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The interaction between clonidine and various neuroleptic agents and some benzodiazepine tranquillizers*

P. A. VAN ZWIETEN†

Department of Pharmacy, Division of Pharmacotherapy, University of Amsterdam, Plantage Muidergracht 24, Amsterdam-C, The Netherlands

The central hypotensive action of clonidine, infused into the vertebral artery of chloralose-anaesthetized cats was antagonized by several phenothiazine-neuroleptics (chlorpromazine, promazine, promethazine, thiethylperazine, thioridazine), by chlorprothixene and to a limited extent by haloperidol administered via the same route. Pimozide and some benzodiazepines (chlordiazepoxide, diazepam and flurazepam) hardly influenced the central hypotensive response to clonidine. The antagonism between clonidine and the psychotropic drugs is probably associated with central α-adrenoceptors, clonidine being the agonist and the neuroleptic agents the antagonists at these receptors. Virtually the same type of antagonism was observed in conscious, spontaneously hypertensive rats where both clonidine and the neuroleptic drugs were injected intravenously. The phenothiazines and also piperoxane effectively diminished the centrally induced hypotensive response to clonidine, whereas the initial pressor effect to clonidine was not reduced.

The therapeutic effect of several antihypertensive agents is significantly diminished by various tricyclic antidepressants. The dimunition of the effect of guanethidine by amitriptyline (Meyer, McAllister & Goldberg, 1970) is attributed to the cocaine-like activity of the tricyclic antidepressant, which induces an impaired accessability of guanethidine to postganglionic sympathetic neurons.

The impairment of the therapeutic effect of centrally acting antihypertensive drugs like clonidine and α-methyldopa by tricyclic antidepressants has been reported (Briant & Reid, 1972; Briant, Reid & Dollery, 1973; Schmitt, Schmitt & Fénard, 1973; van Spanning & van Zwieten, 1973, 1975; van Zwieten, 1975a,b; 1976, 1977), both under clinical conditions and also in animals. This process of interaction has been shown to occur at the central α-adrenoceptors, presumed to be involved in the hypotensive effect of clonidine and α-methyldopa.

The antagonism of central α-adrenoceptors is probably competitive, clonidine and α-methylnoradrenaline (from α-methyldopa) being the agonists and the tricyclic antidepressants the α-receptor antagonists (van Zwieten, 1975a, 1976, 1977). It seems likely that the cocaine-like component of most tricyclic antidepressants is not involved (van Zwieten, 1976, 1977).

Little is known about the influence of neuroleptic agents of various categories on the hypotensive effect of antihypertensive drugs. Janowsky, El-yousef & others (1972) showed that chlorpromazine reduces the hypotensive effect of guanethidine. Since neuroleptics of the phenothiazine-type are usually potent α-sympatholytic agents (Takanayagi, 1964) neuroleptic drugs of this kind might be expected to diminish the central hypotensive effect of clonidine. Animal experiments now described demonstrate such an antagonism, which fits in with the hypothesis on central α-adrenoceptors. Clinically, such an antagonism remains to be investigated.

MATERIALS AND METHODS

Methods

Chloralose-anaesthetized cats. Cats of either sex (2–4 kg), anaesthetized with an intraperitoneal injection of α-glucochloralose (60 mg kg^{-1}) and artificially respirated via a tracheal cannula connected to a pump (Braun Melsungen), were thoracotomized on the left and the left subclavian artery was cannulated. The catheter tip was placed just distal from the ostium of the left vertebral artery and all other side-branches of the subclavian artery were ligated, thus allowing the administration of drug into the vertebral artery where it rapidly reaches

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the ponto-medullary area in the brain (for details see Bock & van Zwieten, 1971; van Zwieten, 1975b).

Blood pressure was taken from a cannulated femoral artery and recorded via a Statham transducer and a Hellige HE 86 amplifier and recorded. If necessary the pulse rate was established at high speed of the recording paper. A catheter was also inserted into a femoral vein to administer heparin (5000 I.U. per animal). In most experiments the neuroleptic drugs were infused into the left vertebral artery and their effect on blood pressure was recorded. After the development of a new steady state, clonidine was injected via the same route. The mean arterial pressure of all the cats before any drug treatment but after surgical intervention amounted to 127·6 ± 2·6 mm Hg (n = 105).

Spontaneously hypertensive rats. Male spontaneously, hypertensive rats (strain: SHR-NIH/Cp6, TNO, Zeist, The Netherlands; 180–250 g) kept on a standardized diet of Muracon I pellets, and with free access to water were anaesthetized with hexobarbitone sodium (150 mg kg^{-1}, i.p.) and a catheter inserted into the left jugular vein. A second catheter introduced into the left common carotid artery had its other end exteriorized through the neck muscles and the skin of the back and this end was attached to a blood pressure transducer and recorder. Both catheters were filled with a solution of 100 I.U. of heparin ml^{-1}. After the surgical intervention the conscious animals were allowed to recover for 2½ h before the neuroleptic agent to be tested was injected into the jugular vein. The mean arterial pressure of all the conscious SHR-rats just before drug treatment was 140·5 ± 2·0 mm Hg (n = 75).

Drugs used

α-Glucochloralose (E. Merck A.G., Darmstadt); hexobarbitone sodium (Evipan, Bayer, Leverkusen); clonidine hydrochloride (C.H. Boehringer Sohn, Ingelheim am Rhein); chlorpromazine hydrochloride (Spécia, Paris); chlorprothixene hydrochloride (Hoffmann La Roche A.G., Basel); promazine hydrochloride (Wyeth, U.S.A.); promethazine hydrochloride (Bayer A.G., Leverkusen); thiethylperazine hydrogenmalate (Sandoz A.G., Basel); haloperidol and pimozide (Janssen Research Foundation, Beerse, Belgium); chlordiazepoxide, diazepam (Valium amp.) and flurazepam (Hoffmann La Roche, Basel); (±)-piperoxane hydrochloride (kindly put at our disposal by Prof. Dr H. Schmitt, Paris).

Drug dosage was expressed in terms of the salts. All the drugs were dissolved in saline, with the following exceptions: pimozide (0·01M tartaric acid); diazepam (Valium, amp.); haloperidol (Serenase, amp.). Where control experiments were made with the vehicles, these were shown to be devoid of pharmacological activity.

RESULTS

Chloralose-anaesthetized cats

Clonidine (1 μg kg^{-1}) injected into the left vertebral artery in control experiments showed the well-known, pronounced hypotensive effect (Fig. 1) (Sattler & van Zwieten, 1967). Heart rate fell by about 13% of its original value.

Most phenothiazine neuroleptics were injected in a dose range of 30–300 μg kg^{-1} into the left vertebral artery and caused a modest fall in mean arterial pressure (Fig. 1); the decrease brought

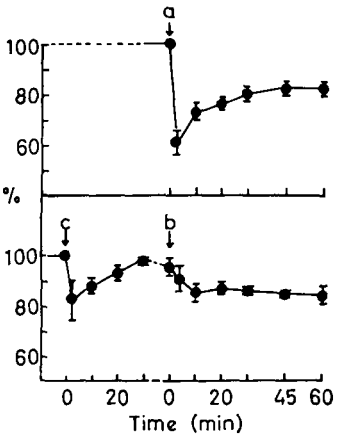

FIG. 1. Hypotensive effect of a–clonidine (1 μg kg^{-1}) alone (top) and that of b–clonidine after pretreatment with c–thioridazine 300 μg kg^{-1} (below). Both clonidine and thioridazine were infused into the left vertebral artery of chloralose-anaesthetized cats. Mean values for at least 6 different cats (± s.e.m.). Note the transient hypotensive effect of thioridazine itself and the diminished hypotensive response to clonidine after pretreatment with clonidine. Ordinate—Blood pressure (% of initial value).

about by thioridazine was transient and reversible. Table 1 summarizes the mean decrease in blood pressure caused by the various neuroleptics and tranquillizers. The new steady state of blood pressure was usually achieved within 10 min after drug administration. The blood pressure values in this new steady state are also listed in Table 1. A similar pattern was seen after injection of haloperidol (300 μg kg^{-1}), a well-known butyrophenone neuro-

Table 1. *Influence of neuroleptic agents and tranquillizers, infused into the left vertebral artery of chloralose-anaesthetized cats, before administration of clonidine (1 μg kg⁻¹) via the same route.* The maximal depressor effect, the new steady state of blood pressure after recovery from pretreatment and the established hypotensive effect of clonidine have been related to the initial mean arterial pressure (=100%) observed before any drug treatment had taken place. The data presented are means ±s.e.m. The relative decrease in pressure, related to the new steady state is shown as well. Details see text.

					Clonidine (10 μg kg⁻¹)	
Neuroleptic or benzodiazepine (pretreatment)	dose μg kg⁻¹	Max. depressor effect of psychotropic drug; residual pressure in % of initial value	n	New steady state of blood pressure; % of initial value	Residual pressure, (% of initial value)	Relative decrease in pressure, based on the new steady state
None (controls)	—	—	9	100	60·8 ± 4·7	−39·2
Chlorpromazine	30	81·7 ± 2·5	7	83·3 ± 1·5	64·8 ± 3·6	−13·8
Chlorpromazine	100	59·7 ± 3·0	12	77·6 ± 4·6	64·8 ± 5·8	−16·5
Chlorpromazine	300	55·3 ± 3·1	7	58·5 ± 3·1	72·4 ± 4·4	+23·8
Chlorprothixene	300	47·8 ± 2·0	4	58·2 ± 5·1	52·9 ± 5·1	− 9·1
Promazine	100	73·6 ± 5·9	8	79·8 ± 3·2	66·9 ± 5·7	−16·3
Promethazine	300	83·5 ± 4·3	7	90·3 ± 2·6	79·0 ± 5·1	−11·85
Thiethylperazine	300	65·4 ± 9·9	6	86·7 ± 5·5	74·3 ± 4·8	−14·3
Thioridazine	300	82·5 ± 8·0	4	96·2 ± 3·4	91·4 ± 5·3	− 4·8
Haloperidol	300	74·2 ± 5·4	8	85·4 ± 3·8	61·9 ± 6·8	−27·5
Pimozide	100	101·0 ± 2·6	9	102·3 ± 6·5	69·1 ± 4·7	−32·5
Chlordiazepoxide	30	88·5 ± 5·7	7	94·8 ± 3·5	56·8 ± 5·8	−40·0
Chlordiazepoxide	300	66·2 ± 8·8	5	86·0 ± 3·9	64·9 ± 7·3	−22·35
Flurazepam	300	62·7 ± 5·4	4	79·2 ± 11·9	54·8 ± 5·4	−30·8

leptic, into the vertebral artery. Pimozide (100 to 300 μg kg⁻¹), a long acting neuroleptic agent distantly related to the butyrophenones, did not cause any significant change in blood pressure when injected via the same route. Chlordiazepoxide and flurazepam also decreased arterial pressure when administered via the vertebral artery route. None of the neuroleptics or benzodiazepines thus applied caused any significant alteration of cardiac frequency.

Clonidine (1 μg kg⁻¹) was injected 30–40 min after blood pressure had achieved a new steady state following the administration of the neuroleptic agents. All the phenothiazines administered before clonidine diminished the hypotensive response to clonidine (1 μg kg⁻¹) (Fig. 1). Table 1 contains the values obtained for the decrease in blood pressure brought about by clonidine in pretreated cats. Chlorpromazine (300 μg kg⁻¹) itself caused a more pronounced hypotensive action than the other phenothiazines and was therefore studied at lower doses; even at 30 μg kg⁻¹ it diminished the response to clonidine (1 μg kg⁻¹) significantly and the antagonism was more obvious after 100 μg kg⁻¹. After a preceding injection of chlorpromazine 300 μg kg⁻¹, clonidine even caused a small increase in pressure (Table 1) but at this dose the depressor effect is strong, so that clonidine was injected at a low level of blood pressure. Haloperidol is a weak antagonist of the central hypotensive effect of clonidine while pimozide (100–300 μg kg⁻¹) did not diminish the response to clonidine significantly. Chlordiazepoxide (300 μg kg⁻¹) exerted a weak inhibitory effect on the central hypotensive effect of clonidine but at 30 μg kg⁻¹ it had no influence on the clonidine effect. Flurazepam (300 μg kg⁻¹), more a hypnotic agent than a tranquillizer, only slightly diminished the response to clonidine.

In cats pretreated with diazepam 3 mg kg⁻¹, solutions (i.p.) once daily for three consecutive days and which were given clonidine (1 μg kg⁻¹) via the left vertebral artery about 5 h after the last injection of diazepam, the residual blood pressure at the moment of maximal response to clonidine amounted to 63·3 ± 7·1% (mean ± s.e.m., n = 4) of the initial value (100% = 132·5 ± 13·1 mm Hg, n = 4). Thus, the hypotensive response to clonidine was not significantly changed by pretreatment for three days with high doses of diazepam. The

recovery of blood pressure towards normal values was the same as in cats that had not been pretreated with diazepam.

Spontaneously hypertensive rats

Clonidine upon intravenous injection into conscious, spontaneously hypertensive rats caused the well-known biphasic response on blood pressure; an initial, transient pressor effect was followed by a pronounced and longer lasting hypotension, which is probably due to a central mechanism. A higher dose (10 μg kg^{-1}) of clonidine than for cats was required to induce a significant and reproducible response.

All the neuroleptics decreased blood pressure upon intravenous injection. In most cases the hypotensive effect was maximal within 5 min after injection but reversible within 20–30 min. The maximal decreases in pressure for the various psychotropic drugs have been summarized in Table 2. Clonidine (10 μg kg^{-1}) was injected intravenously 30 min after administration of the neuroleptic agents. Its maximal pressor and subsequent depressor effects after pretreatment were recorded and evaluated separately. The results are listed in Table 2.

In view of the many experiments required, most studies were limited to a single dose of psychotropic drug, with the exceptions of chlorpromazine and haloperidol, which were studied in two different doses. Most neuroleptics caused a moderate though significant decrease of the hypotensive effect of clonidine, whereas the initial pressor effect was not greatly affected by the relatively low doses of the neuroleptics. In several cases it remained unchanged (Table 2).

Some degree of blockade of clonidine's hypotensive effect was observed after pretreatment with thioridazine. The effect of chlorpromazine proved dose-dependent, since 1 mg kg^{-1} was more effective in blocking clonidine's effect than 300 μg kg^{-1}. Thiethylperazine did not diminish the hypotensive response to clonidine. Haloperidol (1 or 5 mg kg^{-1}) caused a dose-dependent reduction of clonidine's hypotensive effect. A high dose of pimozide (1 mg kg^{-1}) proved only moderately effective in diminishing the depressor effect of clonidine. Pretreatment with a single intravenous injection of diazepam in high dosage (5 mg kg^{-1}) did not reduce the hypotensive response to subsequently administered clonidine.

For reasons explained in the Discussion, piperoxane, an α-sympatholytic agent devoid of neuroleptic activity, was included in our studies. In moderate doses of 300 and 1000 μg kg^{-1}, it significantly decreased the hypotensive effect of clonidine. The initial hypertensive effect of clonidine was not diminished but somewhat enhanced.

Table 2. *Influence of neuroleptic drugs, diazepam and piperoxane on the pressor and depressor effects of clonidine (10 μg kg^{-1}) in conscious, spontaneously hypertensive rats.* All drugs were administered intravenously. Evaluation of the results is as in the legend to Table 1. Details see text.

Preatreatment with	dose (μg kg^{-1})	n	Max. depressor effect of psychotropic drug (or piperoxane); residual pressure in % of initial value	New steady state of blood pressure; % of initial value	Clonidine (10 μg kg^{-1}) Pressor effect: B.P. (% of init. val.)	Pressor effect: Relative increase in pressure (%)	Depressor effect: B.P. (% of init. val.)	Depressor effect: Relative decrease in pressure
None (controls)	—	10	—	100	121·4 ± 6·7	+21·4	78·0 ± 3·1	−22·0
Chlorpromazine	300	4	79·1 ± 3·5	87·0 ± 3·5	102·4 ± 4·8	+17·7	78·0 ± 3·9	−10·0
Chlorpromazine	1000	8	68·1 ± 3·9	73·7 ± 3·4	88·7 ± 2·5	+20·4	73·3 ± 4·1	−0·5
Thiethylperazine	1000	5	91·7 ± 7·9	99·3 ± 3·8	111·2 ± 4·2	+11·95	79·4 ± 4·7	−20·0
Thioridazine	1000	6	92·3 ± 2·5	98·0 ± 2·9	105·9 ±2·2	+8·0	84·9 ± 2·0	−13·3
Haloperidol	1000	5	89·8 ± 2·6	99·5 ± 1·3	120·1 ± 6·5	+21·7	90·8 ± 2·4	−7·7
Haloperidol	5000	5	68·0 ± 7·7	89·2 ± 1·9	97·1 ± 3·2	+8·0	86·7 ± 1·9	−2·8
Pimozide	1000	7	73·9 ± 2·8	84·6 ± 6·3	119·3 ± 4·6	+29·2	75·5 ± 3·7	−10·7
Piperoxane	300	6	94·7 ± 1·8	100·7 ± 1·9	128·4 ± 1·8	+27·6	86·8 ± 2·2	−13·8
Piperoxane	1000	6	86·0 ± 2·9	96·0 ± 2·3	111·4 ± 6·1	+16·1	87·3 ± 2·1	−9·0
Diazepam	5000	4	91·8 ± 3·0	105·1 ± 3·4	128·3 ± 7·7	+22·0	77·6 ± 3·6	−26·1

DISCUSSION

The present studies indicate that in two species the hypotensive response to clonidine is moderated by various phenothiazine neuroleptics, by chlorprothixene and by haloperidol. In some instances the psychotropic drugs themselves caused a hypotensive effect. The hypotensive action of chlorpromazine, other phenothiazines and haloperidol has been attributed to peripheral α-sympatholytic blockade rather than to a central mechanism (van Zwieten, 1975c).

The antagonism between clonidine and the neuroleptics probably occurs in the central nervous system, more precisely in the ponto-medullary region since this is the area perfused when drugs are injected into the vertebral artery of cats (Reneman, Wellens & others, 1974). The site of clonidine's hypotensive effect is generally believed to be located in the brain stem (see reviews by van Zwieten, 1975b; Dollery, Davies & others, 1976).

In earlier studies (van Zwieten, 1975a) pretreatment with cocaine (vertebral artery infusion) was found not to inhibit the central hypotensive effect of clonidine. Hence an antagonism where a reduced accessibility of peripheral or central sympathetic neurons for hypotensive drugs plays a part (like e.g. the diminished hypotensive response to guanethidine in the presence of tricyclic antidepressants or chlorpromazine; Meyer & others, 1970; Janowsky & others, 1972) can be ruled out. All phenothiazines and also chlorprothixene are potent α-sympatholytic drugs (Takanayagi, 1964), whereas haloperidol is less active as an α-blocking agent (Janssen, Niemegeers & others, 1968) and pimozide can not be called an α-sympatholytic agent (Janssen & others, 1968; Bloch, Bousquet & others, 1974). Benzodiazepine tranquillizers do not show α-sympatholytic activity. We therefore submit that the *α-adrenolytic activity* of the neuroleptics is the main reason why they antagonize the central hypotensive action of clonidine. Since atropine does not influence the hypotensive reaction to clonidine it seems most unlikely that the anticholinergic effect of the phenothiazine-neuroleptics is involved in the interaction process. Bloch & others (1974) showed that pimozide antagonizes the hypotensive effect of clonidine, applied topically to the ventral surface of the brain stem of anaesthetized cats. This antagonism was attributed to the dopamine-blocking properties of pimozide. However, various drugs which, like clonidine, possess local anaesthetic activity can diminish blood pressure when topically applied as described by Bloch & others (1974). In this case the antagonism is not specific.

Results similar to those found in cats were obtained in the conscious SHR-rat. In this model, haloperidol was a more effective antagonist of clonidine's hypotensive effect than in the cat, whereas thiethylperazine did not significantly block the clonidine-induced hypotension. The cause of this discrepancy is not known; it may be a matter of different doses, or species differences. In SHR-rats the initial pressor effect of clonidine was hardly or not diminished by the various psychotropic drugs nor by piperoxane. In some incidental experiments, however, tenfold higher doses of piperoxane and thioridazine completely blocked the initial, peripheral pressor effect of clonidine. This finding also points towards a central localization of the site of interaction. The clinical significance of the present findings remains to be demonstrated. However, the ratio of the dosage between psychotropic drugs and clonidine would not exclude clinical relevance of this process of drug interaction.

Acknowledgement

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