanisms. Since glucocorticoids suppress pituitary secretion of TSH,[21-24] the increased serum TSH might be due to possible central antiglucocorticoid effects of mifepristone. On the other hand, the initial transient decrease in T_4 in the face of the increasing levels of TSH suggests that the site of mifepristone action may be the thyroid gland itself. In in vitro culture of porcine thyroid cells, mifepristone alone had no effect on iodine uptake or release of organified iodine.[28] However, the stimulatory actions of glucocorticoids on these parameters were abolished in the presence of mifepristone.[28] We therefore speculate that the alterations seen in the pituitary-thyroid balance are explained by antagonism of glucocorticoid action by mifepristone within the thyroid gland,[28] which in turn leads to a compensatory increase in TSH to maintain ambient secretion of T_4.

In contrast with the transient, dose-dependent elevations of serum prolactin observed with single doses of mifepristone,[13] prolactin levels were not increased in the present study (Fig 2).

Activation of the pituitary-adrenal axis during mifepristone administration is well characterized,[11-12,31] and is most likely mediated via central effects of mifepristone.[32] Moreover, the entry of mifepristone into the central nervous system seems to be limited and related to its serum levels.[33] Thus, increases were seen in serum cortisol and androstenedione (Fig 3). Their closely parallel increases also imply an adrenal origin for the elevation in serum androstenedione.

The pharmacokinetics of mifepristone closely mimicked the results of short-term studies.[34] Concentrations of mifepristone and its three most proximal metabolites were in the micromolar range, and individual levels remained remarkably constant throughout the treatment period. As was observed following single-dose administration,[35] levels of AAG, the serum binding protein for mifepristone, and those of mifepristone were significantly correlated also in the present long-term study. Thus, the stable levels of mifepristone observed over the period of 2 years could be partly attributed to unchanged levels and to the binding characteristics of AAG.

Significant correlations were noted for serum levels of mifepristone versus TSH and cortisol (Table 1). Activation of the HPA axis subsequent to administration of mifepristone is a dose-dependent phenomenon, and can only be seen following single-dose administration of at least 200 to 400 mg mifepristone.[11-13] Simplistically, it would seem to follow that these dose-dependent effects of mifepristone must also be associated with the serum concentrations of mifepristone. However, due to its nonlinear pharmacokinetics, serum levels of mifepristone plateau at the micromolar level at doses of 50 mg and greater.[34-35] Yet, similar to what was previously shown in dogs,[19] significant correlations were found between the serum concentration of mifepristone and the magnitude of pituitary-adrenal axis activation.

It is concluded that long-term mifepristone administration is associated with alterations in pituitary-thyroid homeostasis. The transient initial decline in serum T_4 was associated with persistently increased levels of serum TSH. This could be a consequence of the antiglucocorticoid properties of mifepristone. However, the changes in TSH and T_4 all occurred within the normal range. As expected, mifepristone administration activated the pituitary-adrenal axis, as evidenced by increased levels of serum cortisol and androstenedione. Changes in serum concentrations of TSH and cortisol were significantly correlated

Table 1. Individual Correlation Coefficients Between Serum Levels of Mifepristone and TSH, T_4, fT_4, T_3, Cortisol, Androstenedione, and Prolactin

Hormone	r* Range	r* Mean	*P* Significant
TSH	.1-.7	.49	3/7
T_4	−.5-.4	.18	None
fT_4	−.4-.5	.18	None
T_3	.0-.3	.22	None
Cortisol	.1-.8	.65	6/7
Androstenedione	.2-.7	.50	2/7
PRL	−.7-.5	−.13	1/7

NOTE. Multiple regression analysis of the pooled data showed significant correlations between serum levels of mifepristone and TSH ($P < .001$) and cortisol ($P = .001$). The number of patients with statistically significant r values ($P < .05$) is also shown.

*Analyzed by linear regression.

with those of mifepristone, suggesting that the magnitude of these endocrine responses was dependent on the circulating levels of mifepristone. The clinical implications of these alterations in thyroid parameters remain to be determined. However, monitoring thyroid function might be advisable should mifepristone be administered for prolonged periods.

ACKNOWLEDGMENT

We wish to thank Eeva Harju, Anne Hyvönen, and Marjatta Tevilin of the Steroid Research Laboratory for expert technical assistance. Susan Zaretsky, RN, and Virginia Cortes, RN, are gratefully acknowledged for nursing assistance. The administrative assistance of the Southwest Oncology Group is appreciated.

REFERENCES

1. Murphy A, Kettel M, Morales A, et al: Regression of uterine leiomyomata in response to the antiprogesterone RU486. J Clin Endocrinol Metab 76:513-517, 1993

2. Kettel M, Liu J, Murphy A, et al: Endocrine responses to long-term administration of the antiprogesterone RU486 in patients with pelvic endometriosis. Fertil Steril 56:402-407, 1991

3. Horwitz K: The molecular biology of RU486. Is there a role for antiprogestins in the treatment of breast cancer? Endocr Rev 13:789-794, 1992

4. Grunberg S, Weiss M, Spitz I, et al: Long-term treatment with the oral antiprogestational agent mifepristone (RU486), in Salmon SE (ed): Adjuvant Therapy of Cancer VII. Philadelphia, PA, Lippincott, 1993, pp 55-62

5. Nieman L, Chrousos G, Kellner C, et al: Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU486. J Clin Endocrinol Metab 61:536-540, 1985

6. Chrousos G, Laue L, Nieman L, et al: Clinical applications of RU486, a prototype glucocorticoid and progestin antagonist, in Mantero F, Takeda R, Scoggins B, et al (eds): The Adrenal and Hypertension: From Cloning to Clinic, vol 57. New York, NY, Raven, 1989, pp 273-284

7. Ulmann A, Silvestre L, Chemama L, et al: Medical termination of early pregnancy with mifepristone (RU 486) followed by a prostaglandin analogue. Acta Obstet Gynecol Scand 71:278-283, 1992

8. Peyron R, Aubény E, Targosz V, et al: Early termination of pregnancy with mifepristone (RU 486) and orally active prostaglandin misoprostol. N Engl J Med 328:1509-1513, 1993

9. Coutzinet B, Le Starat N, Ulmann A, et al: Termination of early pregnancy by the progesterone antagonist RU486 (mifepristone). N Engl J Med 315:1565-1569, 1986

10. Birgerson L, Odlind V: The antiprogestational agent RU 486 as an abortifacient in early human pregnancy: A comparison of three dose regimens. Contraception 38:391-400, 1988

11. Bertagna X, Bertagna C, Luton J-P, et al: The new steroid analog RU 486 inhibits glucocorticoid action in man. J Clin Endocrinol Metab 59:25-28, 1984

12. Gaillard R, Riondel A, Müller A, et al: RU 486: A steroid with antiglucocorticosteroid activity that disinhibits the human pituitary-adrenal system at a specific time of day. Proc Natl Acad Sci USA 81:3879-3882, 1984

13. Shoupe D, Mishell D, Lähteenmäki P, et al: Effects of the antiprogesterone RU486 in normal women. I. Single-dose administration in the midluteal phase. Am J Obstet Gynecol 157:1415-1420, 1987

14. Lamberts S, Koper J, de Jong F: The endocrine effects of long-term treatment with mifepristone (RU 486). J Clin Endocrinol Metab 73:187-191, 1991

15. Grunberg S, Weiss M, Spitz I, et al: Treatment of unresectable meningiomas with the antiprogesterone agent mifepristone. J Neurosurg 74:861-866, 1991

16. Grunberg S: Role of antiprogestational therapy for meningiomas. Hum Reprod 9:202-207, 1994 (suppl)

17. Deraedt R, Bonnat C, Busigny M, et al: Pharmacokinetics of RU 486, in Baulieu EE, Segal S (eds): The Antiprogestin Steroid RU 486 and Human Fertility Control. New York, NY, Plenum, 1985, pp 103-122

18. Heikinheimo O, Tevilin M, Shoupe D: Quantitation of RU486 in human plasma by HPLC and RIA after column chromatography. Contraception 34:613-624, 1986

19. Spitz I, Heikinheimo O, Wade C: The divergent effects of RU486 on adrenal function in the dog is related to differences in its pharmacokinetics. Acta Endocrinol (Copenh) 128:459-465, 1993

20. Gharib H, Hodgson S, Gastineau C, et al: Reversible hypothyroidism in Addison's disease. Lancet 7:734-736, 1972

21. Re R, Kourides I, Ridgway E: The effect of glucocorticoid administration on human pituitary secretion of thyrotropin and prolactin. J Clin Endocrinol Metab 43:338-346, 1976

22. Visser T, Lamberts S: Regulation of TSH secretion and thyroid function in Cushing's disease. Acta Endocrinol (Copenh) 96:480-483, 1981

23. Bartalena L, Martino E, Petrini L, et al: The nocturnal serum thyrotropin surge is abolished in patients with adrenocorticotropin (ACTH)-dependent or ACTH-independent Cushing's syndrome. J Clin Endocrinol Metab 72:1195-1199, 1991

24. Samuels M, Luther M, Henry P, et al: Effects of hydrocortisone on pulsatile pituitary glycoprotein secretion. J Clin Endocrinol Metab 78:211-215, 1994

25. Chopra I, Williams D, Orgiazzi J, et al: Opposite effects of dexamethasone on serum concentrations of 3,3′,5′-triiodothyronine (reverse T3) and 3,3′,5-triiodothyronine (T3). J Clin Endocrinol Metab 41:911-920, 1975

26. Burr WA, Ramsdén DB, Griffiths RS, et al: Effect of a single dose of dexamethasone on serum concentrations of thyroid hormones. Lancet 10:58-61, 1976

27. Menjo M, Murata Y, Fujii T, et al: Effects of thyroid and glucocorticoid hormones on the levels of messenger ribonucleic acid for iodothyronine type I 5′-deiodinase in rat primary hepatocyte cultures grown as spheroids. Endocrinology 133:2984-2990, 1993

28. Takiyama Y, Tanaka H, Takiyama Y, et al: The effects of hydrocortisone and RU486 (mifepristone) on iodine uptake in porcine thyroid cells in primary culture. Endocrinology 135:1972-1979, 1994

29. Kaihola H-L, Irjala K, Viikari J, et al: Determination of thyrotropin in serum by time-resolved fluoroimmunoassay evaluated. Clin Chem 31:1706-1709, 1985

30. Jaakkola T, Ding Y-Q, Kellokumpu-Lehtinen P, et al: The ratios of serum bioactive/immunoreactive luteinizing hormone and follicle-stimulating hormone in various clinical conditions with increased and decreased gonadotropin secretion: Reevaluation by a highly sensitive immunometric assay. J Clin Endocrinol Metab 70:1496-1505, 1990

31. Bertagna X, Escourelle H, Pinquier JL, et al: Administration of RU486 for 8 days in normal volunteers: Antiglucocorticoid effect with no evidence of peripheral cortisol deprivation. J Clin Endocrinol Metab 78:375-380, 1994

32. Pesonen U, Koulu M, Heikinheimo O, et al: The glucocorticoid antagonist mifepristone reveals abnormal regulation of the adrenocortical system in obese Zucker rats. J Endocrinol 132:425-431, 1992

33. Heikinheimo O, Pesonen U, Huupponen R, et al: Hepatic metabolism and distribution of mifepristone and its metabolites in rats. Hum Reprod 9:40-46, 1994 (suppl)

34. Heikinheimo O: Pharmacokinetics of the antiprogesterone RU486 in women during multiple dose administration. J Steroid Biochem 32:21-25, 1989

35. Heikinheimo O, Lähteenmäki P, Koivunen E, et al: Metabolism and serum binding of RU 486 in women after various single doses. Hum Reprod 2:379-385, 1987