Adrenocorticotropic Hormone-Dependent Cushing’s Syndrome

Use of an octreotide trial to distinguish between pituitary or ectopic sources

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ABSTRACT: Objectives: Adrenocorticotropic hormone (ACTH) overproduction is usually due to a pituitary tumour which is often not visible on magnetic resonance imaging (MRI). However, ACTH overproduction may be due to an ectopic source. This study aimed to develop a simple non-invasive technique to differentiate these sources. Methods: This study took place in King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, and Sultan Qaboos University Hospital, Muscat, Oman, between 1988 and 2012. Serum cortisol levels were measured in nine patients with ACTH-dependent Cushing’s syndrome before and during a 72-hour trial of octreotide. All patients underwent computed tomography (CT) scans. MRI scans were performed on six patients. Results: CT scans were abnormal in three patients with ectopic ACTH production. MRI scans showed that three patients had pituitary microadenomas. Serum cortisol levels returned to normal in those with confirmed ectopic ACTH production. No response was found in the other six patients. Conclusion: A 72-hour trial of octreotide is recommended for patients with ACTH-dependent Cushing’s syndrome and a normal pituitary MRI. This trial will be a useful alternative to petrosal sinus sampling.

Keywords: Adrenocorticotrophic Hormone; Cushing’s Syndrome; Somatostatin Receptors; Investigational Therapies; Octreotide; Saudi Arabia; Oman.

The most common cause of adrenocorticotropic hormone (ACTH)-dependent Cushing’s syndrome is a pituitary adenoma (90%).1 When this cause is identified, the condition is also known as Cushing’s disease. Other cases of ACTH-dependent Cushing’s syndrome are due to ectopic ACTH secretion, generally by bronchial or pancreatic neuroendocrine tumours (NETs) or, rarely, tumours that secrete corticotropin-releasing hormone (CRH).2 However, in 40% of patients with Cushing’s disease, magnetic resonance imaging (MRI) shows a normal pituitary gland.3 These patients must be distinguished from those with ectopic ACTH production. The gold-standard practice for differentiating pituitary from ectopic ACTH overproduction is performing inferior petrosal sinus sampling (IPSS) with serial ACTH measurements after the intravenous administration of CRH. This procedure

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necessitates the cannulation of both jugular veins and
is therefore invasive and costly. As a result, the Sultan
Qaboos University Hospital (SQUH), a tertiary centre
in Muscat, Oman, relies on indirect testing to confirm
or refute the pituitary source. As most NETs express
somatostatin receptors type 2 and 3, they are therefore
amenable to treatment with octreotide which lowers
ACTH and cortisol levels. Patients with Cushing’s
disease do not respond to octreotide due to the
lack of expression or downregulation of somatostatin
receptors. Furthermore, patients with NETs secrete
chromogranin A (Cg-A) as well; it has therefore been
theorised that the measurement of Cg-A levels may
prove to be of additional diagnostic value. In light of
these factors, and because IPSS is not available in all
centres, the objective of this study was to test the use
of a 72-hour trial of octreotide to distinguish between
pituitary and ectopic ACTH overproduction.

Methods
This study took place in King Faisal Specialist Hospital
& Research Centre, Riyadh, Saudi Arabia, and SQUH
between 1988 and 2012. Nine patients with ACTH-
dependent Cushing’s syndrome confirmed by elevated
fasting serum cortisol and ACTH levels were included
in the study. Four of these patients have previously been
reported in the literature. Computed tomography
(CT) scans of the neck, chest and abdomen were
carried out on all patients. In addition, six patients
underwent MRI scans and two had their Cg-A levels
measured on admission after fasting. Each patient
undertook a 72-hour therapeutic trial of octreotide,
with a dose of 100 mcg administered every eight
hours. Serial cortisol measurements were taken at the
beginning of the trial (8 am) and then subsequently
24, 48 and 72 hours after the trial had begun. Some
patients had basal samples taken 48 and 24 hours before the trial began.

Subjects whose serum cortisol levels were
unchanged throughout the study period were
determined not to have responded to the octreotide
trial, while patients whose serum cortisol levels
decreased to within a normal range were determined
to have responded to the treatment. All patients
and their families gave consent for their inclusion in
the study.

Results
A total of nine patients with ACTH-dependent
Cushing’s syndrome were identified during the study
period. Serum cortisol levels were unchanged in six
patients but fell progressively to normal levels in the
remaining three patients [Figure 1]. The six subjects
who did not respond to the octreotide trial had
normal CT results of the neck, chest and abdomen.
In comparison, the patients who responded to the
treatment had abnormal CT scans of the lung and
pancreas. Cg-A levels were normal in the two patients
who did not respond. Of the six patients who did
not respond to the octreotide, MRI scans revealed
pituitary microadenomas in three, while the other
three patients had normal MRI results.

Among the three subjects who responded to
octreotide, NETs were identified as the source of
the ACTH overproduction. Before the trial started,
one of the three patients was documented to have a
benign bronchial carcinoid tumour while the other
two were identified as having metastatic pancreatic
NETs producing ACTH both radiologically and
histologically. The first patient had no need for
further treatment following the removal of the benign
bronchial carcinoid tumour. The other two patients
died within a year of diagnosis.

For the six patients who did not respond to
octreotide, pituitary adenomas (Cushing’s disease)
were identified as the source of the ACTH over-
production. Of these, five underwent transsphenoidal
surgeries (TSS) [Table 1]. Two patients were cured after
their surgeries, while another two relapsed initially but
at the time of writing were both in complete remission
and receiving cabergoline treatment. One patient
relapsed and received external radiotherapy; after this,
the patient went abroad and was lost to follow up. At
the time of writing, the final patient was in complete
remission and was receiving cabergoline therapy
without any other interventions.

![Figure 1: Serum cortisol levels in nine patients with adrenocorticotropic hormone-dependent Cushing's syndrome before and during a trial of octreotide. Only three patients, all of whom were found to have neuroendocrine tumours, responded to treatment. Grey bar = normal cortisol levels.](image-url)
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Discussion

ACTH-dependent Cushing's syndrome is rare and usually caused by a pituitary adenoma; however, 10% of cases are ectopic.1,2 If the source of the ACTH overproduction is not readily apparent, centres with the necessary resources can carry out IPSS with ACTH measurements. This procedure will distinguish pituitary from ectopic sources and help localise the site of the tumour within the pituitary gland. However, as IPSS is not yet available in all centres, it is important to develop alternative approaches. One such approach consists of a short trial of octreotide, which has been assessed and reported previously.5 As shown in the current study, only three patients with ACTH-dependent Cushing's syndrome were found to have decreased cortisol levels and therefore to have responded to the octreotide treatment; these patients were subsequently found to have NETs. In comparison, there was no response in the remaining six patients who were diagnosed with Cushing's disease.

Somatostatin receptors are expressed in normal pituitary ACTH-producing cells; however, it has been found that the expression of somatostatin receptors 2 and 3 is downregulated by elevated glucocorticoid levels.8 This explains why octreotide is not therapeutically useful in Cushing's disease. A study by de Herder et al. using somatostatin receptor imaging further supports the results of the present study, as octreotide scanning was negative in eight patients with ACTH-secreting pituitary adenomas whereas uptake was positive in all 10 of their patients identified with NETs producing ectopic ACTH.9

Most NETs co-secrete Cg-A with hormones;10 thus, the measurement of circulating Cg-A levels was recently added to the octreotide trial procedure reported in the current study. This measurement was included as a further diagnostic tool to distinguish pituitary from ectopic disease. This combination is currently carried out routinely in SQUH.

In another recent study conducted in Oman, high-dose cabergoline was used successfully to treat four patients with Cushing's disease.11 Although one of the patients refused surgery, they were treated with cabergoline monotherapy; the dosage was reduced from 1 mg/day to 1 mg twice weekly and the patient has remained in complete remission for almost three years since the time of writing.11 As a result of these observations, the current practice at SQUH is to offer a short-term trial of cabergoline to patients with ACTH-dependent Cushing's syndrome who do not respond to octreotide and have normal pituitary MRIs. If the patient responds, they may be offered long-term cabergoline treatment or a laparoscopic adrenalectomy. Should the patient subsequently develop Nelson's syndrome, a TSS may then be carried out.12

Conclusion

The results of this study indicate that a 72-hour trial of octreotide is advisable for all patients with ACTH-dependent Cushing's syndrome and normal MRI results. This procedure has been shown to be a safe and simple method that will effectively distinguish between pituitary and ectopic ACTH overproduction. In addition, it is a useful alternative to IPSS in centres where this procedure is not available.

Table 1: Fasting serum cortisol and ACTH levels and imaging results in nine patients with ACTH-induced Cushing's syndrome at presentation and subsequently identified source of ACTH overproduction

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cortisol levels in nmol/L*</th>
<th>ACTH levels in pmol/L**</th>
<th>CT/MRI</th>
<th>TSS</th>
<th>Source</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>675</td>
<td>25</td>
<td>-</td>
<td>-</td>
<td>Ectopic (lung carcinoid)</td>
</tr>
<tr>
<td>2</td>
<td>826</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>Ectopic (pancreatic carcinoid)</td>
</tr>
<tr>
<td>3</td>
<td>856</td>
<td>27</td>
<td>-</td>
<td>-</td>
<td>Ectopic (pancreatic carcinoid)</td>
</tr>
<tr>
<td>4</td>
<td>612</td>
<td>13</td>
<td>Normal</td>
<td>Performed</td>
<td>Pituitary</td>
</tr>
<tr>
<td>5</td>
<td>812</td>
<td>4</td>
<td>Normal</td>
<td>Performed</td>
<td>Pituitary</td>
</tr>
<tr>
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<td>14</td>
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<td>Not performed</td>
<td>Pituitary</td>
</tr>
<tr>
<td>7</td>
<td>923</td>
<td>24</td>
<td>Microadenoma</td>
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</tr>
<tr>
<td>8</td>
<td>700</td>
<td>16</td>
<td>Microadenoma</td>
<td>Performed</td>
<td>Pituitary</td>
</tr>
<tr>
<td>9</td>
<td>1,100</td>
<td>6</td>
<td>Microadenoma</td>
<td>Performed</td>
<td>Pituitary</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotropic hormone; Cg-A = chromogranin A; CT = computed tomography; MRI = magnetic resonance imaging; TSS = transsphenoidal surgery. *Normal range: 184–580 nmol/L; **Normal range: 1.6–13.9 pmol/L.
References


