Acute Effects of Mazindol on the Secretion of ACTH, 
β-Lipotropin, β-Endorphin and Cortisol in Man

KENSAKU SEKIYA, TAIICHIRO OKAJIMA, KEN-ICH KATO, 
AND HIROSHI IBAYASHI

Third Department of Internal Medicine, Faculty of Medicine, 
Kyushu University, Fukuoka 812

Abstract

The effects of mazindol, an anorexiant, on the secretion of anterior pituitary 
and adrenocortical hormones were examined in healthy male volunteers and in 
patients with Addison’s disease. In healthy male volunteers, significant eleva-
tions in plasma ACTH, β-endorphin, β-lipotropin and growth hormone were 
induced by mazindol administration, though no changes were observed in 
plasma thyrotropin, luteinizing hormone, follicle-stimulating hormone or pro-
lactin. Plasma ACTH increased in patients with Addison’s disease, too. In 
addition, plasma cortisol increased, without a change in the plasma aldosterone 
levels after mazindol administration to normal subjects.

Mazindol is a new non-phenylethylamine 
anorexiant (Barcza and Houlihan, 1975) 
and has similar pharmacological profiles to 
amphetamine, but it does not induce addic-
tion (Carruba et al., 1976). Mazindol is 
known to inhibit the reuptake of norepine-
phrine at the cathecholaminergic terminals 
and to have a dopaminergic effect (Zam-
botti et al., 1976). Mazindol also acceler-
ates the uptake of glucose and increases 
oxygen consumption in fatty tissues (Roth-
well et al., 1981). In the present study, we 
investigated the acute effects of mazindol 
on the secretion of anterior pituitary and 
adrenocortical hormones in healthy male 
volunteers and in patients with Addison’s 
disease.

Received January 31, 1984

A preliminary report of this paper was presented 
at the 56th congress of the Japan Endocrine 
Society, Kyoto Japan (Ikuyama et al., November 
1983)

Materials and Methods

Thirteen healthy young males ranging in age 
from 19 to 32 years (average: 24 years) were 
examined. They were divided into two groups: 
1) mazindol group [body weight: 62.3 ± 4.5 kg 
(mean ± SD), n=9], and 2) placebo group [body 
weight: 63.1 ± 5.2 kg (mean ± SD), n=4]. Two 
patients with Addison’s disease (54 and 61 year 
old males) were also examined. Informed con-
sent was obtained from each subject and patient 
in every experiment.

After overnight fasting, they were kept at rest 
in bed for blood sampling. A heparinized can-
ula was inserted in the vein of the forearm 
close to the elbow. After blood sampling at −30 
min and at 0 min, mazindol 1.5 mg (3 tablets of 
0.5 mg) or 3 placebo tablets were orally admini-
stered with a small amount of water. Blood 
samples were then taken at 30, 60, 90, 120, 150 and 
180 min into cooled siliconized glass tubes con-
taining EDTA-2Na (1 mg/ml blood) and were 
immediately centrifuged at 4°C to obtain plasma 
samples. These samples were stored at −20°C 
until assayed.
Plasma GH, TSH, LH, FSH, PRL, ACTH, cortisol and aldosterone were assayed using commercially available radioimmunoassay (RIA) kits: Eiken Immunochemical Lab. RIA kits (Tokyo, Japan) for GH, TSH, LH and FSH; Daiichi Radioisotope Lab. Ltd. RIA kits (Tokyo, Japan) for cortisol; CIS RIA kits (Atomic Energy Lab. of Biomedical Products, Gif-sur-Yvette, France) for ACTH and aldosterone. Plasma \( \beta \)-endorphin (\( \beta \)-Ep) was extracted using acetone hydrochloride after being absorbed with silica gel (100 mg/ml plasma), and was assayed by RIA using a specific antiserum (Special Reference Lab., Tokyo, Japan) which did not show cross reactivity with \( \beta \)-lipotropin (\( \beta \)-LPH). Plasma \( \beta \)-LPH was directly assayed using a specific antiserum (National Institute of Arthritis, Metabolism and Digestive Diseases, USA) which has no cross reaction with \( \beta \)-Ep but a 100% cross reaction with \( \gamma \)-lipotropin.

The results obtained were expressed as mean ± SE. The data were analyzed previously using F-test and statistically using Student’s t-test.

**Results**

Oral administration of mazindol to healthy male volunteers caused a significant increase in plasma ACTH (36.1 pg/ml → 65.2 pg/ml), \( \beta \)-LPH (110 pg/ml → 286 pg/ml), \( \beta \)-Ep (6 pg/ml → 19.2 pg/ml) at 120 min. (Table 1, Fig. 1) and GH (1.13 ng/ml → 3.37 ng/ml) at 120 min. (Table 1, Fig. 2), while it did not exert any influence on plasma levels of PRL, TSH, LH and FSH (Table 1). Plasma cortisol also showed a significant rise (9.5 µg/dl → 22.2 µg/dl) at 150 min. (Table 1, Fig. 3) after mazindol administration to the healthy subjects, but no significant change in plasma aldosterone level was observed (Table 1).

Plasma ACTH was increased in the two patients with Addison’s disease by mazindol administration (case 1: 470 pg/ml → 860 pg/ml, case 2: 980 pg/ml → 1,670 pg/ml), and also plasma \( \beta \)-LPH was increased in case 1 (4,700 pg/ml → 10,000 pg/ml).

There were no significant changes in systolic or diastolic blood pressure in the

---

**Table 1. Plasma hormone levels after oral administration of mazindol 1.5 mg in normal healthy volunteers.**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0'</th>
<th>15'</th>
<th>30'</th>
<th>60'</th>
<th>90'</th>
<th>120'</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH (ng/ml)</td>
<td>1.01±0.03</td>
<td>1.98±0.6</td>
<td>3.37±0.9*</td>
<td>3.06±0.9*</td>
<td>2.43±0.5*</td>
<td>2.34±0.5*</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>1.13±0.12</td>
<td>1.31±0.31</td>
<td>1.31±0.31</td>
<td>1.31±0.31</td>
<td>1.31±0.31</td>
<td>1.31±0.31</td>
</tr>
<tr>
<td>TSH (mIU/ml)</td>
<td>6.8±1.3</td>
<td>6.7±1.3</td>
<td>6.6±1.3</td>
<td>6.5±1.3</td>
<td>6.4±1.3</td>
<td>6.3±1.3</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>2.7±0.5</td>
<td>2.7±0.5</td>
<td>2.7±0.5</td>
<td>2.7±0.5</td>
<td>2.7±0.5</td>
<td>2.7±0.5</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>5.1±0.15</td>
<td>5.1±0.15</td>
<td>5.1±0.15</td>
<td>5.1±0.15</td>
<td>5.1±0.15</td>
<td>5.1±0.15</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>81±1.5</td>
<td>81±1.5</td>
<td>81±1.5</td>
<td>81±1.5</td>
<td>81±1.5</td>
<td>81±1.5</td>
</tr>
<tr>
<td>( \beta )-LPH (pg/ml)</td>
<td>27.7±0.8</td>
<td>27.7±0.8</td>
<td>27.7±0.8</td>
<td>27.7±0.8</td>
<td>27.7±0.8</td>
<td>27.7±0.8</td>
</tr>
<tr>
<td>( \gamma )-LPH (pg/ml)</td>
<td>10.8±3.6</td>
<td>10.8±3.6</td>
<td>10.8±3.6</td>
<td>10.8±3.6</td>
<td>10.8±3.6</td>
<td>10.8±3.6</td>
</tr>
</tbody>
</table>

Statistically significant differences in % increase vs. basal levels are shown with asterisks (*) (P<0.05).
Fig. 1. Plasma ACTH, \( \beta \)-LPH and \( \beta \)-Ep levels following oral administration of mazindol 1.5 mg (mean \( \pm \) SE, n=9) in normal healthy volunteers. Statistically significant differences in % increase vs. basal levels are shown with by asterisks (\( \star \) P<0.05).
Fig. 2. Plasma GH levels following oral administration of mazindol 1.5 mg (mean ± SE, n=9) in normal healthy volunteers. Statistically significant differences in % increase vs. basal levels are shown with asterisks (★ P<0.05).

Fig. 3. Plasma cortisol levels following oral administration of mazindol 1.5 mg (mean ± SE, n=9) in normal healthy volunteers. Statistically significant differences in % increase vs. basal levels are shown with asterisks (★ P<0.05).
Discussion

In the present study, we investigated the effects of mazindol, an anorexiant, on the plasma concentrations of the anterior pituitary and adrenocortical hormones, and found that this drug increases plasma ACTH, \( \beta \)-LPH and \( \beta \)-Ep levels in healthy volunteers and plasma ACTH and \( \beta \)-LPH levels in patients with Addison's disease. The increase in plasma ACTH might produce a rise in the plasma cortisol level but did not increase plasma aldosterone. Because this drug acts dopaminergically on the nerve terminals, its dopaminergic mechanism might suppress aldosterone release by ACTH (Brown et al., 1982). Plasma GH showed a rise after mazindol administration, but there was no significant change in the plasma PRL, TSH, LH or FSH level observed in healthy volunteers.

Mazindol was smoothly absorbed by the digestive organs, and its blood levels rose one hour (rhesus monkey) or two hours (rabbit and man) after per os administration as a peak (Sandz Ltd. 1973). On the other hand, all peaks of ACTH, \( \beta \)-LPH, \( \beta \)-Ep and GH occurred two hours after per os administration of mazindol. The increase in the amount of these hormones was therefore thought to be due to the effect of the increase in the amount of mazindol in the blood. Mazindol acts at the nerve terminals and inhibits reuptake of norepinephrine and dopamine at the nerve terminals (Powers, 1980). Concerning the involvement of an adrenergic mechanism in the ACTH secretion, Besser, et al. (1969) reported that amphetamine, an adrenergic agonist increased the plasma ACTH concentration. Giguere, et al. (1981) reported that \( \alpha \)-adrenergic agents such as epinephrine and norepinephrine directly stimulated ACTH secretion in cultured rat pituitary cells in vitro. Beny, et al. (1981) claimed that \( \alpha \)-adrenergic mechanism exerts a modulating effect on the secretion of corticotropin-releasing factor (CRF) in the hypothalamus. Therefore, the stimulatory effect of mazindol on ACTH, \( \beta \)-LPH and \( \beta \)-Ep secretion may also be mediated by its \( \alpha \)-adrenergic mechanism.

Since adrenergic stimulating agents such as methoxamine, phenylephrine, are known to exert a stimulatory effect on the secretion of GH in man (Imura et al., 1971), mazindol produces a rise in the plasma GH level probably due to an \( \alpha \)-adrenergic effect of mazindol. Mazindol is also reported to have a dopaminergic activity (Zambotti et al., 1976) in the CNS, which may also stimulate plasma GH secretion (Boyd et al., 1970). Although the dopaminergic mechanism is known to strongly inhibit PRL secretion (Leblanc et al., 1976), this drug did not cause any significant decrease in the plasma PRL level. This may explain why this drug acts dopaminergically only in the nerve terminals but does not increase dopamine in the pituitary portal blood.

Acknowledgements

We wish to express our thanks to Sandoz Ltd. (Basle, Switzerland) for providing mazindol, and to Miss Yosue, Miss Kamioka and Miss Mori for their secretarial help. This study was partially supported by a research grant from the Intractable Diseases Division, Public Health Bureau, Ministry of Health and Welfare, Japan.

References

Beny, J. L. and A. J. Baertschi (1981). Corticotropin-releasing factors (CRF) secreted by the rat median eminence in vitro in the presence or absence of ascorbic acid: Quantitative role of vasopressin and catecholamines. *Endo-


