Pharmacological Management of Cushing’s Syndrome: An Update

ABSTRACT

The treatment of choice for Cushing’s syndrome remains surgical. The role for medical therapy is twofold. Firstly it is used to control hypercortisolaemia prior to surgery to optimize patient’s preoperative state and secondly, it is used where surgery has failed and radiotherapy has not taken effect. The main drugs used inhibit steroidogenesis and include metyrapone, ketoconazole, and mitotane. Drugs targeting the hypothalamic-pituitary axis have been investigated but their roles in clinical practice remain limited although PPAR-γ agonist and somatostatin analogue som-230 (pasireotide) need further investigation. The only drug acting at the periphery targeting the glucocorticoid receptor remains Mifepristone (RU486). The management of Cushing syndrome may well involve combination therapy acting at different pathways of hypercortisolaemia but monitoring of therapy will remain a challenge. (Arq Bras Endocrinol Metab 2007;51/8:1339-1348)

Keywords: Cushing’s syndrome; Drug therapy; Steroidogenesis inhibitor; Hypothalamic-pituitary modulator

RESUMO


Descritores: Síndrome de Cushing; Terapia médica; Inibidores da esteroidogênese; Moduladores hipotalâmico-hipofisários
CUSHING’S IS A RARE DISEASE and therefore of minimal interest to the pharmaceutical industry and hence for many years there were few developments. However in recent times there has been renewed interest in whether agents marketed for other conditions may have a role to play in the medical management of Cushing’s syndrome. This review will endeavour to assess the place of the ‘new’ agents alongside the longer established agents.

The definitive management for Cushing’s syndrome is surgical excision of the underlying cause of the hypercortisolaemia, with the exception of ACTH-independent bilateral macronodular hyperplasia where pharmacological treatment directed against the aberrant receptor can be effective (1). However, in many patients with Cushing’s syndrome there is a role for medical therapy in certain specific circumstances. It is common practice to prepare patients for surgery by lowering circulating cortisol levels to reverse the metabolic consequence of cortisol excess and by implication reduce the complications of surgery. This clearly depends on the interval to surgery and disease severity. As any clinician dealing with Cushing’s syndrome is aware establishing the precise aetiology is a challenge and it is not always possible to make a definitive diagnosis at first investigation, and in such cases medical therapy can be used as a stop gap to control signs and symptoms and thereby allow time for re-investigation. In patients not cured by surgery or in patients with metastatic disease medical therapy can be used to control manifestations of the disease. Pituitary radiotherapy is extremely effective at controlling hypercortisolaemia but can take several years to have its full effect and medical therapy is often required in the interim (see figure 1).

Medical therapy can be separated into agents that inhibit adrenal steroidogenesis and those that modulate pituitary ACTH release. Currently in clinical practice, the most effective, reliable and widely use agents are those that inhibit steroidogenesis.

A major challenge of medical therapy is the monitoring of its effectiveness. Urinary free cortisol (UFC) measurement is widely used but has several major limitations and is intrinsically a poor solution to the problem of disease monitoring. Only a small proportion of cortisol is excreted unaltered in urine and UFC immunoassays to varying extent detect biologically inactive cortisol metabolites, which may be raised in patients treated with agents such as metyrapone. UFC has the additional disadvantages of relying on complete collection and of being unable to detect over-treatment induced hypoadrenalism.

Although more labour intensive, measurement of serum cortisol is a more appropriate means of assessing disease activity. The best validated technique is calculation of a mean serum cortisol from multiple measurements taken during a single day. Studies comparing isotopically calculated cortisol production rates

**Figure 1.** Mean plasma ACTH levels (a) and serum cortisol levels (b) during short-term metyrapone therapy in 53 patients with Cushing’s syndrome. The bars represent the median values. ACTH ng/L x 0.225 = pmol/l. [Courtesy of Verhelst JA, Trainer PJ, Howlett TA, et al. Short- and long-term responses to metyrapone in the medical management of 91 patients with Cushing’s syndrome. Clin Endocrinology (Oxf) 1991;35:169-78]
to serum levels indicate that a mean serum cortisol in the range 150–300 nmol/l equates to a normal cortisol production rate, and this should be the target of medical therapy (2).

The cyclical nature of Cushing’s syndrome in some patients means that even after disease control has been achieved regular treatment monitoring is required.

**STERIOIDOGENESIS INHIBITION**

These agents are the most consistently effective means of controlling cortisol secretion.

**Metyrapone**

In the era before it was possible to measure plasma ACTH, the metyrapone test was used to investigate suspected Cushing’s syndrome and hypoadrenalism but its use now is exclusively therapeutic (3,4). It acts primarily on the final step in cortisol synthesis namely the conversion of 11-deoxycortisol to cortisol and therefore results in a dramatic increase in circulating 11-deoxycortisol levels, which can cross-react in serum and urine cortisol immunoassays. This cross-reactivity may result in spuriously elevated cortisol levels and a failure to appreciate that a patient is over-treated and hypoadrenal.

Metyrapone is the most potent, short-acting inhibitor of cortisol synthesis with a rapid onset of action. Serum cortisol levels fall within four hours of an initial dose and care is required to avoid over-treatment. The routine starting dose is 250 mg three times per day with reassessment of cortisol levels 72 hours later and dose titration as appropriate until a mean cortisol level of between 150 and 300 nmol/l is achieved. In patients with severe hypercortisolaemia up to 8 gm per day in 3–4 divided doses may be necessary. Most patients tolerate the drug without difficulty as long as hypoadrenalism is avoided. Nausea, anorexia and abdominal pain can occur but usually this is a sign of over-treatment. The major limitation of metyrapone is as women as the accumulation of cortisol precursors results in elevated androgens, which frequently is manifest as hirsutism and acne. Although mineralocorticoid precursors levels are elevated, hypokalaemia, hypertension and oedema are not problems, presumably because of the benefits of lower circulating cortisol levels (5,6). In patients with pituitary-dependent Cushing’s disease, ACTH levels rise but there is no evidence that this results in tachyphylaxis (5,7).

**Ketoconazole**

Ketoconazole is an imidazole derivative developed as an oral antifungal agent that inhibits cholesterol, sex steroid and cortisol synthesis by acting on the 11β-hydroxylase and C17-20 lyase enzymes (8-11). It is the most frequently used agent in the treatment of Cushing’s syndrome with the starting dose being 200 mg twice daily increasing as necessary to 1200 mg/day in four divided doses (12,13). In contrast to metyrapone it can take several weeks to see the full benefit of a dose adjustment and there is less risk of over-treatment and hypoadrenalism. With time it is effective at controlling the symptoms of Cushing’s syndrome and in women its antiandrogenic properties are a virtue but in men, gynaecomastia and reduced libido have been reported. The most common side effects are gastrointestinal upset and skin rashes but liver enzyme dysfunction can occur in up to 10% of cases, which rarely has proceeded to acute liver failure and fatality (14-17). Ketoconazole has the added benefit of reducing the total cholesterol and LDL cholesterol (18).

Metyrapone and ketoconazole can be very successfully co-administered as the former controls cortisol secretion while waiting for the slower onset of action of the latter agent, which in turn lowers androgens and thus negates one of the major limitations of the former.

**Mitotane**

Mitotane reduces cortisol production by blocking cholesterol side-chain cleavage and 11β-hydroxylase (19-21). It was introduced in 1960 for the treatment of adrenal carcinoma and subsequently used for the treatment of benign causes of Cushing’s syndrome. The onset of mitotane action is slow with sustained action maintained after discontinuation in up to a third of patients (22). When used to control serum cortisol levels in benign disease, mitotane is initiated at a dose of 0.5–1 gm per day which is increased gradually by 0.5–1 gm every few weeks to minimise side effects. Adverse effects such as nausea, anorexia and diarrhoea are common with doses of 2 gm per day and almost universal at doses greater than 4 gm per day (23). Adrenal insufficiency and neurological side effects including abnormal gait, dizziness, vertigo, confusion and problem of language expression are often seen at higher dose (22). Abnormal liver enzymes, hypercholesterolaemia, skin rash, hyponatraemia, gynaecomastia in male and prolonged bleeding time are also well recognized (24,25). Changes in hormone binding globulins may result in total hor-
mone measurement being unreliable during treat-
ment and thus caution is required when interpreting
serum cortisol levels (26,27). Mitotane increases
the metabolic clearance of exogenously administered
steroid and the replacement dose of steroid is
increased by about a third (28). In order to minimise
side effects mitotane dose should be gradually titrated
up, taken with meals or at bedtime with food. Changing
the schedule to once daily or alternate day may
help with gastrointestinal problems. If side effects are
severe mitotane can be stopped for a week and restarted
at a lower dose. Mitotane may induce spontaneous
abortion and is a teratogen. Its effect may persist for
a number of months after discontinuation and so a
female patient should avoid pregnancy for up to five
years after stopping the drug (29).

**Aminoglutethimide**

Aminoglutethimide, which was introduced in 1959 as
an anticonvulsant, has also been used in the treatment
of breast cancer and was noticed to induce adrenal
insufficiency. It inhibits the side-chain cleavage of cho-
lesterol to pregnenolone and therefore inhibits corti-
sol, oestrogen and aldosterone production and addi-
tionally inhibits 11β-hydroxylase, 18-hydroxylase and
aromatase activity (30,31). Initially aminoglu-
tethimide decreases cortisol production in Cushing’s
syndrome but appears to be less effective in treating
Cushing’s disease (32). The suggested mechanism
may be an increase in ACTH overcoming the enzy-
matic blockade or it may be induction of hepatic enzyme accelerating aminoglutethimide metabolism
(33,34). Adverse effects such as lethargy, dizziness,
ataxia and rashes are common on initiation and limit
its use although they do resolve with time (32,35).
There are better agents for controlling hypercortiso-
laemia and aminoglutethimide does not have a place in
the modern treatment of Cushing’s syndrome (36).

**Trilostane**

Trilostane is a competitive inhibitor of 3β-hydroxyster-
oid dehydrogenase, which is an essential enzyme in
the synthesis of cortisol, aldosterone and androstene-
dione. It is an effective inhibitor of steroid synthesis in
vitro but in man the results have been disappointing
(37). However, it is used in veterinary practice as it is
very effective in controlling pituitary-dependent Cush-
ing’s in dogs (38). The maximum daily dose is 1,440
mg and patients may experience side effects such as
abdominal discomfort, diarrhoea and paraesthesia.
Trilostane has largely fallen out of clinical use but the
very fact that it is so effective in dogs may mean it jus-
tifies reconsideration in man.

**Etomidate**

Etomidate is a parenteral anaesthetic agent which
when first introduced was associated with excessive
mortality in patients in intensive care which was ulti-
mately explained by the recognition it lowered circu-
lating cortisol levels by inhibiting 11β-hydroxylase,
17-hydroxylase, c17-20 lyase as well as cholesterol side
chain at cleavage (39-41). A number of case reports
have shown etomidate at 2.5 mg/hour to be effective
at correcting hypercortisolaemia in seriously ill patients
with ectopic ACTH production (42-44). Etomidate’s
use is limited by the need to be given intravenously
but it has a place in acutely sick patients unable to be
reated orally where rapid correction of hypercortiso-
laemia may be life saving.

**Trilostane**

Trilostane is a competitive inhibitor of 3β-hydroxyster-
oid dehydrogenase, which is an essential enzyme in
the synthesis of cortisol, aldosterone and androstene-
dione. It is an effective inhibitor of steroid synthesis in
vitro but in man the results have been disappointing
(37). However, it is used in veterinary practice as it is
very effective in controlling pituitary-dependent Cush-
ing’s in dogs (38). The maximum daily dose is 1,440
mg and patients may experience side effects such as
abdominal discomfort, diarrhoea and paraesthesia.
Trilostane has largely fallen out of clinical use but the
very fact that it is so effective in dogs may mean it jus-
tifies reconsideration in man.

**HYPOTHALAMIC-PITUITARY
NEUROMODULATORY AGENTS**

Pituitary ACTH secretion is regulated by a number of
neurotransmitters including catecholamines, sero-
tonin, acetylcholine, GABA and peptides. In Cush-

---

**Table 1. Agents inhibiting steroidogenesis in clinical use.**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metyrapone</td>
<td>750–8000 mg daily</td>
<td>Hypoadrenalism, Side effects: nausea, abdominal pain, hirsutism, acne</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>400–1200 mg daily</td>
<td>Slow onset of action, Side effects: gastro-intestinal upset, rashes, abnormal LFT, gynaeomastia &amp; reduced libido in men</td>
</tr>
<tr>
<td>Mitotane</td>
<td>500–8000 mg daily</td>
<td>Gradual dose titration, taken with meal, Side effects: gastro-intestinal upset, neurological disturbances, abnormal LFT, hypercholesterolaemia AVOID pregnancy up to five years after stopping the drug</td>
</tr>
</tbody>
</table>
Pharmacological Management of CS
Dang & Trainer

Inducing complete resolution of the pituitary adenoma twice weekly) normalised the ACTH plasma levels and bromocriptine (7.5 mg/day) but cabergoline (0.5 mg/week for six months normalised UFC in two patients although one patient later did have treatment escape (seven untreated and seven post unsuccessful transsphenoidal pituitary surgery) were treated with 8–16 mg of rosiglitazone for 1–7 months (61). In six patients, plasma ACTH, serum cortisol and 24 hours UFC were lowered but only UFC reached significance. Two of the six patients also noted clinical improvement on follow up at seven months. No clinical side effects were noted but one patient developed hypercholesterolaemia. In a study of seven patients with Nelson’s syndrome who took 8 mg of rosiglitazone for 12 weeks, no significant fall in ACTH was seen (62). Sim-

Dopamine agonists

Bromocriptine is a dopamine agonist which has been widely used in the treatment of hyperprolactinaemia and acromegaly. It is unclear if the action in lowering ACTH secretion by bromocriptine is via CRH or directly on the pituitary (45-47). A single dose of bromocriptine will cause a fall in ACTH in half of the patients with Cushing’s disease but unfortunately this effect is not maintained in the long term (47,48). There are reports that suggest with high dose bromocriptine (40 mg/day) there may be clinical improvement in up to 50% of patients but others have found response rate of only 1–2% in the long term (49,50). Potential side effects of bromocriptine include nasal congestion, nausea, postural hypotension, headaches and hallucination.

The use of cabergoline in the management of Cushing’s disease remains anecdotal. In mixed pituitary tumour secreting prolactin and ACTH with florid clinical signs of Cushing’s disease treatment with cabergoline resulted not only in the normalisation of prolactin but also clinical and biochemical resolution of the features of Cushing’s (51). It has also been used to control Cushing’s disease in failed pituitary surgery (52,53). Recently there has been renewed interest in cabergoline with the publication by Pivonello et al. of a case of lung carcinoid with Cushing’s syndrome treated with rosiglitazone 8–16 mg of rosiglitazone for 1–8 months (median 3 months), immediately after failed surgery treated with 4–16 mg of rosiglitazone for 1–8 months (median 3 months), there was no consistent reduction in urinary free cortisol levels (58). These observations caused great interest but are yet to impact on clinical practice.

In a study of two patients with pituitary-dependent Cushing’s syndrome treated with rosiglitazone 8 mg daily for 33 and 20 days (the second patient was also taking metyrapone 1 gm/day), 24 hours UFC fell in both patients although only in the patient co-treated with metyrapone did it reach statistical significance (59). In a second study of ten patients, four prior to surgery, four following relapse after surgery and two immediately after failed surgery treated with 4–16 mg of rosiglitazone for 1–8 months (median 3 months), in mice with already established corticotroph tumours, rosiglitazone treatment decreased tumour volume in 75% of cases and prevented signs of hypercortisolism in all cases, with 75% reduction in ACTH level and 96% reduction in cortisol levels (58). These observations caused great interest but are yet to impact on clinical practice.

In 2002, the nuclear hormone receptor, peroxisome proliferator-activated receptor-γ (PPAR-γ) was identified in ACTH-secreting pituitary tumour (58). In an in vivo experiment, innoculating mice with corticotroph AtT20 tumour cells, treating with extremely high dose of rosiglitazone (150 mg/kg/day) prevented the development of tumours. In mice with already established corticotroph tumours, rosiglitazone treatment decreased tumour volume in 75% of cases and prevented signs of hypercortisolism in all cases, with 75% reduction in ACTH level and 96% reduction in cortisol levels (58). These observations caused great interest but are yet to impact on clinical practice.
Pharmacological Management of CS
Dang & Trainer

Similarly in another study of six patients with Nelson’s syndrome given rosiglitazone 12 mg per day for 14 weeks, there was no fall in ACTH levels (63).

Although most studies used rosiglitazone in treating Cushing’s disease, pioglitazone has also been tried. In a study of five patients with Cushing’s disease treated with pioglitazone 45 mg for 30 days, no alteration in 24 hours UFC, or ACTH and cortisol responses to CRH administration was seen (64).

Currently the success of PPAR agonists in treating Cushing’s disease remains disappointing, failing to reproduce the success seen in the in vitro and mouse model. However with the small number of patients and short duration of treatment, further studies are still needed. The discrepancy between the in vitro and human experience may reflect the differences in the order of magnitude in the dose of rosiglitazone.

Somatostatin analogues

Octreotide, an analogue of somatostatin, has been used extensively to treat neuroendocrine tumours and acromegaly. In the 1990s five subtypes of somatostatin receptors were identified with expression of somatostatin receptor subtypes in mammalian corticotrophs being variable (65).

In one study all five subtype somatostatin receptors were co-localised in rat pituitary cells expressing ACTH (66). Yet in another study only 38% of corticotrophs expressed somatostatin receptor subtype 5 (sst5) and 3% expresses somatostatin receptor subtype 2 (sst2) (67). In contrast Smith et al. found a predominance of sst2 rather than sst5 (68). It is generally accepted that sst2 and sst5 are involved in the regulation of growth hormone, prolactin and TSH (69).

In vitro studies suggested that normal corticotroph only responds to somatostatin with inhibition of ACTH release if the cells have been cultured in glucocorticoid free medium (70-74). In agreement with this is the finding that ACTH secretion in normal individuals is not affected by infusion of somatostatin or octreotide but this is affected in patients with Addison’s disease (75,76).

Initial reports did show that somatostatin infusion decreases plasma ACTH level by between 40% to 70% in patients with Nelson’s syndrome (77). However, subsequent studies in Nelson’s syndrome have been less impressive and most patients with Cushing’s disease have failed to respond (78-82). The chronic treatment of rat pituitary tumour cells and mouse corticotroph cells with glucocorticoids results in decreased binding of somatostatin (83). In cultured human corticotroph, adenoma cells pre-treated with hydrocortisone resulted in abolition of octreotide-induced inhibition of basal and CRH induced ACTH release (82). The lack of clinical efficacy of octreotide may be due to the down regulation of somatostatin receptors by glucocorticoids. In fact in the mouse, sst2 gene promoter sequence is the only somatostatin receptor shown to be directly transcriptionally regulated by glucocorticoids (84,85). There has been speculation that octreotide may have a role in treating ectopic ACTH producing tumours or in Cushing’s disease in combination with ketoconazole but the available evidence is unconvincing that it has any role in Cushing’s disease (86,87).

There is renewed interest in somatostatin analogues in Cushing’s disease because of encouraging data emerging from early studies with SOM-230 (pasireotide, Novartis Pharmaceuticals UK Ltd). It is a new somatostatin analogue with affinity to all the somatostatin receptor subtypes but with 40 fold higher affinity for sst5 than octreotide (88-90).

Compared to octreotide, SOM-230 is more potent at suppressing ACTH release and at inhibiting CRH-induced ACTH release in corticotroph tumour cells (91-93). Dexamethasone (10 nM) pre-treatment of mouse corticotroph cells fails to suppress SOM-230 inhibition of CRH-induced ACTH release whereas the suppressive effect of octreotide is blocked (92).

The preliminary results of an open label, single arm phase 2 study of fourteen patients with persistent or recurrent Cushing’s disease treated with pasireotide 600 µg subcutaneously twice daily for fifteen days, were reported as an abstract at ENDO 2006 (94). Pasireotide normalised UFC in 3 patients (21%) and in a further 7 patients there was at least 40% reduction in UFC compared to baseline. There was significant improvement in symptoms including weight loss, facial rubor, abdominal obesity, fatigue and proximal weakness in over 40% of patients. The drug was well tolerated but common side effects were mild to moderate gastrointestinal upset, injection site reaction and a transient increase in fasting blood glucose with one pre-existing diabetes mellitus patient stopping treatment early. Although the results of this preliminary study are encouraging the final results are awaited and further studies will be required to confirm these results.

Cyclophosphamide

Cyclophosphamide is a non-selective histamine and serotonin antagonist. In a small series, at a dose of 24 mg/day, it was effective at reducing ACTH in three patients with Cushing’s disease (95). There is disagreement on whether cyclophosphamide acts either directly on the pituitary or through the inhibition of CRH (96-99). It is rarely effective and has no place in current practice. Its main side effect is sedation.
Ritanserin
Ritanserin is a specific 5-HT₂ antagonist which has been used in a few patients but its effects do not appear to be sustained in most patients (100,101).

Sodium valproate
Sodium valproate is mainly used as an anti-epileptic agent. Evidence for its effectiveness in treating Cushing’s disease remains conflicting. There are reports suggesting it is successful at suppressing ACTH at a daily dose of 600 mg, but more recent data have failed to demonstrate benefit either as primary therapy or after failed pituitary surgery (102,103). However, it may have a role as add on therapy to metyrapone at a daily dose of 1–2 g (104,105).

Retinoic acid
Since the 1980’s retinoic acid derivatives are widely used by dermatologists in the treatment of acne and psoriasis as well as in certain malignancy such as acute promyelocytic leukaemia (106,107). Retinoic acid is a ligand for Nur77/Nurr1 receptor which is involved in the physiological stimulation of ACTH by CRH (108). Retinoic acid inhibits cell proliferation and induces cell death in ACTH secreting tumours but not in normal pituitary cells. In the adrenal cortex it inhibits corticosterone secretion and cell proliferation, while in a mouse model, it blocks tumour growth and reduces circulating ACTH and cortisol. The dose was 10 mg/kg which is within the dose range in human cancer therapy (108). Studies in rodents and dogs models of Cushing’s disease have been successful but there is now a need for studies in human (108,109).

Agents blocking cortisol action
Mifepristone (RU486) is a potent antagonist of the glucocorticoid and progesterone receptors (110). In man mifepristone blocks glucocorticoid action resulting in negative feedback at the hypothalamic-pituitary level leading to a rise in ACTH, arginine-vasopressin and therefore cortisol (111). Mifepristone, at doses of up to 20 mg/kg, has been successfully used to treat a small number of patients with ectopic ACTH syndrome and there is every reason to believe that it could be successfully used in all patients if it were not for the problem of monitoring therapy (112). As a receptor antagonist it does not lower circulating cortisol levels, which in fact rise, and therefore it is very difficult to dose titrate and judge effectiveness. The GH receptor antagonist pegvisomant has gained widespread acceptance as a treatment for acromegaly because its effectiveness can be judged by monitoring IGF-1. Unfortunately, the HPA axis lack a marker analogous to IGF-1. Even with short term use, a number of patients did develop symptoms of hypoadrenalism, which is problematic as there is no effective method of monitoring over treatment (113). There has also been report of a case of mifepristone causing severe hypokalaemia that is attributed to excess cortisol activation of mineralocorticoid receptor which responded to spironolactone therapy (114). With caution, mifepristone may have a role in the treatment of Cushing’s syndrome and could be first line treatment if a biochemical measure of disease were identified (115).

CONCLUSIONS
A number of drugs have been used in the management of Cushing’s syndrome. Regardless of the aetiology, steroid biosynthesis remains the most effective and widely used agent. The preferred treatments are metyrapone or ketoconazole as monotherapy, or in combination. Careful monitoring of therapy is important as all agents have the potential of causing hypoadrenalism.

Currently drugs acting on the hypothalamic-pituitary pathways have been less successful in clinical practice and their role is likely to be limited to add on therapy on an individual basis. However, with the identification of new receptors and development of agent blocking these receptors, there remains the hope that they may still prove to be useful in the future.

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Agents</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>Cabergoline</td>
<td>Poor long term results but renewed interest especially in treating Nelson’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Bromocriptine</td>
<td>In vitro success not reproduced in clinical practice</td>
</tr>
<tr>
<td>PPAR-γ</td>
<td>Rosiglitazone</td>
<td>In vitro success not reproduced in clinical practice</td>
</tr>
<tr>
<td></td>
<td>Pioglitazone</td>
<td>Phase 2 study show promising results</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>SOM-230 (pasireotide)</td>
<td>Phase 2 study show promising results</td>
</tr>
<tr>
<td>Nu77/Nurr1</td>
<td>Retinoic acid</td>
<td>Evaluated in mouse model</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>Mifepristone</td>
<td>Successfully utilised in a small number of patients Inability to monitor treatment limits usefulness</td>
</tr>
</tbody>
</table>
Pharmacological Management of CS
Dang & Trainer

REFERENCES

27. van Seters AP, Mooleenaar AJ. Mitotane increases the blood levels of hormone-binding proteins. Acta Endocrinol (Copenh) 1991;124:526-33.


Pharmacological Management of CS
Dang & Trainer


86. Bertagna X, Favrod-Coune C, Escourroule H, Beuzeboc P, Christofoor B, Girard F; et al. Suppression of ectopic adrenocorticotropin secretion by the long-acting somatostatin anal-


89. Lewis I, Bauer W, Albert R, Chandramouli N, Pless J, Weck-

90. Bruns C, Lewis I, Briner U, Meno-Tetang G, Weckbecker G; et al. A novel somatostatin mimic with broad soma-


93. Strowski MZ, Dashkevich MP, Parnam RM, Wilkinson H, Kohler M, Schaeffer JM; et al. Somatostatin receptor sub-

94. Koppeschaar HP, Croughs RJ, Thijssen JM, Schwarz F. Sodi-

95. Krieger DT, Amorosa L, Linick F. Cyproheptadine-induced supression of ectopic adrenocorticotropin release inhibitory factor receptor binding and super-

96. Suda T, Tozawa F, Mouri T, Shibasaki T, Demura H, Shizume K. Effects of cyproheptadine, reserpine, and synthetic corti-

97. Waveren Hogervorst CO, Koppeschaar HP, Zalissem PM, Lips CJ, Garcia BM. Cortisol secretory patterns in Cushing’s dis-

98. Colao A, Pivonello R, Tripodi FS, Orio F Jr, Ferone D, Cerbone D; et al. New insights on SOM230, a universal soma-


108. Paz-Pereda M, Kovalovsky D, Hopfer U, Theodoropoulou M, Pagotto U, Uhl E; et al. Retinoic acid prevents experimen-


110. Baulieu EE. The steroid hormone antagonist RU486. Mech-

111. Healy DL, Chrousos GP, Schulte HM, Hodgen GD. Increased adrenocorticotropin, cortisol, and arginine vaso-


