REVIEW ARTICLE

Drug-Induced Parkinsonism and Other Movement Disorders

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ABSTRACT: This is a review of reserpine, haloperidol, and various phenothiazines that produce parkinsonism and other movement disorders. The by-products of illicit meperidine synthesis, MPTP and its more sinister companion, MPP, are also discussed. Movement disorders, transient or fixed, frank parkinsonism and/or dyskinesia, due to a variety of other medications and toxic agents are included. These are methanol, lithium, methyldopa, antimetabolites, antidepressants, sympathomimetic anorexiants, some types of antihistamines, and various combinations of agricultural chemicals.

RÉSUMÉ: Parkinsonisme et autres anomalies du mouvement induits par des médicaments Nous revoyons la réserpine, l'halopéridol et différentes phénothiazines qui provoquent le parkinsonisme et d'autres anomalies du mouvement. Nous discutons également de dérivés de la synthèse illégale de la mépéridine, le MPTP et son compagnon encore plus sinistre, le MPP. Nous incluons les anomalies du mouvement, qu'elles soient passagères ou fixes, le parkinsonisme franc et/ou les dyskinésies, dus à une variété d'autres médicaments et agents toxiques. Ces agents toxiques sont le méthanol, le lithium, le méthyldopa, les antimétabolites, les antidépresseurs, les anorexiants sympathicomimétiques, certains types d'antihistaminiques et différentes combinaisons de produits chimiques agricoles.

Can. J. Neurol. Sci. 1990; 17:155-162

Secondary parkinsonism has received increased attention since the illicit use and manufacture of the neurotoxin 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP).[1,2] It has been suggested that idiopathic Parkinson's disease may be due to some similar substance.[3,4] The age of onset and mortality of Parkinson's disease over the last half century makes this unlikely. The common form of the disease remains idiopathic.[5] Eldridge and Rocca[6] have emphasized the unchanging death rate and the age-specific incidence rates over the past fifty years[5,7,8] (Figure 1). The disease does not commonly occur in clusters or particular geographic areas, and is of extremely low concordance in monozygotic twins, There are rare kindreds with the disease. Calne et al[9] reported six families in which the symptoms occurred over a short period of time but with a great range in age of onset. This suggests an environmental rather than genetic cause. The family reported by Golbe et al[10] contained 27 patients over four generations. The inheritance was autosomal dominant, male to male, and afflicted members lived in both Italy and America. The age of onset was 47 ± 9 and age of death 56 ± 8.

Parkinsonism may result from infection, hypoxaemia, hypoglycaemia, metallic intoxication, possibly trauma, brain tumour,[11] and from an increasing number of medications. This paper deals with parkinsonism plus other basal ganglia signs and symptoms attributable to drugs and some of these other factors.

Rauwolfia Alkaloids; Reserpine

There is a curious feature common to several totally unrelated classes of both ancient and modern medications used to treat the insane. When effective they produce parkinsonism or other signs of a striatal disorder, i.e. tics, dystonia, torsion spasm, catatonia, etc. Reserpine, effective treatment for psychosis and hypertension,[12] depletes dopamine and other catecholamines from the brain and adrenal medulla by interferring with presynaptic vesicular storage while monoamine oxidase degradation perseveres.

The modern understanding of Parkinson's disease was associated with the widespread use of reserpine and the recognition by Carlson and colleagues in 1957[12] that it produced the disease by dopamine depletion. Further, they showed that parkinsonian manifestations and diminished brain dopamine could both be reversed with parenterally administered dopa.

Levodopa will reverse reserpine-induced parkinsonism in both humans and animals as will apomorphine and amphetamine, both dopamine agonists. Amphetamine does so by releas-
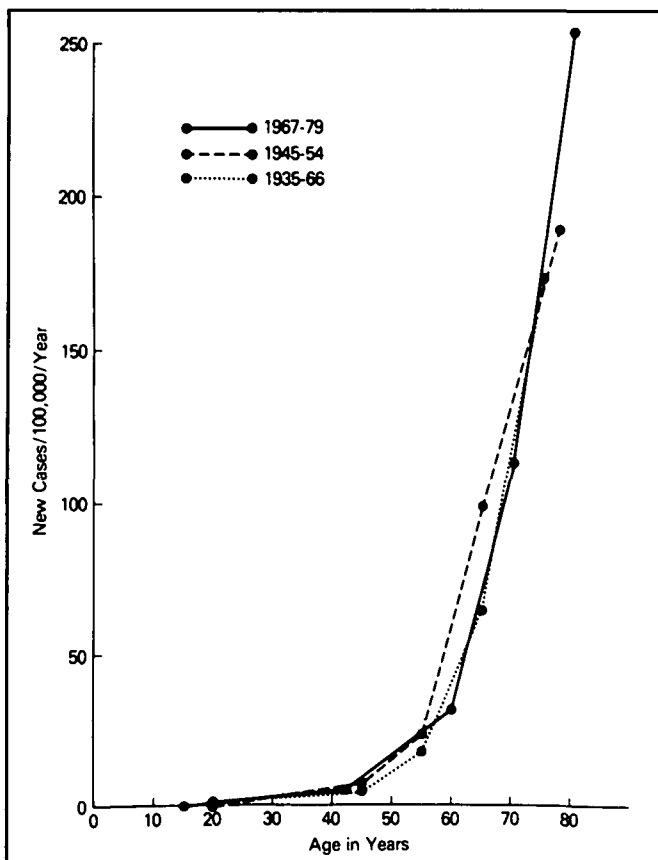
Figure 1 — Average annual age-specific incidence rates for parkinsonism in Rochester, Minnesota, in three epochs.
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ing unbound dopamine while reserpine depletes the vesicle-stored bound dopamine.[13]

Haloperidol

Haloperidol, 4-[4-(4-chlorophenyl)-4-hydroxy-1-piper-idinyl]-1-(4-fluophenyl)-1-butanone was synthesized in 1958 by Janssen and Jageneau.[14] Its structure resembles meperidine, and it was the attempt to illicitly manufacture the latter that resulted in MPTP which produced permanent, severe, parkinsonism in a number of young drug addicts.[1] Although haloperidol shares the three ring nucleus of the phenothiazines, it more closely resembles the 4-phenylpiperidines related to meperidine.

It is considered to have less anticholinergic effects and greater extra-pyramidal producing effects than the phenothiazine neuroleptic drugs. Dyskinesiae occur in up to 50% of patients treated with haloperidol.[15] Dystonias (of eye movement, neck, lip, jaw, tongue, face, and throat) are more common in young adults and children, particularly with dehydration, and are said to be twice as common in men as in women. Parkinsonism is more common in women and the elderly. Dyskinesiae may be immediate or appear weeks or months after the initiation of therapy,[16,17] while akathisia, dysphoria, and anxiety have been reported after a single dose in normal subjects.[18]

The adverse effects of the drug always appear to be reversible when it is stopped and may be ameliorated by a vari-ety of agents even when it is continued. These include amantadine hydrochloride,[19] diphenhydramine,[20] and benzotropine.[21]

Haloperidol blocks striatal post-synaptic dopamine receptors.[22] Piribedil, a dopamine receptor agonist, reduces parkinsonian manifestations when given in high doses.[23] In lower doses, it has antimanic properties and would seem to be the ideal adjunctive medication with haloperidol for the treatment of schizophrenia. Paradoxically, when given to schizophrenic patients in combination (low dose piribedil), all showed marked akinesia and rigidity. Either drug alone produced mild or no parkinsonism.[22] It has been suggested that low dose piribedil may have a preferential action on a particular type of dopamine receptor that "inhibits dopaminergic nerve activity and dopamine synthesis" (Carlsson,[24] Bunney and Aghajanian[25]). Further, there is evidence that stimulation of some dopamine receptors inhibits dopamine synthesis and the electrical activity of dopamine neurons. Low dose piribedil can selectively stimulate these receptors in animal and man. The effect of these two agents in combination, therefore, would be blockade of post-synaptic dopamine receptors by haloperidol while the low dose piribedil would counteract the "compensatory increase in firing rate and dopamine synthesis by dopamine neurons secondary to the blockade".[22] This would potentiate the blockade of dopaminergic activity and compound the rigidity and akinesis.

Phenothiazines

Parkinsonism due to neuroleptic (antipsychotic) medication has been recognized since the 1950's.[26] The action of the phenothiazines is similar to the butyrophenones (blockage of post-synaptic dopamine receptors) and unlike reserpine (dopamine depletion).

The neuroleptics (reserpine, butyrophenones, and phenothiazines) are all nerve impulse blocking agents and are also potent dopamine-releasing agents, possibly by potentiating exocytosis as well as membrane expansion and fluidization.[27]

These effects could increase spontaneous secretion of dopamine which in turn would disinhibit tyrosine hydroxylase[28,29] presynaptically allowing more dopamine synthesis locally and intraneuronally.[30,31,32]

Seeman et al, in a review of the membrane actions of neuroleptics in relation to drug-induced parkinsonism and tardive dyskinesia have suggested a presynaptic site.[33]

It is possible to identify in advance the patients most likely to develop phenothiazine-induced parkinsonism. Crowley et al found that psychiatric patients who excreted larger amounts of urinary free dopamine before treatment were significantly less likely to develop phenothiazine-induced parkinsonism than patients excreting smaller amounts.[34]

The individual sensitivity to phenothiazine and its duration has been demonstrated by Cahan and Parrish.[35]

Some patients develop parkinsonism on a small dose of phenothiazines after a few days of treatment, some only after large doses, and some never, irrespective of the dose or duration. Factors that increase the likelihood of a patient developing parkinsonism from this class of drugs are advanced age, female gender,[36] higher doses, coexisting organic brain disease, and the use of the powerful piperazine side chain phenothiazines, plus the important but unidentifiable, individual sensitivity.

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Preclinical or latent Parkinson's disease readily predisposes patients without overt manifestations of the disease to drug-induced parkinsonism.[37] Rajput et al described two patients with parkinsonism secondary to neuroleptics with remission of all signs when the drugs were withdrawn. Histological examination subsequently showed the characteristic abnormalities of idiopathic Parkinson's disease. Homovanillic acid levels were low in both and dopamine was reduced in the striatum of one.[38] Similar information was found by Wilson and Primrose[39] by following 48 patients with drug-induced parkinsonism initially reported by Stephen and Williamson.[40]

There is a certain capriciousness in the relationship between the duration and size of the dose of neuroleptics and the time of onset of extrapyramidal symptoms. When a large dose is given, particularly if intramuscular, dyskinesiae will be seen in 24 to 48 hours. In contrast, Kruse reported three psychotic patients with no extrapyramidal signs when on 20 to 45 mgs of fluphenazine, all of whom developed parkinsonism with facial dyskinesiae when the dose was reduced to 2 to 5 mgs per day.[32] These symptoms abated within days when the medication was stopped.

Both parkinsonism and the acute distressing hyperkinetic states which occur at the beginning of treatment with phenothiazines are more common in women. The latter are predominantly face, head, neck, mouth, and tongue dystonias, torsions, grimaces, and tics. The limbs may also be involved. Delay et al[42] noted the similarity of these movements to the post-epidemic encephalitis "excito-motor" syndromes described by Marie and Levy in 1920.[43,44,45]

Hunter et al have studied phenothiazine dyskinesiae by surveying 450 mental hospital patients.[46] All were demented, only women (200 of the 450) were affected, and the incidence of the movement disorder was 5%. The interval from the start of phenothiazines to the onset of the movements varied from 18 months to five years. The doses were conventional. The majority had also developed parkinsonism for which they were being treated. Eight months to three years after cessation of the phenothiazines, the movements persisted unchanged.[46]

Klawans et al have reported the persistence of neuroleptic induced parkinsonism for 18 months after the drug was stopped, with eventual complete recovery.[47] Hirschberg's 40 year old patient lost her phenothiazine induced parkinsonism only 20 months after the medication was stopped.[48] Dyskinesiae and akathisia both may persist long after phenothiazines have been stopped.[49] Additionally, parkinsonian symptoms may worsen after the withdrawal of neuroleptic medication.[50]

The fact that parkinsonism is drug-induced is not always obvious and the past and current history of drug consumption is often forgotten or minimized particularly in the elderly. Murdoch and Williamson described "occult" drug-induced parkinsonism[51] and Stephen and Williamson[40] found that half of 95 new cases of parkinsonism referred to a geriatric department were unknowingly drug-induced or drug aggravated. Two-thirds of these lost their parkinsonism when the medication was stopped, some taking as long as 36 weeks to do so.

Drug-induced dyskinesiae do not often occur simultaneously with drug-induced parkinsonism and need not be "tardy". Either movement disorder may appear or worsen after medication is stopped. Crane has reported withdrawal dyskinesiae after all

neuroleptics were discontinued and this was significantly more common in patients who had previously displayed drug-induced parkinsonism.[52]

Patients with acquired immuno-deficiency disease (AIDS) appear to be unusually sensitive to the extrapyramidal side-effects of phenothiazines, even low potency drugs such as prochlorperazine.[53] HIV infection is neurotropic and may render AIDS patients more susceptible to the central nervous system effects of even the milder phenothiazines.

In addition, AIDS patients are known to be subject to a variety of movement disorders, independent of medication and sometimes before other manifestations of AIDS appear.[54]

Meperidine-Analog Synthesis

A major turn occurred in the understanding of parkinsonism with the report of Davis et al in 1979.[55] Their patient was manufacturing 1-methyl-4-phenyl-4-propionoxy-piperidine (MPPP) for his own intravenous use. He had done this without undesired side-effects for some months, until a change in the process resulted in a mixture of MPPP and 1-methyl-4-phenyl-1,2,4,6-tetrahydropine (MPTP). The injection of the combination resulted in marked parkinsonism that persisted for 18 months and responded to treatment. Autopsy two years later revealed nerve cell loss in the zona compacta of the substantia nigra with extra-neuronal melanin and melanin within microglia cells plus an astrocytic response. A single (possible) Lewy body was seen. Four years later, Langston et al reported the same permanent result in four young people who were also synthesizing "synthetic heroin" for their own use.[1]

Further information suggested that MPTP was toxic when inhaled or absorbed through the skin. A chemist synthesizing the substance for legitimate purposes in his own laboratory from 1964 onward developed parkinsonism in 1970 at age 38. The disease has progressed with some response to conventional therapy.[57]

The mechanism of action of MPTP is clearly important. Selegiline, a monoamine oxidase inhibitor, is protective suggesting that some product of oxidation causes the damage.[58,59] Melanin affinity of MPTP is part of the answer. Loss of this pigment and degeneration of the cells containing it are conspicuous features of Parkinson's disease[60] and manganese induced parkinsonism (monkey) produces a similar lesion in melanin containing cells.[61] MPTP has a high melanin affinity for both isolated beef eye melanin and synthetic dopamine melanin *in vitro*.[62] Further, tritiated MPTP binds to brain membranes with very high receptor densities in the caudate, substantia nigra, and locus coeruleus in the human brain.

It has been suggested that MPTP may not be the neurotoxic agent but the conversion of MPTP to 1-methyl-4-phenylpyridinium (MPP) results in the true toxic substance.[63,64]

There are biochemical similarities and differences in Parkinson's disease and MPTP-induced parkinsonism. In both, the cerebrospinal fluid level of homovanillic acid (the major dopamine metabolite) is reduced while 5-hydroxyindolacetic acid (the major serotonin metabolite) is normal. The cerebrospinal fluid level of 3-methoxy-4-hydroxyphenylethylene glycol (the major metabolite of brain norepinephrine) was elevated in MPTP parkinsonism and reduced in Parkinson's disease. While central norepinephrine containing neurons are abnormal in Parkinson's disease they are not in the MPTP-induced state.[65]

In humans, tritiated MPTP binds densely to the substantia nigra of both normal and idiopathic parkinsonian brains in spite of the loss of dopaminergic neurons in the latter. This further supports the contention from animal work that MPTP binds to an extraneuronal enzyme, monamine oxidase converting it to a toxic substance which then accumulates intraneuronally.[66] In animal studies the pathogenic metabolite that accumulates within the dopaminergic neurons is MPP.[67] In parallel studies using tritiated pargyline and tritiated MPTP the binding sites were found to be almost identical.[66]

Although MPP appears to be the toxic metabolite of MPTP-induced parkinsonism and the conversion is via a monamine oxidase, the molecular mechanism has not been established. Conversion to a free radical or uptake by mitochondria and inhibition of mitochondrial respiratory enzymes, leading to calcium release and cell death have been suggested.[68] Blair et al found that MPTP inhibited dihydropteridine reductase (DHPR).[69] This enzyme regenerates the coenzyme tetrahydrobiopterin required for dopamine formation.[70] Further, there may be two sources of cytotoxic oxygen-derived free radicals causing neuronal loss: one derived from the oxidation of catecholamines, and the other from the conversion of MPTP.[71]

Forno et al have augmented the MPTP-induced lesions in the squirrel monkey brain by giving the drug over a longer time to older animals.[72] They found the usual substantia nigra lesions plus lesions in the locus coeruleus as well as eosinophilic inclusion bodies. The latter were only in areas where Lewy bodies are customarily present in human Parkinson's disease. Subsequent electron microscopic examination of these objects revealed they were not Lewy bodies.[73]

Various Substances Causing Movement Disorders

Organophosphate insecticides

Malathion® and Parathion® may produce transient or permanent central or peripheral nervous system abnormalities. They competitively inhibit the acetylcholine metabolizing enzyme, acetylcholinesterase. Davis et al[74] reported a cropduster who had several episodes of acute intoxication with malathion and parathion. He took 1.0 mg atropine tablets to relieve the nausea, diaphoresis and diarrhea that recurred with each attack. He developed right-sided tremor and stiffness after eight years of exposure to the two substances. Treatment with levodopa was not helpful. The authors speculate that his parkinsonism could have been related to increased cholinergic activity rather than decreased dopaminergic activity.

Organic Solvents and Mercury

Ohlson and Hogstedt[75] assessed 91 parkinsonian patients for occupational exposure to carbon disulfide, agricultural chemicals, and mercury. The controls were 75 patients, age and residency mated, with subarachnoid hemorrhage (SAH) from the same hospital population. There were no significant differences in exposure frequency to organic solvents.

Barbeau and Roy reported a high correlation between Parkinson's disease and pesticide use in Quebec.[76] Bocchetta and Corsini have reported two cases of early age parkinsonism associated with pesticide exposure.[77] One had been exposed to chlorinated cyclodienes and carbofuran as well as chlorophenoxy herbicides. The other had worked in a chemical plant making petroleum derivatives and pesticides, largely morpholine compounds.

In addition, Peters et al have linked incipient or manifest parkinsonism in grain storage workers to the use of liquid-solvent fumigants and pesticides, principally a carbon disulphide/carbon tetrachloride mixture.[78] Carbon disulphide alone has a known association with parkinsonism[79] and carbon tetrachloride has also been incriminated as a cause of parkinsonism.[80] Disulfiram (antabuse) is metabolized to carbon disulphide and an example of peripheral neuropathy and transient parkinsonism after ingestion of large amounts of the former has been reported.[81]

Peters et al have also reported parkinsonism after the inadvertent ingestion of the fungicide hexachlorobenzene.[82]

Paraquat, a herbicide similar in structure to MPTP, has been suggested as a possible neurotoxin capable of producing parkinsonism. Although water soluble and unable to penetrate the blood brain barrier and not metabolized into a substance which might penetrate the blood brain barrier it may be reduced outside the body into a substance that can.

Sanchez-Ramos et al have reported a citrus farmer with 15 years of exposure to paraquat and the development of parkinsonism at age 32[83] but Koller has presented reasons why paraquat is probably not the etiological agent.[84,85]

Methyldopa

This substance, 3-hydroxy-a-methyl-L-tyrosine, is useful in the treatment of arterial hypertension by reduction of central sympathetic outflow.

It inhibits L-amino acid decarboxylase and similar to dopa is successively decarboxylated and hydroxylated to form the false neurotransmitter, a-methylnorepinephrine, which displaces norepinephrine. Methyldopa is a competitive inhibitor of dopa decarboxylase essential to the conversion of dopa to dopamine. In addition, the false neurotransmitter a-methyl-norepinephrine, may compete with dopamine for post-synaptic receptors in the striatum.[86]

Frank, transient, parkinsonism or aggravation of pre-existing parkinsonism in association with methyldopa has been reported by Groden,[87] Peaston,[88] Strang,[89] and others.

Alcohols

Ethanol

It has been suggested that alcohol can facilitate the emergence of drug-induced parkinsonism and lower the tolerance to neuroleptic medication. The suggested mechanism is the selective impairment of the tyrosine hydroxylase enzyme system.[90] Akathisia and dystonia related to neuroleptic medication also appear to have been precipitated by alcohol.[91] Seven chronic alcoholics demonstrated transient parkinsonism from alcohol withdrawal or chronic intoxication.[92]

In contrast, Lang et al examined the drinking habits of 125 patients with Parkinson's disease and found no difference in the amount of alcohol consumed by a control population.[93] Koller reported the same findings as well as minimal changes in parkinsonian symptoms after the controlled infusion of intravenous alcohol.[94]

Methanol

McLean et al reported two survivors of methanol poisoning.[95] They developed parkinsonism, blindness, and dementia.

CT scans showed bilateral symmetrical infarction of the fronto-central white matter and putamen. At autopsy, cystic resorption of the putamen and fronto-central white matter as well as neuronal damage throughout the cerebrum, cerebellum, brainstem, and spinal cord, were found.[95] A similar case has been described by Ley and Gali.[96]

MISCELLANEOUS

Lithium

Acute parkinsonism has occurred in a manic depressive patient treated with 900 mgs of lithium per day for the previous five years. Lithium serum levels had varied between 0.74 mEq/L and 1.1 mEq/L with no neurotoxic side effects but for an occasional fine tremor of the hands. Acute parkinsonism was precipitated by a trial on a liquid protein diet producing a rise of lithium to toxic levels. The signs were promptly reversed when the lithium dosage was reduced by a third, the diet was discontinued, and benztropine mesylate (Cogentin®) was given.[97]

Carbon Monoxide

There are many reports of parkinsonism after exposure to carbon monoxide and some with an unusually prolonged interval following the exposure.[98] The clinical picture may be either pure parkinsonism or a mixed state of apathy, dementia, plus parkinsonian features.

Hypoglycaemia

Sulphonylurea induced a reversible parkinsonism in a 63 year old diabetic. He had been treated with Tolbutamide® for years and had recently reduced his food intake to 600 calories per day. The following week he was withdrawn and confused and became unconscious. After intravenous dextrose he recovered consciousness and in the next few days developed tremor, rigidity, dysarthria and a mask-like face, all of which disappeared after a week.[99]

Antineoplastic Agents

A combination of vincristine and adriamycin has produced head and limb tremor as well as a "parkinsonian-like syndrome" in a nine month old child with leukemia.[100] 5-fluorouracil has also produced a neurological syndrome consisting of ataxia, masked facies, weakness, rigidity and tremor, increased by voluntary movement. The signs vanished when the drug was discontinued and reappeared with a second trial.[101]

Antidepressants

The tricyclic antidepressant, amoxapine, is a metabolite of the neuroleptic loxapine. Although used as an antidepressant, it has established antidopaminergic properties.[102,103]

Steele[104] has reported an example of torticollis, tongue protusion, and eye deviation dystonia in a 27 year old man after two days of amoxapine. All symptoms were reversed within one-half hour after he was given 50 mg of diphenydramine intramuscularly. Thornton and Stahl have described a 49 year old woman who developed both parkinsonism and dyskinesia after being treated for depression with amoxapine[105] while the patient of Lesser developed dyskinesia only after withdrawal of the drug.[106]

Perhaps paradoxically, there are reports of drug-induced dyskinesiae (from neuroleptics and L-dopa) improving after the patient was started on the tricyclic, desipramine hydrochloride.[107] The authors suggested that the antidepressant may decrease beta-adrenoreceptor sensitivity and density which in turn diminishes dopamine release.

Imipramine hydrochloride was tested as a therapeutic agent for parkinsonism in a doubleblind placebo study in 1965 by Strang.[108] The results were strongly in favour of the benefits of the drug and were independent of any improvement in depression.

Monamine Oxidase Inhibitors

These substances, selegiline (Deprenyl®) and tranyl-cypramine sulphate (Parnate®) improve the symptoms of parkinsonism probably by increasing the availability of dopamine in the striatum. The former is said to have the advantage of not carrying the "old cheese and red wine" precautions.[109] Teusink et al have reported the development of parkinsonism in a 75 year old lady after her depression was treated with the MAOI phenelzine.[110] The parkinsonism cleared when the drug was stopped and they offer several explanations for this yet another paradoxical example of the relationship between the relief and the cause of a disease by a single agent.

Stimulants

Methylphenidate (Ritalin®) probably has central dopaminergic properties. It can cause chorea in minimally brain damaged children and in apparently normal family members at risk for Huntington's disease.[111] Persistent shoulder tics have occurred in another child treated concurrently with methylphenidate plus thioridazine.[112] The movements stopped promptly with the administration of haloperidol, a potent dopamine blocking agent. Other stimulants like dextro-amphetamine and pemoline cause movement disorders (tics, chorea) and worsen tardive dyskinesiae. Methylphenidate and amphetamine increase presynaptic dopamine release and also block the re-uptake.[113] Clearly the common feature among the agents that cause chorea and similar movements (d-amphetamine, methylphenidate and levodopa in parkinsonism) is the ability to increase cerebral dopamine. In the last of these situations denervation hypersensitivity may contribute to the problem but as the prevalence of the dyskinetic movement is directly proportional to the duration of exposure to the drug, denervation is not the whole answer.

Amphetamine[114] and contraceptives[115,116] can each produce chorea. Psychosis and chorea appeared in a young woman 48 hours after starting amphetamine. She had been on oral contraceptives for 10 years.[116]

Amphetamine releases norepinephrine from central noradrenergic neurons and epinephrine increases rigidity and tremor in Parkinson's disease.[117] Increasing brain norepinephrine in the guinea pig inhibits tyrosine conversion at the hydroxylase level blocking the initial catecholamine metabolic step, i.e. tyrosine to dopa.[28]

Another sympathomimetic agent, phenylpropranolamine, is used with caffeine as an anorexiant. It has caused catatonic posturing and cogwheel rigidity in a patient previously treated with doxepin hydrochloride and fluphenazine. The signs were relieved with intramuscular benztropine mesylate (Cogentin®).[118]

Parkinsonism has been reported in six patients between 36 and 52 years of age, all of whom had consumed large amounts of common drugs for many years.[119] The drugs included antihis-

tamines; diphenydramine (Sominex®), chlorpheniramine (Chlor-tripolon®), dimenhydrinate (Dramamine®) as an antinauseant; anorexiants, dextro-amphetamine and diethylpropion (Tenuate®) as well as the sympathomimetic nasal spray xylometazoline (Otrivin®). One used trimethoprim-sulphamethoxazole (Septra®) for seven years. The structural and pharmacological similarities between some antihistamines and the phenothiazines suggest the former can produce dyskinesiae and parkinsonism if used over a long enough time. Oral/facial dyskinesiae associated with prolonged antihistamine use have been reported in two patients both with reduced homovanillic acid accumulation induced by probenecid loading. Improvement and worsening of the symptoms were related to the blind consecutive withdrawal and re-establishment of the medication.[120]

Included in the more bizarre examples of reversible parkinsonism are a 47 year old female who developed the classic signs and symptoms after the intramuscular injection of procaine[121] and a 78 year old woman with reversible parkinsonism and peripheral neuritis after taking perhexiline maleate for intractible angina pectoris.[122]

The beta adrenergic blocker pindolol combined with clopamide used in the treatment of hypertension has been reported as causing or precipitating parkinsonism in two patients[123] and meperidine[124] as well as the neuroleptanalgesic mixture of fentanyl and droperidol have each produced a reversible parkinsonism.

Intraventricular amphotericin B has produced both transient and permanent parkinsonism[125] as has intravenous cephalosporin.[126] Pseudo and idiopathic hypoparathyroidism may present as parkinsonism. Correction of the hypocalcaemia improves the neurological condition.[127]

Metoclopramide, a benzamide neuroleptic, used as an anti-nauseant and anti-emetic has dopamine antagonist properties. It commonly provokes tardive dyskinesiae and can produce parkinsonism in the same patient if taken long enough.[128]

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