

Glucocorticoid-induced diabetes and adrenal suppression

(NOVEMBER 2011)

TO THE EDITOR: We found the article by Drs. Lansang and Kramer¹ on glucocorticoid-induced diabetes and adrenal suppression in the November 2011 issue to be a useful and clinically oriented review. However, we strongly believe there is an issue that should be addressed.

It is well accepted that the short cosyntropin (Cortrosyn) stimulation test is the best screening maneuver for assessing adrenocortical insufficiency. The authors state, however, that 250 µg is preferable to lower doses (10 µg or 1 µg), since these are not yet widely accepted, and refer to an article by Axelrod from 1976.²

Based on studies showing that 250 µg of cosyntropin is a pharmacologic rather than a physiologic stimulus that may overstimulate partially atrophied or mildly dysfunctional adrenal glands, multiple studies in the last 20 years have shown that the low-dose test has an equal or better result than the classic 250-µg dose test.³ Dorin et al,⁴ in a meta-analysis of the diagnosis of adrenocortical insufficiency that included more than 30 studies, found similar sensitivity and specificity in primary and secondary adrenal insufficiency comparing the 250-µg dose vs the low dose. In cases of mild primary adrenal failure, the low-dose test has better performance. A previous investigation in our research center contrasting 250 µg vs 10 µg proved that 10 µg had a better sensitivity than the standard dose, with excellent reproducibility and interchangeability.⁵ Similar findings have been shown by other authors contrasting 1 µg vs 250 µg of cosyntropin.⁶

We believe that the limited use of the low-dose cosyntropin test is not a matter of acceptance or performance but a consequence of the lack of vials containing lower doses of cosyntropin (1 to 10 µg), which makes this test technically challenging.^{2,4} The steps needed for one-dose testing and

the preservation time of the preparation are strong limitations to its wide use in clinical practice and endocrine laboratories.

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■ REFERENCES

1. **Lansang MC, Hustak LK.** Glucocorticoid-induced diabetes and adrenal suppression: how to detect and manage them. *Cleve Clin J Med* 2011; 78:748–756.
2. **Axelrod L.** Glucocorticoid therapy. *Medicine (Baltimore)* 1976; 55:39–65.
3. **Dickstein G, Shechner C, Nicholson WE, et al.** Adrenocorticotropin stimulation test: effects of basal cortisol level, time of day, and suggested new sensitive low dose test. *J Clin Endocrinol Metab* 1991; 72:773–778.
4. **Dorin RI, Qualls CR, Crapo LM.** Diagnosis of adrenal insufficiency. *Ann Intern Med* 2003; 139:194–204.
5. **González-González JG, De la Garza-Hernández NE, Mancillas-Adame LG, Montes-Villarreal J, Villarreal-Pérez JZ.** A high-sensitivity test in the assessment of adrenocortical insufficiency: 10 microg vs 250 microg cosyntropin dose assessment of adrenocortical insufficiency. *J Endocrinol* 1998; 159:275–280.
6. **Abdu TA, Elhadd TA, Neary R, Clayton RN.** Comparison of the low dose short synacthen test (1 microg), the conventional dose short synacthen test (250 microg), and the insulin tolerance test for assessment of the hypothalamo-pituitary-adrenal axis in patients with pituitary disease. *J Clin Endocrinol Metab* 1999; 84:838–843.

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TO THE EDITOR: Drs. Lansang and Hustak¹ provide a comprehensive and useful review of steroid-induced diabetes and adrenal suppression.

In their section on local steroids, they discuss the side effects of topical and inhaled glucocorticosteroids. Much has been made of the fact that certain steroids, such as mometasone (Elocon, Nasonex) and fluticasone (Flonase), have a higher "therapeutic index" or ratio of local anti-inflammatory effect to systemic side effects, due to extensive hepatic first-pass metabolism, than older agents such

as beclomethasone (Qvar) and betamethasone (Diprosone).² Ciclesonide (Alvesco, Omnaris), a newer inhaled steroid, is said to have an enhanced therapeutic index because it is a prodrug that is activated by metabolism in the lungs; it reportedly has an even less suppressive effect on hypothalamic-pituitary-adrenal axis function.³

Are the authors aware of any other evidence that clinical outcome, such as adrenal suppression or hyperglycemia, is improved by the use of steroids with a higher therapeutic index?

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■ REFERENCES

1. **Lansang MC, Hustak LK.** Glucocorticoid-induced diabetes and adrenal suppression: how to detect and manage them. *Cleve Clin J Med* 2011; 78:748-756.
2. **Drug Bank.** Mometasone. <http://www.drugbank.ca/drugs/DB00764>. Accessed February 17, 2012.
3. **Derom E, Louis R, Tiesler C, Engelsäter R, Kaufman JM, Joos GF.** Effects of ciclesonide and fluticasone on cortisol secretion in patients with persistent asthma. *Eur Respir J* 2009; 33:1277-1286.

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IN REPLY: We thank Drs. Rodríguez-Gutiérrez and González-González and Dr. Keller for their thoughtful comments.

In our paper, we did not elaborate on the low-dose cosyntropin stimulation test. The 1- μ g test, in particular, has been shown to have similar or better sensitivity, with similar or lower specificity, compared with the 250- μ g dose, depending on the study design. Unfortunately, the administration of the 1- μ g dose presents more technical difficulty than the 250- μ g dose, thus limiting its use. Cosyntropin (used in the United States) comes in a vial with 250 μ g of powder. This must be reconstituted with 250 mL of normal saline, and only 1 mL is to be given. Adherence to the plastic tubing may occur, and more precise timing is needed as the cortisol levels may decrease.¹⁻³

Responding to Dr. Keller, we were unable to find any systematic reviews comparing inhaled corticosteroids that have a “higher therapeutic index” as a class vs older inhaled corticosteroids. There are several studies, however, comparing individual inhaled corti-

costeroid preparations with each other in terms of adrenal effects, and we feel that it is beyond the scope of this response to perform a systematic analysis. In addition, the determination of adrenal function used in studies comparing one inhaled corticosteroid with another were varied, including cosyntropin stimulation tests and surrogates such as the urinary cortisol-creatinine ratio, a morning plasma cortisol level less than 5 μ g/L, and serum cortisol concentration curves, preventing more definitive conclusions even if the data were to be pooled.⁴⁻⁶ A double-blind, randomized study comparing the adrenal effects of ciclesonide and fluticasone showed a smaller reduction in the peak serum cortisol level achieved with ciclesonide compared with fluticasone, in both low-dose and high-dose cosyntropin stimulation tests, with the results in the ciclesonide group being similar to placebo.⁷ However, the mean peak serum cortisol levels after exposure to these inhaled corticosteroids were not presented in table format, and the results have to be inferred from the figures and the narrative description of the baseline mean peak cortisol levels⁸ (ie, before exposure to these inhaled corticosteroids). Case reports have suggested that changing the inhaled corticosteroid formulation from fluticasone to ciclesonide allowed for improvement of adrenal function.⁸ The purported mechanism of decreased adrenal effects of ciclesonide is its greater deposition in the lungs and, hence, less entry into the systemic circulation and fewer systemic adverse effects.⁹

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1. **Dorin RI, Qualls CR, Crapo LM.** Diagnosis of adrenal insufficiency. *Ann Intern Med* 2003; 139:194-204.
2. **Dickstein G.** High-dose and low-dose cosyntropin stimulation tests for diagnosis of adrenal insufficiency. *Ann Intern Med* 2004; 140:312-314.
3. **Rose SR, Lustig RH, Burstein S, Pitukcheewanont P, Broome DC, Burthen GA.** Diagnosis of ACTH deficiency. Comparison of overnight metyrapone test to either low-

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- dose or high-dose ACTH test. *Horm Res* 1999; 52:73–79.
4. **Chrousos GP, Ghaly L, Shedden A, Iezzoni DG, Harris AG.** Effects of mometasone furoate dry powder inhaler and beclomethasone dipropionate hydrofluoroalkane and chlorofluorocarbon on the hypothalamic-pituitary-adrenal axis in asthmatic subjects. *Chest* 2005; 128:70–77.
 5. **White M, Crisalida T, Li H, Economides A, Kaliner M.** Effects of long-term inhaled corticosteroids on adrenal function in asthmatics. *Ann Allergy Asthma Immunol* 2006; 96:437–444.
 6. **Fardon TC, Lee DK, Haggart K, McFarlane LC, Lipworth BJ.** Adrenal suppression with dry powder formulations of fluticasone propionate and mometasone furoate. *Am J Respir Crit Care Med* 2004; 170:960–966.
 7. **Lipworth BJ, Kaliner MA, LaForde CF, et al.** Effects of ciclesonide and fluticasone on hypothalamic-pituitary-adrenal axis function in adults with mild-to-moderate persistent asthma. *Ann Allergy Asthma Immunol* 2005; 94:465–472.
 8. **Heller MK, Laks J, Kovesi TA, Ahmet A.** Reversal of adrenal suppression with ciclesonide. *J Asthma* 2010; 47:337–339.
 9. **Kaliner MA.** Pharmacologic characteristics and adrenal suppression with newer inhaled corticosteroids: a comparison of ciclesonide and fluticasone propionate. *Clin Ther* 2006; 28:319–331.

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Essential tremor, beta-blockers, and calcium channel blockers

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TO THE EDITOR: In their thorough review of essential tremor,¹ Drs. Abboud, Ahmed, and Fernandez make a statement that needs clarification. In their list of absolute contraindications to propranolol (Inderal), the authors include “concurrent use of a calcium channel blocker.” This warning applies only to the nondihydropyridine calcium channel blockers, which are diltiazem (Cardizem) and verapamil (Calan). These two medications slow the heart rate and generally should not be combined with beta-blockers such as propranolol unless the patient requires this combination to control tachycardia. Most calcium channel blockers are dihydropyridines, which include amlodipine (Norvasc), nifedipine (Procardia), felodipine (Plendil), nisoldipine (Sular), isradipine (DynaCirc CR), and nicardipine (Cardene). These agents do not slow the heart rate significantly and therefore can be used freely in combination with propranolol. Of course, the dose of the calcium channel blocker may need

to be decreased because of the antihypertensive effect of propranolol.

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REFERENCES

1. **Abboud H, Ahmed A, Fernandez HH.** Essential tremor: choosing the right management plan for your patient. *Cleve Clin J Med* 2011; 78:821–828.

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IN REPLY: We agree and thank Dr Keller for raising this valid point. The two classes of calcium channel blockers are distinct in their actions, and the warning about not combining a calcium channel blocker with a beta-blocker because of the increased risk of developing significant bradycardia applies only to the nondihydropyridine class.

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Parkinson disease

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TO THE EDITOR: I have the following comments and questions regarding the excellent Medical Grand Rounds article on Parkinson disease by Dr. Fernandez in your January 2012 issue.¹

The author mentions that when “cost may be of concern, levodopa is the preferred starting drug.”¹ Generic versions of pramipexole and ropinirole are now available and have made these medications more affordable. For example, the cash price of generic ropinirole 5 mg was recently \$66 for 100 tablets, comparable with generic carbidopa/levodopa (25/100 mg) priced at \$46 for 100 tablets.² And even though the price of generic pramipexole was \$240 for 90 tablets, seniors with Medicare Part D drug coverage can usually get any generic medication for a low copay.

When choosing a dopamine agonist, how does Dr. Fernandez decide between ropinirole and pramipexole (aside from the price difference noted above)? Pramipexole has a longer elimination half-life (8 to 12 hours) compared with ropinirole (6 hours).³ Does this imply a significantly longer effective dosing interval for pramipexole? Are there other significant clinical differences between these agents?

Isradipine (DynaCirc CR), a dihydropyridine calcium channel blocker, has shown promise as a neuroprotective agent for slowing the progression of Parkinson disease in epidemiologic and laboratory studies, as noted by the author. In addition, immediate-release isradipine, with its relatively short elimination half-life of 8 hours,³ may be well suited for treating Parkinson patients whose essential hypertension is complicated by episodes of orthostatic hypotension. It should be noted that dihydropyridines that do not cross the blood-brain barrier (such as amlodipine [Norvasc]) have shown no evidence of neuroprotection.

Ibuprofen is another drug that has fairly strong epidemiologic and laboratory evidence that it might be neuroprotective,⁴ although the other nonsteroidal anti-inflammatory drugs (NSAIDs) have proven disappointing as a class.⁵ Lacking any prospective randomized trials, the evidence is not strong enough to recommend ibuprofen solely for neuroprotection. Does Dr. Fernandez, however, consider it reasonable to suggest ibuprofen to Parkinson patients who need to take an NSAID for an approved indication (such as pain)?

Dexpramipexole has recently demonstrated great promise in a phase 3 clinical trial as a neuroprotective agent in amyotrophic lateral sclerosis.⁶ How does this compound relate to pramipexole, and does the author believe it may offer neuroprotection in other neurodegenerative diseases like Parkinson disease?

The author discusses the use of catechol-O-methyltransferase (COMT) inhibitors (such as Comtan and Tasmar) and the monoamine oxidase (MAO) type-B inhibitors rasagiline (Azilect) and selegiline (Eldepryl, Zelapar) for prolonging the effects of levodopa by slowing the breakdown of dopamine. However, it is important to note that it is contraindicated to prescribe both a COMT

inhibitor and an MAO-B inhibitor, because these agents also inhibit the breakdown of other catecholamines and can lead to adrenergic crisis when taken concomitantly.

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REFERENCES

1. Fernandez HH. Updates in the medical management of Parkinson disease. *Cleve Clin J Med* 2012; 79:28–35.
2. Drugstore.com. www.drugstore.com. Accessed February 5, 2012.
3. PDR.net. www.pdr.net. Accessed February 25, 2012.
4. Gao X, Chen H, Schwarzschild MA, Ascherio A. Use of ibuprofen and risk of Parkinson disease. *Neurology* 2011; 76:863–869.
5. Driver JA, Logroscino G, Lu L, Gaziano JM, Kurth T. Use of non-steroidal anti-inflammatory drugs and risk of Parkinson's disease: nested case-control study. *BMJ* 2011; 342:d198.
6. Cudkovic M, Bozik ME, Ingersoll EW, et al. The effects of dextramipexole (KNS-760704) in individuals with amyotrophic lateral sclerosis. *Nat Med* 2011; 17:1652–1656.

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IN REPLY: I thank Dr. Keller for his thoughtful comments. They are most appreciated.

It is true that with availability of generic ropinirole and pramipexole, there are now cheaper alternatives to levodopa. Nonetheless, levodopa remains the cheapest and most efficacious medication for Parkinson disease to date. Whenever levodopa is compared head-to-head with any dopamine agonist, the general results remain consistent: levodopa affords better motor improvement with lesser side effects, but is more likely to lead to motor fluctuations, specifically dyskinesias. Therefore, in general, levodopa is the first choice in elderly patients where tolerability may be an issue, whereas a dopamine agonist may be the initial treatment of choice in younger Parkinson patients, who are able to tolerate the drug better and have a higher likelihood of developing dyskinesias.

It is a tougher task to determine which among the dopamine agonists is superior. The newer dopamine agonists have not been compared head-to-head. Therefore, it is practically a “coin toss” when selecting which dopamine agonist to try. Their mechanism of action (D2 and D3 receptor agonist activity) and frequency of intake (three times per day for generics; once daily for long-acting formulations), cost, and side effect profile are nearly identical,

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despite minor differences in their half-lives.

Regarding putative neuroprotective agents in Parkinson disease, indeed, isradipine is one of the medications currently undergoing investigation for its potential neuroprotective effect. While I personally have no objection to using it for a Parkinson disease patient who also happens to need an antihypertensive agent, I am more cautious about endorsing it as a neuroprotective agent until results of clinical trials have been released. Similarly, while a large epidemiologic study has shown that people who take ibuprofen are less likely to develop Parkinson disease, there has been no robust human trial that has shown the drug to slow the progression of Parkinson disease among patients who are already suffering from the disorder. Therefore, the current use of ibuprofen in Parkinson disease should be based more on its anti-inflammatory indications rather than its possible neuroprotective effect. Finally, we have shown, in a large, multicenter, global randomized controlled trial with a delayed-start design, that pramipexole is unlikely to possess any meaningful neuroprotective

effect. Therefore, I am personally not that optimistic that dextropramipexole would demonstrate such an effect.

While in theory combining the use of catechol-O-methyltransferase (COMT) inhibitors and monoamine oxidase (MAO) type B inhibitors can synergistically work to inhibit the breakdown of other catecholamines and lead to adrenergic crisis when taken concomitantly, this has not been our experience. Perhaps it is because at recommended doses, the MAO inhibition is selective to type B (where receptors are more confined to the brain) and not type A (where receptors are more distributed throughout blood vessels, thereby having a higher likelihood of causing a hypertensive crisis as is seen in the use of nonselective MAO inhibitors). Therefore, at our center, we routinely use the two classes of agents concomitantly with minimal safety concerns.

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