MANAGEMENT OF ORTHOSTATIC HYPOTENSION FROM AUTONOMIC DYSFUNCTION IN DIABETICS ON PERITONEAL DIALYSIS

Autonomic neuropathy occurs in over 50% of chronic dialysis patients (1). Since the autonomic nervous system innervates almost every organ of the body, the clinical features may be diverse and widespread. Most of the nerve fibers in the autonomic nervous system are small myelinated or unmyelinated fibers that are affected early in diabetes mellitus (2).

Neurogenic orthostatic hypotension is the most common, challenging, and often frustrating manifestation of autonomic dysfunction secondary to diabetes mellitus that we encounter in patients on peritoneal dialysis (PD). Orthostatic hypotension, which can also occur from nonneurogenic causes, is defined as a "fall in systolic blood pressure of over 20 mmHg or diastolic blood pressure of over 10 mmHg within 3 minutes of standing or head up position at an angle of 60°" (3). This is accompanied by reflex tachycardia in individuals with intact autonomic function. In neurogenic orthostatic hypotension from various causes, including diabetes mellitus, because of parasympathetic dysfunction from autonomic neuropathy there is a lack of this reflex tachycardia upon standing.

While evaluating a diabetic patient on PD with orthostatic hypotension, it is important that we exclude nonneurogenic causes before attributing it to autonomic neuropathy. Intravascular volume depletion, low cardiac output states and conduction abnormalities, severe anemia, and medications can all lead to blood pressure drop on standing. A significant portion of diabetic dialysis patients are on various combinations of diuretics, antihypertensives, phenothiazines, antidepressants, nitrates, and a host of other medications that can cause orthostatic hypotension (4).

Unfortunately there is no known specific or effective treatment for orthostatic hypotension. The principles of management in dialysis and non-dialysis patients are the same. In nondialysis patients it has been suggested that the goal of treatment should be to improve functional capacity, and not just achieve a target blood pressure. To that end, both nonpharmacologic and pharmacologic modalities of treatment have been used independently or in combination. Prior to use of drugs, various nonpharmacologic interventions, including patient education, should be attempted as listed in Table 1. Frequently, patients have intravascular volume depletion, and it has been recommended that diabetic patients with orthostatic hypotension on dialysis be kept slightly overhydrated by reducing diuretic dosage and decreasing ultrafiltration (5). Other nonpharmacological measures that have found favor in neurogenic orthostatic hypotension from all causes are the use of compression garments, which reduce venous pooling when upright, and eating small frequent meals rather than large meals rich in carbohydrates (6). It is essential that such garments extend up to the waist to minimize splanchnic venous pooling. The other maneuver that may be effective is leg crossing while standing on both legs (7,8). Squatting also has been shown to have similar benefits. The common offending drugs mentioned above should be avoided if possible.

Nonpharmacologic agents are often insufficient to improve symptoms of orthostatic hypotension; drugs may have to be used in such cases. Pharmacologic agents used for the treatment of neurogenic orthostatic hypotension from any cause in patients with or without renal disease are generally helpful but do not restore normotension. These agents are listed in Table 2 (6). Fludrocortisone, a synthetic mineralocorticoid, is currently the most commonly used agent in the treatment of patients on PD (5). It increases circulating blood volume, enhances sensitivity to circulating catecholamines, and enhances release of norepinephrine. Caffeine, an adenosine receptor blocker, causes vasoconstriction in the dose of 250 mg, or two cups of coffee prior to meals, and improves orthostatic and postprandial hypotension in patients with autonomic dysfunction. Midodrine, a selective alpha-1 adrenergic receptor agonist, was recently ap-

<table>
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<th>TABLE 1 Nonpharmacological Interventions</th>
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<tr>
<td>Do's</td>
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<tr>
<td>Decrease ultrafiltration</td>
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<tr>
<td>Elastic stockings and abdominal binders</td>
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<tr>
<td>Head up-tilt during sleep</td>
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<td>Leg crossover during standing</td>
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<td>Don'ts</td>
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<td>Large meals rich in carbohydrates</td>
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<td>Sudden head up postural change</td>
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<td>High environmental temperature</td>
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<td>Offending agents</td>
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proved by the FDA (Food and Drug Administration, U.S.A.) and appears to be a promising agent (9). It causes both arterial and venous constriction. It is a prodrug that is converted to an active metabolite desglymidodrine, which does not cross the blood-brain barrier and is therefore free of the central nervous system side effects seen with other sympathomimetics. An advantage in patients with autonomic dysfunction is that it is almost totally absorbed after oral administration, with a bioavailability of 93%, even with gastroparesis. It is a short-acting drug with a duration of action about of 4 hours. The largest trial showing its efficacy is a double-blind, placebo-controlled, randomized, parallel group multicenter study involving 171 patients, reported from the Mayo clinic in 1997 (10). The commonest side effects in this study were pilo-erection (13%), pruritus of scalp (10%), paraesthesia (7%), urinary retention (6%), and supine hypertension (4%). Supine hypertension is a common and troublesome adverse effect with higher doses of the drug (11) if given closer to bedtime, or with recumbency during daytime after it is ingested. The incidence of supine hypertension was lower in this study, probably because the last dose of midodrine was given at least 4 hours prior to bedtime. The group concluded that midodrine 10 mg, used orally three times per day, is effective and safe in the treatment of neurogenic orthostatic hypotension.

In another double-blind, placebo-controlled, four-way cross-over trial in patients with neurogenic orthostatic hypotension, once again an oral dose of 10 mg, two to three times daily, was found effective in improving standing blood pressure and symptoms in 25 patients (11). The mean increases in standing systolic blood pressure 1 hour post dose were shown to be 5 mmHg with placebo, 7 mmHg with 2.5 mg, 10 mmHg with 5.0 mg, 34 mmHg with 10 mg, and 43 mmHg with 20 mg of midodrine. However, more than 41% of the patients had a supine systolic blood pressure of greater than 200 mmHg as opposed to 17% with 10 mg of midodrine. It has also been shown to significantly improve standing time, energy level, dizziness, weakness, and blurred vision secondary to orthostatic hypotension (12). While there are no studies in patients on PD, trials in patients on hemodialysis have shown that it is useful in the treatment of symptomatic intradialytic hypotension for extended periods of time when used in an oral dose of 10 mg a half hour prior to initiation of hemodialysis (13).

A recent study with another agent concluded that short-term (6 weeks) use of sertraline hydrochloride (Zoloft, Pfizer Inc., NY, U.S.A.) reduces hemodialysis hypotension significantly (14).

In conclusion, the problem of orthostatic hypotension in diabetic patients on dialysis is very common. We need to perform trials to determine the efficacy of various nonpharmacologic interventions and pharmacologic modalities of treatment, alone or in combination, to determine their role in dealing with this frequent problem. Studies need to be done with midodrine and sertraline to help determine their dosage and safety in diabetic PD patients.

Meanwhile, in patients on PD, in our opinion midodrine in lower doses (2.5 mg), two to three times per day, with the first dose about 30 minutes prior to getting up in the morning and the last dose at least 4 hours, if not more, before bedtime to avoid supine hypertension, may be effective. The dosage can subsequently be titrated up. Other medications mentioned in Table 2 can also be considered individually or in combination.

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### TABLE 2
Pharmacological Interventions

<table>
<thead>
<tr>
<th>Vasoconstriction</th>
<th>Prevent vasodilatation</th>
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<tr>
<td>Midodrine</td>
<td>Prostaglandin synthetase inhibitors</td>
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<tr>
<td>Phenylpropanolamine</td>
<td>Indomethacin</td>
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<td>Phenylephrine</td>
<td>Domperidone</td>
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<td>Alpha adrenoceptor sensitivity increase</td>
<td>Alpha adrenoceptor sensitivity increase</td>
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<td></td>
<td>Fludrocortisone</td>
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<tr>
<td>Adenosine receptor blockade</td>
<td>Erythropoietin</td>
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<tr>
<td>Caffeine</td>
<td>Increase red cell mass</td>
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