ADVERSE REACTIONS TO ANTIHYPERTENSIVE DRUG THERAPY: CENTRAL NERVOUS SYSTEM

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The introduction of reserpine and other extracts of Rauwolfia into antihypertensive treatment and the ensuing outbreak of reserpine-induced depressions made physicians painfully aware of central nervous side effects of antihypertensive agents. It should be noted that unwanted effects of this kind are frequently very difficult to anticipate from animal experiments and depend almost entirely on a careful clinical assessment. So far, surprisingly little quantitative information is available on this subject. It appears that a major reason why so little attention has been paid to this aspect in clinical trials is related to the inherent difficulties in separating central nervous symptoms, caused by pharmacological actions of the drugs concerned, from secondary reactions to other side effects, or to other factors, e.g. the effect of being diagnosed as a victim of a life-long disease with treatment according to this.

In attempting to classify central nervous side effects of antihypertensive agents several possibilities arise. The simple process of cataloguing the various drugs and their reported side effects has been avoided. It is clear that drugs interfering with central nervous system (CNS) neurotransmitter metabolism are liable to affect various systems utilizing such transmitters, and a classification might be accordingly based. However, in many instances the precise nature of the influence of antihypertensive drugs on central neurotransmitters is not known and therefore a more clinically oriented approach to classification of CNS side effects has been adopted, using the type of symptoms as a basis (Table I). No attempt has been made to cover the full panorama of CNS side effects as found in e.g. Physician's Desk Reference or package inserts. CNS reactions secondary to the lowering of blood pressure are considered elsewhere in this symposium. Whenever possible reference has primarily been made to papers of review character.

1. MENTAL CHANGES

A. Sedation

The term sedative effect is notoriously vague in its definition and is observed with most drugs including placebo. Sedation is also not easily defined in psychological terms and the physiological and pharmacological basis for a sedative action is obscure. Common clinical translations of sedation would appear to be drowsiness, weakness, feeling of lassitude, fatigue or sleepiness during the day. Symptoms such as decrease in ability to concentrate, forgetfulness and prolongation of reaction time are probably other representations of sedation.

As might be expected the patient's experience of this will vary considerably depending on mental set-up, activities etc. People engaged in intellectually demanding tasks will naturally suffer more from a sedative effect as will of course those employed in work requiring constant alertness and attention, e.g. operating complicated machinery or driving a car.

Table I. Central nervous side effects of antihypertensive drugs.

1.	Mental changes	
	A. Sedation	clonidine methyldopa reserpine ß-adrenergic receptor blockers
	B. Depression	reserpine methyldopa ß-adrenergic receptor blockers
2.	Sleep disturbances	ß-adrenergic receptor blockers clonidine reserpine
3.	Extrapyramidal symptoms	reserpine methyldopa
4.	Neuroendocrinological symptoms	reserpine methyldopa

The antihypertensive drugs most frequently reputed to affect such activities are nowadays no doubt methyldopa and clonidine, reserpine being less commonly employed (Tester-Dalderup 1975). The pharmacological basis for the sedative effect of these drugs is probably related to their interfering with central adrenergic neurone systems which are engaged in the regulation of wakefulness and alterness (Lidbrink 1974). The incidence of troublesome sedation in patients taking these drugs is dose-dependent but probably quite high, amounting in one careful survey to 51% for methyldopa (Dollery & Bulpitt 1975). With clonidine it appears to be even more common; Onesti et al. (1971) in a series of 90 patients on oral clonidine report sedation in 64%. Recent studies have indicated that the sedative action of methyldopa may be diminished without losing the antihypertensive effect by giving the drug as a single dose at bedtime (Wright et al. 1976). So far no reports are available on the possible influence of this procedure on sleep quality. A decrease in mental acuity, forgetfulness and prolongation of reaction time are other symptoms reported after methyldopa (Tester-Dalderup 1975). A number of experimental agents pharmacologically related to clonidine seem to share the sedative effect with this drug (see e.g. Jäätelä 1976).

Treatment with ß-receptor blocking drugs is almost invariably associated with a feeling of tiredness, drowsiness or lassitude. That these agents do exert a sedative action by a direct effect on the CNS is highly probable; the existence of central adrenergic receptors of the ß-type is by now fairly well established (see Conway et al. 1978) and these drugs are currently being tried in various neuro-psychiatric disorders including anxiety and similar symptoms (Symposium 1976). However, it is not known to what extent the peripheral effects of ß-blockade, e.g. lowering of cardiac output and blood pressure and alterations in tissue perfusion may contribute to cause what the patient experiences as a feeling of tiredness etc. Further, the sedative effect of ß-blocking drugs is considerably less troubling than for the drugs previously discussed and is usually of little concern compared to other central side effects (vide infra).

Out of other antihypertensive drugs reported to elicit sedative effects, diuretics (Dollery & Bulpitt 1975) and agents blocking peripheral sympathetic nerve function (e.g. ganglion blocking agents, guanethidine or betanidine) are occasionally mentioned. In these cases, sedation might be secondary to other actions of these drugs, e.g. electrolyte disturbances or orthostatic reactions.

Drug treatment associated with heavy sedation may secondarily lead to disturbances of male sexual functions. This seems to be the case with methyldopa and clonidine both of which, although not interfering directly with erection or ejaculation (Dollery & Bulpitt 1975) have been reported to cause impotence (Tester-Dalderup 1975).

B. Depression

As in the case of sedation there are both semantic and diagnostic problems associated with the evaluation of mental depression as a side effect of drug therapy; patients as well as physicians may differ in their criteria when applying the term depression. However, it will usually be expressed as a psychic disturbance of varying severity including one or several of the symptoms of spontaneously occuring endogenous depression, i.e. lowering of mood, anxiety and psychomotor inhibition. A few studies are available (Bant 1974, Snaith & McCoubrie 1974) in which special psychiatric rating scales have been employed to quantitate the data; however, the majority of investigators use the term depression with little or no diagnostic specification.

When attemping to relate antihypertensive drug therapy to depression it must be taken into account that this may be caused by (a) the antihypertensive agent(s) administered either primarily due to CNS actions or secondarily due to other side effects (e.g. orthostatic reactions, impotence etc.); (b) a secondary reaction to the psychological consequences of being diagnosed as the victim of hypertension; (c) a pure coincidence with spontaneous depression occurring during the treatment. Incidentally this leads to the interesting question whether depressive illness is perhaps more commonly associated with hypertensive disease.

In the individual case it is probably often impossible to systematize in the way outlined above but it seems quite clear that a number of antihypertensive drugs

may produce depressional states by a direct action on the CNS. The common denominator seems to be that these agents interfere with the metabolism of CNS neurotransmitters involved in the regulation of mood etc., notably 5-hydroxytryptamine. The best known example of this is the Rauwolfia alkaloids such as reserpine. Several records of reserpine-induced suicidal depression are available (see Goodwin & Bunney 1971, Tester-Dalderup 1975) but the picture includes a full spectrum of symptoms down to quite subtle changes of mood. The incidence of depression during reserpine treatment varies considerably in the literature, many investigators failing to observe significant differences in this respect compared to control groups while other studies indicate figures as high as 25 per cent (Tester-Dalderup 1975). While some of the factors mentioned earlier may contribute to obscure the true incidence it is my personal belief that, using careful diagnostic criteria, the proportion of patients showing reserpine-induced depressive symptoms is really quite high and well motivates the declining usage of this drug in many countries. Apparently, the risk increases with large doses but it should be noted that long-term treatment with even small doses affect CNS 5-hydroxytryptamine stores similarly as do large doses for brief periods (Rand & Jurevics 1977).

Methyldopa also depletes CNS monoamine stores although by a mechanism of action different from that of reserpine and affecting chiefly catecholamines; in fact, the antihypertensive effect of methyldopa is largely related to this central effect (Henning 1975). It is not known whether the feeble action of methyldopa on central 5-hydroxytryptamine metabolism explains why this drug is considerably less likely to cause depression than the Rauwolfia alkaloids but it seems quite clear from the literature that frank depression during methyldopa treatment is rare (Tester-Dalderup 1975, Tester-Dalderup 1978). In fact, some investigators found no significant association between methyldopa and depression (Dollery & Bulpitt 1975, Snaith & McCoubrie 1974), or, in one instance not between any of the antihypertensive drugs studied (reserpine, methyldopa and adrenergic blocking agents) and the occurrence of depressive symptoms (Bant 1974). This author concludes that depressions occurring during antihypertensive drug therapy are reflexions of the hypertensive disease itself. In spite of this it seems safest to avoid methyldopa in patients with a history of psychiatric disturbance of the depressive type.

The ß-adrenergic blocking agents so frequently used in antihypertensive treatment have recently been incriminated in depressional states (Greenblatt et al. 1976, Robinson 1978) but a clear-cut dissociation from peripheral effects of ß-adrenergic receptor blockade is hardly possible. In view of the previously mentioned pharmacological prerequisites (Conway et al. 1978) a careful observation of the ß-blocker treated patient for the appearance of symptoms of depression would seem indicated. Rare reports of confusional or stuporous states, particularly in elderly people have been associated with ß-blocking drugs (Robinson 1978).

Clonidine and its congeners also influence central neurotransmitter metabolism and, like methyldopa, their hypotensive effect depends on an interaction with central catecholamines (Henning 1975). As mentioned, sedation is the outstanding central side effect of clonidine and depressional states are but rarely reported; it would appear that most if not all such cases fall within the categories (b) and (c) listed above. The same probably holds true also for the occasional reports of depression associated with other antihypertensive drugs (Bant 1974, Tester-Dalderup 1975, Tester-Dalderup 1978). In one study patients treated with adrenergic neurone blockers of the guanethidine type tended to be more depressed than those on reserpine and methyldopa (Bant 1974) but this is undoubtedly secondary to the severe peripheral side effects of the neurone blockers.

2. SLEEP DISTURBANCES

The physiological mechanisms underlying sleep-wakefulness regulation are little known but catecholamine pathways from part of the brainstem reticular formation and particularly noradrenaline neurons seem to play a role in such functions (Lidbrink 1974). Drugs interfering with the function of catecholamine neurons are known to affect sleep-wakefulness control; all the agents discussed in the previous section have documented effects on various aspects of this parameter (Greenblatt et al. 1976, Robinson 1978, Tester-

Dalderup 1975, Tester-Dalderup 1978). The table lists ß-blockers, clonidine and reserpine but it is difficult to establish whether any clearcut difference exists between the three drugs. The ß-blocking agents, through their common use will be recognized as most commonly causing disturbances of sleep ranging from insomnia to vivid, sometimes hallucinatory dreams, somnambulism and violent behaviour with ensuing amnesia. These sometimes alarming but rarely serious central side effects of ß-blocking agents can be prevented or minimized by administering the major part or the full daily dose of the drug early in the day, avoiding dosage at night. It has been claimed that certain ß-blocking agents are less prone to this type of side effect and this has been related to a poor penetration through the blood-brain barrier (Robinson 1978). Although these agents certainly differ in their avidity to pass this barrier it is doubtful whether such differences are of significance in the clinical situation involving long-term treatment in which some kind of an equilibrium is probably established. Carefully controlled studies allowing a settlement of this issue are not available but certainly called for.

Clonidine has been reported to cause insomnia and vivid dreams (Tester-Dalderup 1975) but the incidence of this side effect is probably lower than after ß-blockers. Reserpine treatment may lead to an increase in the duration of paradoxical (REM) sleep and to nightmares (Tester-Dalderup 1975). Methyldopa appears to affect sleep to a less extent than the previously mentioned drugs; there was a slight prolongation of the time slept in one study (Dollery & Bulpitt 1975) but no mention is made of the quality of the sleep. Tester-Dalderup (1975) lists occasional disturbing nightmares during methyldopa therapy.

3. EXTRAPYRAMIDAL SYMPTOMS

Extrapyramidal side effects of antihypertensive drugs are almost exclusively encountered in patients receiving reserpine who may display symptoms of the parkinsonian type ranging in severity from relatively mild rigidity and dyskinesia to a full-blown Parkinson's syndrome, indistinguishable from the spontaneously occuring variety (Goodwin & Bunney 1971, Tester-Dalderup 1975). These cases are usually seen after large doses of reserpine and their pharmacological background is an interference of reserpine with brain dopamine metabolism (Rand & Jurevics 1977). Extrapyramidal symptoms have also been reported during methyldopa treatment but the incidence is considerably lower than after reserpine (Sweet et al. 1972). Methyldopa has actually been tried in conjunction with levodopa in parkinsonian patients (Sweet et al. 1972) but in view of the ambiguous results it is recommended that methyldopa should be avoided in patients with extrapyramidal disturbances.

4. NEUROENDOCRINOLOGICAL DISTURBANCES

Neuroendocrine effects are caused by drugs interfering with the catecholamine neurone systems controlling the release of the hypothalamic hypophyseotropic hormones or "factors" (Buckingham 1977). Among drugs used in the therapy of hypertension these central side effects are confined to reserpine and its analogues and methyldopa. Both drugs, by impairing dopamine neurotransmission in the hypothalamis cause an increase in the release of prolactin; hyperprolactinemia is apparently quite common during treatment with these drugs but it is comparatively rare that this leads to symptoms such as gynaecomastia or galactorrhea (Tester-Dalderup 1975). The highly controversial issue of reserpine treatment possibly being associated with mammary cancer is aptly reviewed by Tester-Dalderup (1978). Clonidine which in clinical doses does not appreciably interfere with dopamine neurotransmission has not been reported to influence neuroendocrine functions.

CONCLUSIONS

Most antihypertensive drugs cause central nervous system side effects but it is difficult to single out primary central nervous actions from those secondary to other side reactions. This is particularly evident in the case of mental symptoms such as sedation or depression. However, antihypertensive agents which interfere with CNS neurotransmitter functions are clearly able to elicit primary CNS side effects. Although many of these adverse reactions may appear quite alarming to the patient, they are, with the notable exception of depressive states, rarely of a serious nature quo ad vitam. However, by their subjective unpleas-

antness these side effects frequently contribute to poor compliance with therapy and, hence, may necessitate a change in the therapeutic regimen. As indicated in the introduction, there is a regrettable paucity of quantitative data on the problem of CNS side effects of antihypertensive agents. Therefore, this field would profit from closer attention in future clinical trials of both old and new drugs, particular focus being placed on quantitation of data.

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