Withdrawal Reactions Following Cessation of Central α-Adrenergic Receptor Agonists

JOHN L. REID, BRIAN C. CAMPBELL, AND CARLENE A. HAMILTON

SUMMARY Interruption of long-term treatment with α2-adrenergic receptor agonists may be associated with reversal of their hemodynamic effects, clinical and biochemical evidence of increased peripheral sympathetic activity, and behavioral responses similar to those seen after narcotic or alcohol withdrawal. Reactions are most commonly observed after short-acting imidazoline drugs such as clonidine and tiamenidine. Reactions are less common after longer acting agents such as guanfacine. A new management approach to withdrawal has been evaluated, which uses a combination of α1-blockade (prazosin) and cardioselective β-blockade (atenolol) together with a benzodiazepine (chlor Diazepoxide). Withdrawal reactions were not observed in eight patients in whom clonidine was withdrawn under cover of these agents. The mechanism of the withdrawal reaction may involve agonist-induced down regulation of α2-adrenergic receptor affinity, number, or both. Experimental studies with the irreversible α-antagonist phenoxybenzamine on the turnover of α2-receptors suggest that recovery of receptor number may be much slower in the brain than in the periphery.

KEY WORDS • α2-adrenergic receptors • withdrawal hypertension • central blood pressure control • clonidine • phenoxybenzamine

S OON after the introduction of the centrally acting antihypertensive drug clonidine, there appeared in the literature case reports of hypertensive reactions and subjective symptoms that followed abrupt withdrawal of the drug.1,2 In a formal study a group of these patients who had reported withdrawal symptoms was studied intensively in hospital during withdrawal of clonidine. There was rapid reversal of antihypertensive effect together with symptoms and biochemical indications of increased sympathetic activity.3 Several subsequent studies have confirmed that these withdrawal reactions are relatively common in unselected groups of patients after interruption of clonidine therapy.4,5 The frequency and severity of symptoms appears to be greater in patients treated with higher doses for longer periods (> 3 months) and in those with more severe hypertension before treatment. Concurrent therapy with other antihypertensive drugs, particularly nonselective β-adrenergic receptor antagonists, may exacerbate withdrawal symptoms.6,7 There remain several controversial aspects to clonidine withdrawal reactions.8,9,10 These are in large part a result of different criteria or definitions, different or poorly characterized patient populations, and wide ranges of dose and duration of treatment.11 There has been considerable debate whether blood pressure “overshoots” on withdrawal or rebounds rapidly to return to untreated levels. As reliable pretreatment blood pressure recordings often are not available and those from years before not relevant, it is difficult to confirm overshoot. Subjective symptoms, which include sweating, palpitations, anxiety, insomnia, nausea, and vomiting, may be severe during withdrawal and may occur in the absence of marked changes in blood pressure. As an operational definition of the withdrawal syndrome, we prefer: a rapid reversal of antihypertensive effect within 24 to 48 hours up to or above pretreatment levels, a rise of systolic blood pressure of more than 40 mm Hg or diastolic pressure of 25 mm Hg, or blood pressure greater than 225/125 with or without characteristic symptoms of catecholamine excess. Using this definition we have often observed a withdrawal syndrome if patients are examined closely.4 Half of the patients developed an excessive rise in blood pressure and severe symptoms in a study of clonidine withdrawal.4

The withdrawal syndrome is not restricted to clonidine therapy. It has been shown to occur with other α2-adrenergic receptor agonists. Using the definition above we have studied withdrawal of the imidazoline tiamenidine12 and the longer acting guanine derivative guanfacine.13

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Tiamenidine (Table 1) caused a spectrum of symptoms and frequency of withdrawal hypertension similar to those of clonidine but guanfacine appeared to lead to a slower offset of hypotensive effect and fewer symptoms, perhaps because of pharmacokinetic or pharmacodynamic differences. Another centrally acting antihypertensive, methyldopa, does not appear to cause withdrawal reactions with any measurable frequency. The occasional anecdotal reports\(^{2,13}\) contrast with more than 20 years of worldwide clinical experience. \(\alpha\)-methylnorepinephrine, the active metabolite, may persist in nerve endings for some time and permit a gradual offset of effect. Alternatively methyldopa and clonidine-like drugs may differ in their pharmacological actions, in particular in their effects on adrenergic receptor dynamics.

As clonidine withdrawal reactions have been described even when the drug was slowly and gradually withdrawn,\(^{2,13}\) we have been investigating strategies for safe discontinuation of clonidine without adverse effects.\(^{12}\) These studies have documented that while some symptoms are related to increased peripheral sympathetic activity others, such as anxiety and insomnia, are central in origin.

There has been recent interest in the relationship between central \(\alpha_2\)-adrenergic receptors and opiate receptors. Clonidine has been reported to attenuate symptoms of opiate withdrawal.\(^{18}\) There are reports that the \(\mu\)-opiate-receptor antagonist naloxone can modify the hemodynamic effects of clonidine\(^{19}\); however, other groups have failed to confirm such an interaction.\(^{20}\) Although there are superficial similarities between clonidine withdrawal and opiate withdrawal, the syndromes differ both qualitatively and quantitatively.

Further experimental studies are indicated on the relationship among opiate receptors, endogenous opioids and \(\alpha_2\)-adrenergic receptors involved in central circulatory control.

Management of Withdrawal Reactions

Early studies reported that the hypertensive reactions evoked by withdrawal could be controlled or abolished by \(\alpha\)-adrenergic receptor blockade that used phentolamine together with the \(\beta\)-blocker propranolol.\(^{3}\) Withdrawal effects improved with the reintroduction of clonidine treatment. Pretreatment with reserpine also reduced the severity of the withdrawal syndrome.\(^{21}\) More recently the combined \(\alpha_1\)- and \(\beta\)-blocker labetalol has been used\(^ {22}\) to control blood pressure and heart rate, although symptoms of tremor, anxiety, and insomnia were still observed.\(^{22}\)

We have evaluated an alternative regimen that used a selective \(\alpha_2\)-adrenergic receptor antagonist, a selective \(\beta_1\)-antagonist, and a benzodiazepine, chloridiazepoxide, as a central anxiolytic (Table 2).\(^ {17}\) A preliminary report previously had demonstrated that prazosin did not antagonize the antihypertensive effect of clonidine and that it might protect against clonidine withdrawal syndrome.\(^{23}\) We believed that this regimen offered the possibility of controlling hemodynamics and subjective symptoms and that selective \(\alpha_1\)- and \(\beta_1\)-blockade might reduce the likelihood of increased transmitter overflow or peripheral vasoconstriction, which results from blockade of \(\alpha_1\)- and \(\beta_1\)-receptors respectively.

Clonidine therapy was abruptly withdrawn in hospital in six patients following exactly the protocol described in previous studies,\(^ {2,12,13}\) apart from the use of the drug regimen detailed in Table 2. Patients had been on clonidine for at least 1 year and were comparable in terms of severity of hypertension, dose of clonidine, and additional treatment to those reported previously (Table 3).\(^ {4}\)

No patient managed under the new protocol developed a hypertensive withdrawal reaction as defined above.

Average blood pressure and heart rate for the day before and after clonidine withdrawal are shown in Table 4. Unlike the previous study, without adrenergic receptor antagonists there was no rise in blood pressure on withdrawal and a modest fall was noted with the institution of the new regimen. We examined the maximum or highest blood pressure recording on the day before withdrawal and at any time after withdrawal. Maximum supine pressure was 170 ± 9/101 ± 4 (mean ± SEM) before and 180 ± 9/104 ± 4 after withdrawal. Heart rates were 83 and 95 ± 7 beats/minute respectively. Standing pressures were similar at 159 ± 8/100 ± 3 and 171 ± 7/99 ± 5 and heart rate 85 ± 5 and 110 ± 10 before and after withdrawal. It was notable that the intraindividual variation of blood pressure was not increased when clonidine was withdrawn under pharmacological cover. Increased variability or lability has been a feature of clonidine withdrawal in humans and animals.\(^ {24}\) In spite of high doses of prazosin only modest orthostatic falls in pressure were observed overall. In spite of \(\beta_1\)-blockade with atenolol, heart rate erect and supine was increased after withdrawal, which suggests that sympathetic neuron activity was still increased although its hemodynamic consequences were competitively antagonized. In retrospect a higher dose of atenolol might

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**Table 1. Withdrawal Studies on Central \(\alpha_2\)-Adrenergic Receptor Agonists**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Design</th>
<th>Number</th>
<th>Reversal of antihypertensive effect</th>
<th>Number of studies* interrupted within</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine (Reid et al. 1977)</td>
<td>Single blind</td>
<td>6</td>
<td>18–24 hr</td>
<td>2/6</td>
</tr>
<tr>
<td>Tiamenidine (Campbell et al. 1980)</td>
<td>Double blind placebo</td>
<td>10</td>
<td>24 hr</td>
<td>4/10</td>
</tr>
<tr>
<td>Guanfacine (Zamboulis and Reid 1981)</td>
<td>Double blind</td>
<td>5</td>
<td>48–72 hr</td>
<td>0/5</td>
</tr>
</tbody>
</table>

*Criteria for interruption are defined in Campbell et al. 1980 and Zamboulis and Reid 1981.
Table 2. Protocol for Withdrawal of Clonidine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Starting dose</th>
<th>Final dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prazosin</td>
<td>Competitive α-adrenergic receptor antagonist</td>
<td>0.5 mg the night before: 10 mg b.i.d.</td>
<td>10-20 mg b.i.d.</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Competitive β-adrenergic receptor antagonist</td>
<td>50 mg daily</td>
<td>100 mg daily</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>Benzodiazepine anxiolytic</td>
<td>10 mg b.i.d.</td>
<td>10 mg b.i.d.</td>
</tr>
</tbody>
</table>

Table 3. Summary of Clinical Features of Patients Withdrawn from Clonidine with New Regimen

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Clonidine daily dose (mg)</th>
<th>Duration of clonidine (years)</th>
<th>Serum creatinine level ((\mu)mol/L)</th>
<th>Drugs</th>
<th>Diuretics</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>M</td>
<td>0.9</td>
<td>10</td>
<td>85</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>M</td>
<td>1.8</td>
<td>9</td>
<td>82</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>F</td>
<td>0.9</td>
<td>12</td>
<td>113</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>M</td>
<td>0.6</td>
<td>1</td>
<td>108</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>M</td>
<td>0.3</td>
<td>4</td>
<td>441*</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>M</td>
<td>0.6</td>
<td>9</td>
<td>—</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>51</td>
<td>F</td>
<td>0.4</td>
<td>2</td>
<td>67</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>M</td>
<td>0.6</td>
<td>4</td>
<td>161</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

+ = hydralazine (2) and methyldopa (2).
*Chronic glomerulonephritis; all other patients had essential hypertension.

Table 4. Daily Average Blood Pressure and Heart Rate (mean ± SEM) Before and After Withdrawal of Clonidine with Additional Pharmacological Treatment

<table>
<thead>
<tr>
<th>Day</th>
<th>Supine systolic</th>
<th>Supine diastolic</th>
<th>Supine heart rate</th>
<th>Erect systolic</th>
<th>Erect diastolic</th>
<th>Erect heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>153 ± 6</td>
<td>92 ± 3</td>
<td>75 ± 4</td>
<td>141 ± 7</td>
<td>90 ± 4</td>
<td>77 ± 5</td>
</tr>
<tr>
<td>1</td>
<td>144 ± 5</td>
<td>85 ± 5</td>
<td>79 ± 6</td>
<td>133 ± 5</td>
<td>80 ± 1</td>
<td>82 ± 7</td>
</tr>
<tr>
<td>2</td>
<td>147 ± 5</td>
<td>87 ± 4</td>
<td>80 ± 6</td>
<td>133 ± 9</td>
<td>77 ± 3</td>
<td>89 ± 6</td>
</tr>
<tr>
<td>3</td>
<td>147 ± 9</td>
<td>85 ± 4</td>
<td>77 ± 4</td>
<td>126 ± 9</td>
<td>73 ± 6</td>
<td>90 ± 6</td>
</tr>
<tr>
<td>4</td>
<td>146 ± 13</td>
<td>84 ± 4</td>
<td>78 ± 4</td>
<td>129 ± 11</td>
<td>76 ± 5</td>
<td>83 ± 4</td>
</tr>
<tr>
<td>5</td>
<td>152 ± 18</td>
<td>77 ± 12</td>
<td>88 ± 3</td>
<td>134 ± 11</td>
<td>77 ± 6</td>
<td>87 ± 5</td>
</tr>
</tbody>
</table>

Day -1 = the last day on clonidine. The last dose was given between 1800 and 2000 hours on Day 1.

have been used. Our regimen permits flexibility of α- and β-blocker doses to optimize the actions in individuals.

Unlike the study of Rosenthal et al., which used labetalol alone, in our study subjective symptoms of sympathetic overactivity were not observed.

We assessed symptoms using a standard questionnaire completed twice daily by the patient. Ten symptoms were assessed as absent (0), mild (1), moderate (2), or severe (3). The highest total symptom score for a patient was thus 30 at any time. In Table 5 the average symptom scores are shown after withdrawal of clonidine under the present regimen. At no time after withdrawal did the average symptom score exceed that reported before withdrawal. In a group of three patients in whom clonidine was withdrawn without the present regimen the symptom score ranged from 7 to 12 on Days 2 to 5 after withdrawal. The average score after clonidine or tiamenidine withdrawal in previous studies was 8 to 12 using the above criteria. Thus a regimen of high-dose α-blockade, cardioselective β-blockade, and benzodiazepine, appears

Table 5. Average Daily Score of Symptoms Associated with Increased Sympathetic Activity and Clonidine Withdrawal

<table>
<thead>
<tr>
<th>Day</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before withdrawal</td>
<td>-1</td>
</tr>
<tr>
<td>After withdrawal</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

Symptoms were graded on a 3-point scale with 3 being the most severe (from Campbell et al. 1980). Day -1 was the last day of clonidine treatment.
not only to prevent clonidine withdrawal hypertension but also to control the other features. The benzodiazepine appears to be necessary to control the central behavioral symptoms of the withdrawal reaction.

### Mechanism of Withdrawal Reactions

Increased peripheral sympathetic activity clearly determines many but not all the features of clonidine withdrawal. The increase appears to be centrally mediated as is the case in alcohol and opiates withdrawal. The syndrome, however, clearly involves other brain mechanisms. The range of hemodynamic effects together with changes in arousal suggests a generalized brain mechanism via changes in α₂-adrenergic-receptor-mediated functions.

Until recently there was disagreement about the validity of animal models of withdrawal. New information about the pharmacokinetics and concentration effect relationships in animals together with the use of osmotic "mini pumps" as a delivery system has led to improved models, which have recently been reviewed. Animal withdrawal reactions are dose- and time-dependent and can be provoked by acute dosing with α₂-adrenergic receptor antagonists; however, the biochemical basis of these reactions remains unclear. It has been proposed that chronic treatment with an α₁-agonist leads to changes in the receptor population similar to the down regulation observed with β-adrenergic receptors. According to this hypothesis, after cessation of clonidine drug action would disappear rapidly as the drug is cleared from plasma but receptors would take a longer time to return to normal. For a period there would be a disequilibrium when central α₂-adrenergic receptor mechanisms would fail in their normal regulatory role with failure to inhibit sympathetic outflow and modulate baroreflex function.

There is no definitive study on adrenergic receptor number and affinity after clonidine in brain and periphery. The dose regimen, route of administration, radioligands used, and conditions of assay would have to be optimized for such a study.

We have been interested in the factors that regulate α-adrenergic receptor responsiveness and in the number of binding sites. We have identified differences between α₁- and α₂-adrenergic receptors in animals in response to 6-hydroxydopamine treatment and to aging.

Recently we have studied α-adrenergic receptor dynamics in rabbits by observing the recovery of binding sites and function after noncompetitive irreversible α-adrenergic receptor blockade with phenoxybenzamine. Phenoxybenzamine alkylates the receptor binding site. Recovery of the number of binding sites appears to depend on new receptor protein synthesis as it is impaired by inhibition of protein synthesis. Thus recovery after high doses of phenoxybenzamine (5 mg/kg) may give an indication of dynamics and receptor turnover. The α₁- and α₂-adrenergic receptors in spleen differ in their rate of recovery after phenoxybenzamine administration (Table 6).

### Table 6: Half-life (±SE) of Recovery of α-Adrenergic Receptor Binding Sites in Spleen Membranes After Phenoxybenzamine (5 mg/kg i.v.)

<table>
<thead>
<tr>
<th>Adrenergic Receptor</th>
<th>Ligand</th>
<th>Half-life of Recovery (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α₁</td>
<td>[³H]-Prazosin</td>
<td>3.6 ± 0.1</td>
</tr>
<tr>
<td>α₂</td>
<td>[³H]-Clonidine</td>
<td>1.6 ± 0.9</td>
</tr>
</tbody>
</table>

We have extended these studies to examine recovery of brain α-adrenergic receptor numbers after phenoxybenzamine administration. These studies, while confirming differences between α₁- and α₂-adrenergic receptors, highlight marked differences in the rate of recovery of receptors in brain compared with the periphery with much delayed return of binding site number.

Studies were performed in groups of male New Zealand white rabbits (n = 6). [³H]-Prazosin and [³H]-clonidine were used as α₁- and α₂-adrenergic receptor ligands respectively. A preliminary dose-ranging study revealed that phenoxybenzamine 0.001–5.0 mg/kg caused dose-dependent reduction in specific binding sites. There was a greater reduction in α₂-binding sites than in α₁-adrenergic receptors. Phenoxybenzamine 5.0 mg/kg i.v. was chosen for further study. Binding assays were performed on forebrain and hindbrain membranes prepared as described in detail by Berthelot et al. with phentolamine 10⁻⁵M as displacing agent. Neither guanosine triphosphate (GTP) nor mono- or divalent cations were added to the incubation mixture. Binding data were analyzed by Scatchard analysis to derive the maximum number of binding sites (Bmax) and their dissociation constant (Kd).

The number of binding sites was examined at several times (30 minutes to 21 days) after phenoxybenzamine. Recovery was modeled with a nonlinear least squares fitting procedure and was expressed as the half-life of recovery (t½).

Recovery of binding of [³H]-prazosin was slow in both forebrain and hindbrain. The half-life of recovery was 10.8 ± 2.6 and 13.3 ± 3.1 days (mean ± SD) respectively (Table 6). These were significantly longer than the half-life of recovery in the spleen. The number of [³H]-clonidine binding sites was only reduced to 40% to 50% of control.

The fall in [³H]-clonidine binding sites was maximal 2 days after dosing with slow recovery in hindbrain (t½ = 19 ± 12 days).

The dissociation constant for [³H]-prazosin did not change at any time; however, Kd for clonidine binding in both forebrain and hindbrain was increased 1 day after phenoxybenzamine administration but not different from control at all other subsequent times studied.

We currently are investigating the functional implication of the slow recovery of α-adrenergic receptor binding sites in brain after phenoxybenzamine. Slow recovery, particularly in the forebrain, would not be inconsistent with the hypothesis that recovery required synthesis of new receptors. In the brain such protein
synthesis may occur in cell bodies with axonal transport to terminals or dendrites. Prejunctional receptors on noradrenergic or adrenergic terminals in forebrain may take a considerable time to recover after phenoxybenzamine administration.

These results illustrate the differences in regulation between central and peripheral α-adrenergic receptors. Although effects observed were those of a profound functional disturbance after high doses of the irreversible α-blocker phenoxybenzamine, they may be relevant to the problem of long-term treatment with an α2-adrenergic receptor agonist like clonidine, particularly at high doses. If agonist-induced down regulation occurs at central α2-adrenergic receptors, recovery in brain after cessation of clonidine may be slow. This could result in a period of impaired regulation of circulatory control and other behaviors mediated by α2-adrenergic receptors.

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