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THE CLINICAL PHARMACOLOGY OF CLONIDINE AND RELATED CENTRAL ANTIHYPERTENSIVE AGENTS

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Introduction

Although centrally acting drugs are less widely used in the treatment of hypertension now than 10 years ago, studies with this group of agents continue to provide important contributions to clinical pharmacology and our understanding of the physiology of cardiovascular regulation and autonomic adrenergic mechanisms in particular. The serendipidous recognition of the hypotensive action of clonidine in man (Graubner & Wolf, 1966) stimulated studies to identify the mechanism by which an α-adrenoceptor agonist *lowered* blood pressure. Within a short time the central site of action of clonidine on sympathoinhibitory α-receptors in the brain stem was identified (Kobinger & Walland, 1967; Schmitt *et al.*, 1967) and methyldopa was shown to act centrally by similar mechanisms (Henning, 1969; van Zwieten, 1975). The recognition of the role of central catecholamine neurones not only in cardiovascular control but also in arousal, motor, neuroendocrine and other behavioural functions has been facilitated by the use of clonidine as a model compound in experimental and clinical studies.

A second development related directly to studies with clonidine was the heterogeneity and subclassification of α-adrenoceptors. It had been recognised that clonidine was not a classical α-adrenoceptor agonist and its effects not always blocked by classical α-adrenoceptor antagonists (Schmitt, Schmitt & Fenard, 1973). When the presynaptic α-receptor which exerted negative feed-back control of noradrenaline release from peripheral nerves was proposed (Starke, 1977; Langer, 1977), clonidine was found to be more effective at blocking transmitter release (presynaptic) than stimulating postsynaptic receptors (Starke, 1977). The order of agonist and antagonist potency for presynaptic receptors was similar to that for α-adrenoceptors mediated central hypotension and these two receptor types are believed to be very similar. However it is not certain that the central α-adrenoceptors are all presynaptically located and to avoid assumptions implicit in the terms pre- and postsynaptic, many workers prefer the classification α_1 and α_2 for classical postsynaptic and presynaptic or central hypotension respectively (Berthelsen & Pettinger, 1977). Further justification for this nomenclature derives from recent identification of α_2-adrenoceptors on platelets (Grant & Scrutton, 1979), cholinergic neurones in the myoenteric plexus of the gut (Starke & Docherty, 1980) and vascular smooth muscle (Drew & Whiting, 1979) for all of which the term presynaptic would be inappropriate. Table 1 summarises this classification and proposed locations of α-adrenoceptors.

Table 1 Proposed sites of α_2-adrenoceptors

Location	*Functional role*
Sympathetic nerve endings (presynaptic)	Negative feedback control of transmitter release
Brain stem and other areas of CNS (? pre- or post-synaptic or both)	Reduce efferent sympathetic outflow (and blood pressure) Reduce arousal and increase sedation Zerostomia
Platelets	Increase aggregatory responses
Vascular smooth muscle (postsynaptic)	Vasoconstriction
Cholinergic neurones of the enteric plexus of gut	Inhibit acetylcholine release and contractile response

Developments in catecholamine receptor pharmacology using classical methods and newer radioligand binding techniques indicate that clonidine although a relatively selective α_2-adrenoceptor agonist also has some α_1-adrenoceptor agonist activity (Doxey, 1979). There are analogues which have substantially more (and some with less) α_2-receptor specificity and it is not yet clear whether these compounds could have greater clinical usefulness than clonidine.

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There had been interest in centrally acting drugs at the Royal Postgraduate Medical School for over 12 years. While we, and others, had confirmed the therapeutic efficacy of clonidine in essential hypertension alone or in combination with diuretics (Connolly *et al.*, 1972) we were not satisfied that the drug was being used optimally in practice. Several patients failed to respond and others showed apparent acquired resistance to high doses. Side effects were common but their relationship to dose, duration of treatment and to hypotensive effect was not clear. In particular there were few clinical pharmacological studies carefully quantifying dynamic drug effects and no clinical pharmacokinetic studies. Progress in analytical technology permitted the development of a stable isotope dilution method of analysis utilizing gas chromatography – mass spectrometry (G.C.M.S.) to measure the very low concentration of clonidine in plasma (Draffan *et al.*, 1975; Dollery *et al.*, 1976). The development of the assay and the availability of clonidine, a re-evaluation of the clinical use of clonidine and an assessment of the therapeutic potential of several analogues. In this review the clinical pharmacokinetics and pharmacodynamics together with concentration effect relationship of clonidine are discussed and compared with other agents now available.

Clinical pharmacokinetics of clonidine

The physiological disposition of clonidine has been studied in normal volunteers (Davies *et al.*, 1977) and hypertensive patients (Wing *et al.*, 1977a) using the stable isotope dilution assay described by Draffan *et al.* (1975). The method utilises a deuterium labelled analogue of clonidine as internal standard. The assay is specific and sensitive but expensive and time consuming. More recently the pharmacokinetic results and conclusions have been confirmed using radioimmunoassay techniques (Arndts, Stahle & Struck, 1979).

Table 2 Summary of clinical pharmacokinetics of clonidine

(a) *Intravenous clonidine*

	Mean	Range
$T_{1/2}\alpha$ (min)	10.8	2.2–28.7
$T_{1/2}\beta$ (h)	8.5	6.9–11.1
Volume of distribution at steady state (l/kg)	2.09	1.70–2.79
Clearance (ml min^{-1} kg^{-1})	3.05	1.87–4.74

(b) *Oral clonidine*

	Mean	Range
$T_{1/2}$ (h)	8.6	5.2–13.0
Bioavailability (%)	75.2	70.6–81.5

(from Davies *et al.*, 1977)

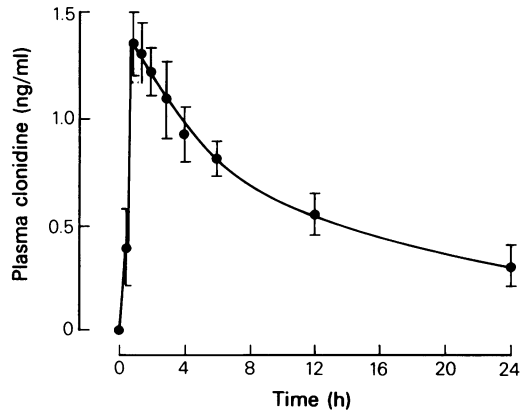

Figure 1 Mean ± s.e. mean plasma concentration of clonidine in five subjects after an oral dose of 300 μg clonidine hydrochloride.
(reprinted from *Clin. Pharmac. Ther.*, **21**, 593–601, 1977).

Clonidine is rapidly and almost completely absorbed after oral dosing. Peak plasma levels after 300 μg were 1–2 ng/ml and occurred 60–90 min after dosing. The terminal plasma half-life ranged from 6–12 h. Studies with intravenous drug administration confirmed the terminal half-life and indicated an oral bioavailability of over 80%. Pharmacokinetic parameters are summarised in Table 2 and the results of a representative subject are shown in Figure 1. Kinetics following i.v. administration could be adequately described by a two compartment open model. The total body clearance of clonidine was made up of a renal contribution (as unchanged drug in the urine) and a non-renal component predominantly resulting from metabolism. Renal clearance in some subjects exceeded the glomerular filtration rate as measured by creatinine clearance suggesting that in addition to filtration, tubular secretion of clonidine might occur.

In studies in which clonidine was administered chronically there was no evidence that the disposition changed with prolonged treatment (Wing *et al.*, 1977a). In a study during withdrawal of the drug after 6 months–5 years treatment, there were no striking differences in drug disposition and half-life in particular when the half-life after first dose was compared with decline after the last dose. Furthermore in studies over a range of doses 75 μg to 6.4 mg daily there has been no indication of dose dependent pharmacokinetics (Reid *et al.*, 1977a). There is

no evidence that poor clinical responses to clonidine are consequent upon genetic or acquired differences in drug disposition but rather that resistance to clonidine must depend on insensitivity or reduced responses to stimulation of central α-adrenoceptors and/or presence of counter-acting peripheral mechanisms, as will be discussed later.

There is less information available on the pharmacokinetics of other imidazoline derivatives. Tiamenidine has a similar half life to clonidine but guanfacine has a longer half life ranging from 15 to over 30 h (Zamboulis & Reid, 1981). The relevance of these kinetic differences remains to be established and can only be fully explored when the time course of dynamic effects is also considered.

Clinical pharmacodynamics of clonidine

Clonidine lowers blood pressure, both systolic and diastolic in the erect and supine posture. We have observed significant falls in pressure not only in essential hypertensives but also in normal subjects (Figure 2) (Wing *et al.*, 1977a). The fall in pressure which is usually accompanied by a modest bradycardia appears to result from a fall in peripheral resistance and an additional but variable fall in cardiac output (Muir, Burton & Lawrie, 1969; Barnett & Cantor, 1968).

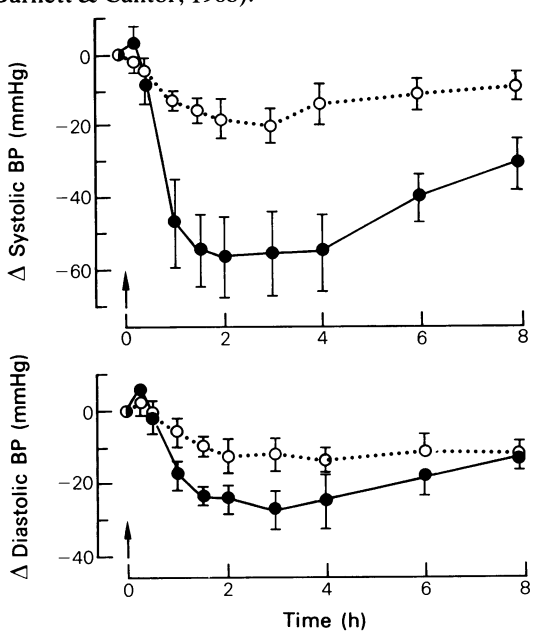

Figure 2 Changes in systolic and diastolic blood pressure (mean ± s.e. mean) in five normotensive subjects (O - - - - O) and in five essential hypertensives (● —— ●) after 300 μg of oral clonidine hydrochloride. (reprinted from *Eur. J. clin. Pharmac.*, **12**, 463–469, 1977).

After 300 μg orally, the fall in blood pressure is apparent by 1 h, maximal between 2 and 4 h and recovery takes place over 8–12 h. The fall in blood pressure after intravenous clonidine 300 μg was of similar magnitude and although the pressure fell within minutes of dosing the maximum fall was not observed for 1–2 h (Davies *et al.*, 1977). Plasma noradrenaline and urinary total metanephrines both fall after clonidine (Hokfelt, Hedeland & Hansson, 1975; Wing *et al.*, 1977b). These observations support the conclusions of animal experiments that clonidine lowers blood pressure by reducing sympathetic nervous activity. A central sympatho-inhibitory site gains further credibility from studies in which clonidine did not lower resting blood pressure in patients with high cervical spinal cord transection and tetraplegia (Reid *et al.*, 1977c) although these subjects had similar plasma clonidine levels to neurologically intact controls. Further studies in tetraplegics, however, indicate that clonidine can exert peripheral, possibly presynaptic modulatory, effects in man as the drug reduced both the blood pressure rise and the increase in plasma noradrenaline produced after vigorous bladder percussion or distension by a spiral reflex pathway (Mathias *et al.*, 1979). In studies in patients with orthostatic hypotension the hypotensive effect of clonidine was not present in a patient with idiopathic postural hypotension, noradrenaline supersensitivity and presumed peripheral sympathetic degeneration (Reid, Tangri & Wing, 1977b). However, in a patient with postural hypotension secondary to amyloidosis with involvement of afferent baroreceptor neurones and intact central and efferent pathways, clonidine lowered blood pressure, as the central effector mechanism were still functioning. In phaeochromocytoma where increased plasma catecholamine levels (and blood pressure) were being maintained by autonomous output from an adrenal medullary tumour, neither catecholamines or blood pressure fell (Reid *et al.*, 1980b).

In addition to haemodynamic changes, the other prominant effects of clonidine in man are dry mouth and sedation or drowsiness. Both are common dose limiting side effects in practice. After 300 μg of clonidine dry mouth is a frequent spontaneous complaint which may be severe enough to impair articulation. Using a simple method with preweighed cotton rolls placed in the mouth for fixed times we have measured the resting saliva production after clonidine. There is a profound reduction to 15–20% of precontrol by 2–3 h which persists for 8–12 h (Dollery *et al.*, 1976). The time profile of sedation is similar. The sedated subjects frequently distinguish this sedation from true sleepiness as in the former they are in a 'twilight' state and can relatively easily pass from 'sleep' to wakefulness. Sedation has been quantified using self rating analogue scales and also EEG monitoring systems (Dollery *et al.*, 1976; Wing

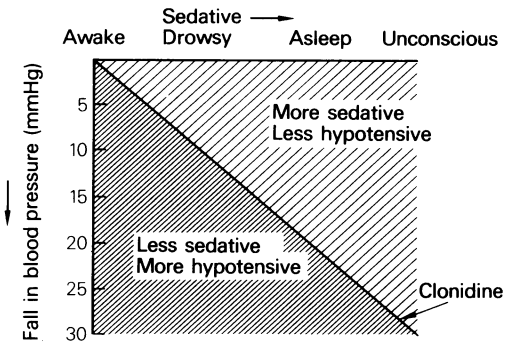

Figure 3 Schematic diagram of relative hypotensive and sedative properties of centrally acting drugs.

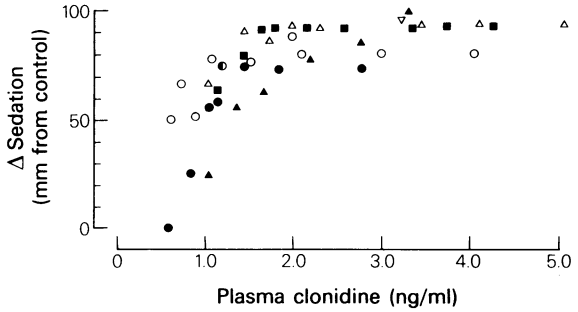

Figure 4 The relationship between the sedative effect of clonidine (measured by self assessment visual analogue rating) and the plasma level of clonidine in normal subjects.
(reprinted from *Clin. Pharmac. Ther.*, **21**, 593–601, 1977).

et al., 1977a; Maling, Dollery & Hamilton, 1979). All imidazolidines examined have had some sedative properties when single doses were examined in normal volunteers. Unfortunately it does not appear that any compound possesses substantially greater hypotensive efficacy without causing increased sedation (Figure 3). The separation of sedative and hypotensive action remains an attractive goal in the development of centrally acting drugs. It has not been convincingly achieved with currently available drugs. Guanfacine which has a substantially longer duration of hypotensive action than clonidine with recovery after 24–36 h rather than 8–12 h for equi-hypotensive doses also causes sedation and prolonged dry mouth (Dollery & Davies, 1980; Reid, Zamboulis & Hamilton, 1980c). Reports that guanfacine caused less sedative-like effects in anmials (Kleinlogel, Scholtysik & Sayers, 1975) has not been universal experience in man (Dollery & Davies, 1980).

Concentration-effect relationships

As the symptom side effects of sedation and dry mouth are frequently dose limiting it is of relevance to consider the relationship between plasma clonidine concentration and intensity of side effect. In both hypertensives (Wing *et al.*, 1977a) and normal subjects (Davies *et al.*, 1977) there is a close relationship between the intensity of sedation and plasma drug concentration (Figure 4) at levels up to 1.5–2.0 ng/ml. At higher concentrations the maximal degree of sedation persisted. A similar relationship over a similar range of drug levels was observed for saliva production and thus dry mouth.

In a study of concentration effect relationships before and after 1 week's treatment there was some indication that the concentration effect relationship for dry mouth was shifted to the right after treatment thus reducing the intensity of side effect for a given plasma level (Wing *et al.*, 1977a). This is objective support for the clinical observation of some tolerance to the side effects of clonidine.

When the hypotensive effect was examined the relationship appeared qualitatively different in both normal subjects (Figure 5) and hypertensives (Figure 6). At lower plasma levels a similar relationship to that seen for side effects was found. However at the highest levels there was a loss of effect with apparent

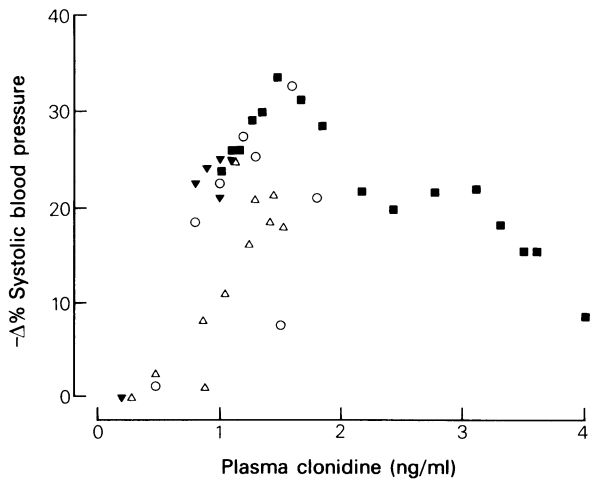

Figure 5 The relationship between hypotensive effect and plasma clonidine concentration in a normotensive subject (M. 35 years) studied on several occasions after oral and intravenous clonidine.
(reprinted from *Clin. Pharmac. Ther.*, **21**, 593–601, 1977).

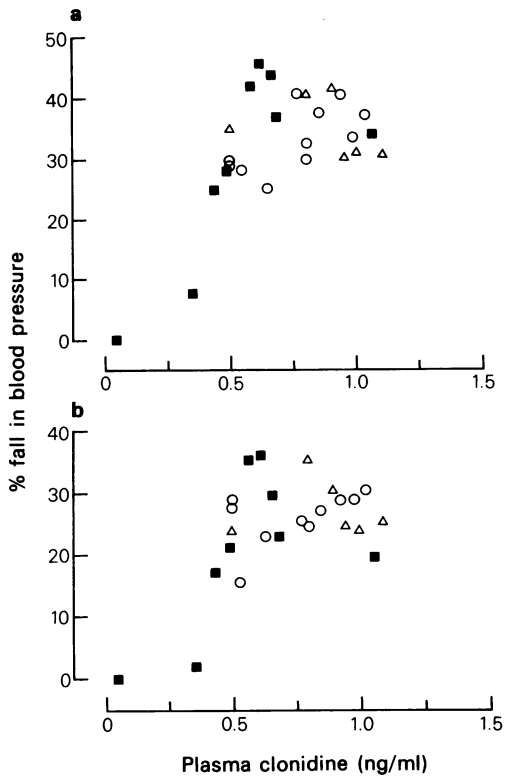

Figure 6 Relationship between plasma clonidine concentration and percentage change in systolic blood pressure (a) and diastolic blood pressure (b) in a patient with essential hypertension during single dose (■), multiple oral dosing (○) and after the last dose (△).
(reprinted from *Eur. J. clin. Pharmac.*, **12**, 463–469, 1977).

reversal of the hypotensive effect. Maximum fall in blood pressure occurred at plasma levels between 0.5 and 2.0 ng/ml and this optimal plasma level varied somewhat between individuals.

Thus there appeared to be a narrow therapeutic window of optimum effect of clonidine; very low levels having little effect on blood pressure and very high levels also having little effect. When the concentration effect relationships for blood pressure fall and side effects are examined together, the limits of the therapeutic range are further apparent. These observations have been confirmed by other groups in animals and man (Frisk Holmberg, Edlund & Paalzow, 1978; Frisk Holmberg & Paalzow, 1979). There are few published studies with other imidazolidine derivatives of the concentration effect relationship. However, sedation has been observed during clinical trials in the dose range required to lower blood pressure. In acute studies with guanfacine, the magnitude of the fall in blood pressure and the intensity of sedation were similar to those for clonidine (Dollery & Davies, 1980). In Figure 3 the relationship has been represented diagrammatically. If a centrally acting antihypertensive lowered pressure without sedation it would undoubtedly be of clinical interest. Unfortunately at present, no available drugs have been conclusively shown to possess such selectivity.

Concentration hypotensive effect studies (Figures 5 and 6) suggest that at high plasma levels hypotensive effect is lost and may even be reversed. What is the mechanism and clinical relevance of these observations? Clonidine given by rapid intravenous injection to animals (van Zwieten, 1975) and man (Mroczek, Davidov & Finnerty, 1973) causes a transient hypertensive effect by direct stimulation of peripheral vascular α-adrenoceptors either via a partial agonist action on α_1-receptors (Doxey, 1979) or by stimulation of putative postsynaptic α_2-receptors (Drew & Whiting, 1979). This effect occurs at higher plasma levels than those responsible for the centrally mediated hypotensive effect. The latter usually predominates at lower plasma concentration. Animal studies confirm the shape of the concentration effect relationship (Reid, Barber & Davies, 1980a). Clinical support for a loss or reversal of hypotensive effect comes indirectly from a patient who took clonidine in large amounts in a self poisoning attempt (Hunyor *et al.*, 1975). Hypertension preceded later falls in blood

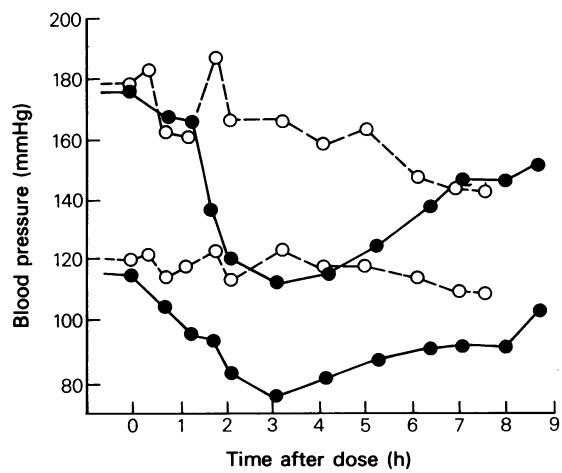

Figure 7 Systolic and diastolic blood pressure in a 51 year old woman with essential hypertension after 1.8 mg of clonidine at time 0 h (long term high dose clonidine) (○ - - - - ○) and on a further occasion 8 months after stopping clonidine after a single dose of 0.3 mg orally (● —— ●).
(reprinted from *Br. med. J.*, **1**, 136–138, 1977).

pressure. Intensive study of two patients who were apparently resistant to very large doses of clonidine (and other drugs) lends support to the concept of a narrow optimal range of dose (Wing *et al.*, 1977c). While taking clonidine 5.4 mg daily in divided doses plasma clonidine levels exceeded 20 ng/ml and blood pressure was not affected (Figure 7). Re-examination several months after clonidine had been withdrawn confirmed that clonidine 0.3 mg which raised plasma levels to 1–2 ng/ml was accompanied by substantial falls in pressure similar to other hypertensive patients. Clearly peripheral and central pharamcodynamic mechanisms are only part of the explanation of unusual responses to high doses of clonidine. Some degree of 'tolerance' to the central sedative effect must also occur mediated by as yet unidentified mechanisms.

In view of the evidence for an optimal range of therapeutic response and the possibility of loss or reversal of effect at high plasma levels it is reasonable to limit the daily dose of clonidine to 1.2 mg daily or less. Little advantage is to be expected at higher doses where side effects will be prominent, antihypertensive effect may be reduced and the risk of withdrawal hypertension or symptoms increased.

Withdrawal hypertension

Soon after the introduction of clonidine into clinical practice it was recognized that abrupt withdrawal of drug treatment was associated with symptoms of increased sympathetic activity, rapid return of blood pressure to pretreatment levels and in some patients overshoot or rebound above these levels (Hunyor *et al.*, 1973). Although the frequency of withdrawal hyptertension is controversial there is good evidence that interruption of long term clonidine treatment in patients with hypertension is associated in a considerable number of patients with biochemical evidence in plasma and urine of sympathetic overactivity (Hokfelt *et al.*, 1975; Reid *et al.*, 1977a; Geyskes, Boer & Dorhout-Mees, 1979). Headache, anxiety, palpitation, insomnia, tremor and nausea may occur. These symptoms and withdrawal hypertension are more common in patients on long term (more than 3 months), high doses of clonidine, other drug therapy (particularly β-adrenoceptor blockers) and previously severe hypertension. Reversal of hypotension and withdrawal symptoms may occur within 12–18 h of the last dose of clonidine and severe symptoms and hypertension may occur after only a brief interruption of therapy. This presents problems for patients with intercurrent illness and particularly for those who follow medical instructions only erratically (poor compliers). Withdrawal hypertension may last for up to 7–10 days and can still occur when clonidine is reduced in a gradual manner. Withdrawal of clonidine treatment should be undertaken under careful supervision. The mechanism of the withdrawal syndrome has not been established. In general terms it appears likely that on long term treatment functional changes in α_2-adrenoceptors in the brain and possibly the periphery occur. The time of offset or reversal of these changes is slower (days) than the decline of clonidine levels after stopping drug therapy (hours). Thus for several days there is a disturbance of regulation of the sympathetic nervous system. There is no good evidence that a similar symptom complex with rapid reversal of hypotensive effect regularly follows withdrawal of other drug groups particularly diuretics or vasodilators. The consequences of β-adrenoceptor blocker withdrawal also appear to include long term regulatory changes in receptors, but blood pressure does not rise rapidly and symptoms are not frequently encountered in hypertensives.

Withdrawal symptoms, hypertension and increased sympathetic activity have been reported after withdrawal of clonidine analogues. Tiámenidine withdrawal in two separate studies caused similar features to those reported after clonidine (Campbell *et al.*, 1980; Hansson & Hokfelt, 1981). Guanfacine which as noted earlier has a longer plasma half-life and duration of action after single doses, had a slower offset of action on withdrawal and less subjective symptoms. However, guanfacine has also been reported to cause withdrawal hypertension (Jerie, 1980) and 3–4 days after withdrawal plasma noradrenaline was significantly higher than pretreatment levels (Zamboulis & Reid, 1981). These latter results suggest that while withdrawal symptoms may be a general feature of centrally acting drugs, differences in drug disposition and especially prolongation of drug action may modify the intensity and severity of these effects. It is possible that the infrequency of reports of withdrawal hypertension after methyldopa withdrawal is a result of a very long offset of drug action and replacement of α-methylated monoamines and metabolites in brain neurones.

Conclusions

Study of the pharmacological actions of clonidine and related drugs have greatly contributed to understanding of central cardiovascular regulation and adrenoceptor function. Clinical pharmacological studies with these agents have extended the relevance of such observations to man and in addition 'identified a potentially useful therapeutic mechanism in the treatment of hypertension.' Clinical pharmacological studies have improved the usage of these drugs and clearly identified directions for future development.

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