Clinical Pharmacology of Psychotropic Drugs

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Psychotropic or psychoactive substances are drugs which act on the brain and nervous system in such a manner as to have a prevailing or exclusive effect on the higher psychological functions. Consequently, psychopharmacology is a special branch of pharmacology and psychiatry which is concerned with the accumulation of information on psychotropic substances and with the use of these agents to extend the frontiers of knowledge concerning the pathology and therapy of patients with psychological disorders.

The pharmacology of psychotropic drugs includes studies of: their physical and chemical properties; their sites of action; their clinical effects including indications, contraindications and adverse reactions. Exploration of their therapeutic value in different psychiatric conditions and description of psychopathological changes which are uncovered, amplified, altered or induced by psychotropic drugs are two further aspects of psychopharmacology.

This series will be limited to the pharmacology of the best known and most extensively used groups of psychotropic drugs: the barbiturates, propanediols, benzodiazepines, phenothiazines, Rauwolfias, butyrophenones, amphetamines, piperidyls, monoamine oxidase inhibitors, and the tricyclic antidepressants. Each of these groups will be discussed in detail in separate sections, after a brief historical survey.

Historical Review

Barbiturates

Among widely used groups of psychotropic drugs, the barbiturates, well known for their sedative action, are the oldest. Fischer and von Mering, in 1903, introduced barbital, the first significant member of this group of synthetic compounds. Chemically the barbiturates are diureides, derivatives of urea

$$O{=}C{<}^{NH_2}_{NH_2}$$

which in itself has no psychoactive properties. The condensation of one of the amino groups of urea with a carboxyl group led to the different monoureides, the majority of which have some hypnotic properties. More potent in this respect are the diureides in which both of the amino groups of urea are condensed with a carboxyl group, i.e. with a dicarboxylic acid. Among the diureides the most important is barbituric acid, the condensation product of urea and malonic acid, and the mother compound of the entire barbiturate group. The first compound, barbital or diethylbarbituric acid (diethyl malonylurea) was the result of the replacement of two hydrogens of barbituric acid by two ethyl groups; the second oldest barbiturate, phenobarbital, synthesized simultaneously but independently by Loewe, Juliusberger, and Impens in 1912, was the result of the replacement of one of the ethyl groups of barbital by a phenyl group. Since the early years of this century the barbiturates have been extensively and successfully used for day-time sedation and insomnia.

Amphetamines

The second important group of psychoactive drugs is the amphetamines. Their history goes back to the early years of the century when first Stolz (1904) and then Dakin (1905) synthesized epinephrine, the *vasopressor* principle of the adrenal medulla. The parent compound of epinephrine is phenylethylamine which is a composite of dihydroxybenzene and ethanolamine. After the synthesis of epinephrine a large number of synthetic amines structurally related to it, and similar in their *sympathomimetic* action were examined by Berger and Dale in 1910. Among these

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were the aromatic, methylated, phenylethylamines, i.e. the amphetamines. Renewed interest in the amphetamines in the 1930's led to the discovery of the potent stimulating effect of these drugs on the central nervous system, and on behavior (Piness 1930, Myerson 1936, Ivy and Krasno 1941).

Phenothiazines

The modern psychopharmacological era in psychiatry started in 1952 with the introduction of the phenothiazines in the treatment of the psychiatric patient. The phenothiazine nucleus, two benzene rings joined by a sulfur and nitrogen atom, was first synthesized by Bernthsen in 1883. The drug is the parent substance of the thionine dyes of which methylene blue was used as an intestinal and urinary antiseptic (Einhorn 1891). Then the toxic effect of phenothiazine to various bacteria, insects and helminths was discovered and the drug was extensively used as an antihelminthic in the treatment of enterobiasis (Kuitunen-Ekbaum 1941). This application was followed by a systematic, exploratory study designed to reveal whether or not any of the derivatives of phenothiazine would be effective in protozoal infections. While no antiprotozoal effect was found during this thorough investigation, it was revealed that one derivative, promethazine (Phenergan®), has a particularly potent and long-lasting antihistaminic action. Replacing the dimethylamino-methyl-ethyl group in position 10 with a longer dimethylamino-propyl side chain resulted in the synthesis of chlorpromazine (Largactil®) in 1950 by Charpentier in the Rhône-Poulenc Laboratories. That promethazine might benefit schizophrenics was based on the possibility that some forms of acute schizophrenia might be related to allergic encephalitis. These forms of schizophrenia would then possibly respond favorably to antihistamines (Spencer Patterson 1963).

While promethazine remained rather ineffective in the treatment of schizophrenics, more favorable responses were soon reported with chlorpromazine, a dimethylaminopropyl-phenothiazine derivative. Although the antihistaminic potency of chlorpromazine was definitely inferior to that of promethazine, it had a more pronounced blood pressure and temperature lowering effect together with marked potentiation of the action of general anesthetics. The crucial observations on chlorpormazine were then made in 1951 by Laborit. While using the drug for general anesthesia, either alone or in combination with other drugs, he described how patients exhibited a characteristic disinterestedness in their surroundings while remaining fully conscious and aware of all the procedures. Although Laborit appreciated the possible value of chlorpromazine in excited psychotics, it was Hamon, Paraire and Velluz (1952) who first reported the successful treatment of a case of manic excitement with the drug. Finally, after Delay and Deniker's report (1952) in Europe, and Lehmann's and Hanrahan's report in Canada, chlorpromazine, and consecutively a number of newer phenothiazines, were introduced into clinical practice.

Rauwolfias

In the same year that the first clinical reports on chlorpromazine appeared (1952), Mueller, Schlittler and Bein of the Ciba research laboratories, isolated reserpine (Serpasil®), a new antihypertensive and tranquilizing alkaloid from Rauwolfia Serpentina Bentham. The plant Rauwolfia Serpentina grows in many tropical countries including India, Java, and Africa. It was first described by Rauwolf and named after him by Plumber in 1703. Although for centuries the roots and extracts of this plant had been used in India under the name *paglaka - dacra,* meaning *insanity herb,* to treat nervousness, anxiety, excitement and insomnia, the first note on this particular tranquilizing activity in Western literature was made by Rumpf in 1755. Then, after a long period of silence, the antihypertensive and concomitant antianxiety effects of Rauwolfia were rediscovered by Sen and Bose (1931). In the same year Ray also reported on its sedative properties.

The first promising findings with Rauwolfia Serpentina in psychoses were those of Gupta et al. in 1943, although it was only in 1953 that Hakim reported on the therapeutic effect of reserpine, the isolated active alkaloid of the plant, in psychoses. Clinical investigations began in the same year in Switzerland where Weber revealed certain similarities in the action mechanism of chlorpromazine and reserpine (1954).

Propanediol Derivatives

Prior to the introduction of chlorpromazine and reserpine for the treatment of psychotic patients, mephenesin, a centrally-acting muscle relaxant was used extensively in psychiatric therapy. In 1951 meprobamate, a derivative of mephenesin, and the therapeutically most successful and important propanediol, was synthesized (Ludwig and Piech 1951). Although the drug's sedative and muscle relaxant properties were pharmacologically established by Berger in 1954, it was not until 1957 that its particular therapeutic action on psychiatric patients was revealed.

Mephenesin (3-0-toloxy-1,2-propanediol) was the result of the condensation of o-cresol with glycerine by Zivkovic in 1908. Almost thirty years passed before its prominent pharmacological properties, muscular relaxation and paralysis, were described by Berger and Bradley in 1946. It was first used by anesthesiologists to produce muscular relaxation under general anesthesia, and by neurologists as an adjunct in the treatment of Parkinsonism. The usefulness of mephenesin in the treatment of psychiatric patients was first revealed by Gammon and Churchill in 1949. The first therapeutic uses of the drug were in reactive depression and schizophrenia. These were soon replaced when claims of its particular effective-

ness in psychoneurotic patients appeared (Schlau and Unna, 1949), especially its effectiveness in anxiety states (Dixon et al. 1950).

A great handicap of mephenesin administration is its rapid oxidation. To prolong its action a great number of propanediol derivatives were produced. Substitution and esterification resulted in meprobamate (2-methyl-2-n-propyl-1,3-propanediol dicarbamate), a compound with basically similar but longer duration of action, and a wider margin of safety. In contrast to the phenothiazines and Rauwolfia alkaloids meprobamate remained ineffective in the treatment of psychoses but Osinski (1957) and Dixon (1957) swiftly revealed its therapeutic value in the neuroses.

Piperidyl Derivatives

After the introduction of chlorpromazine and reserpine emphasis was turned towards finding drugs which antagonize the occasionally cumbersome oversedation and depression produced by these drugs and towards finding compounds with beneficial effects on the chronic, inactive, psychiatric patient. In this search, the piperidyl derivatives (2-benzyl-piperidines), and in particular methylphenidate (Ritalin®), were found promising.

2-benzylpiperidine is the outcome of specific modifications of the structure of certain phenylisopropylamines with known central nervous system stimulating effects. Pyridilacetonitriles are the result of condensation of halopyridines. The transformation of the nitrile function of pyridilacetonitriles and reduction of their pyridine ring yielded a number of new preparations (Krueger and McGrath) including the methylated derivative, methylphenidate (methyl α-phenyl-2 piperidine acetate) which was synthesized by Hartmann and Pannizzon in 1950.

The central nervous system and behavioral stimulating effects of methylphenidate were revealed in 1954 by Meier et al. in parmacological studies on animals. They also described how the drug antagonized the *depressant effect* of certain drugs, including chlorpromazine. Both effects were confirmed two years later in humans when the stimulating effect of methylphenidate on psychomotor activity was demonstrated by Gruber et al. (1956) and when an actual increase in the alertness of somnolent patients during prolonged tranquilizer therapy was described by Ferguson (1956). While the beneficial effect of the drug on chronic, inactive psychiatric patients could not be substantiated, a possible further therapeutic indication of the drug for mild cases of neurotic depression was found by Kerenyi et al. in 1960.

Monoamine Oxidase Inhibitors

The first reports on the modern pharmacological treatment of depression with monoamine oxidase inhibitor (MAOI) drugs, of which iproniazid is a representative member, were published almost five years after the original publications on the therapeutic effectiveness of chlorpromazine in acute manic and schizophrenic patients.

Iproniazid, the first clinically employed MAOI, is the isopropyl derivative of isoniazid. The parent compound, iproniazid, was first used extensively in the treatment of tuberculosis.

The history of these drugs in the chemotherapy of tuberculosis goes back to 1945 when Chorine reported on the tuberculostatic action of nicotinamide. This finding was confirmed by McKenzie (1948) and consequently it was revealed that many pyridine derivatives related to nicotinamide, for example isonicotinic acid, also possess tuberculostatic activity. Knowing the potent tuberculostatic action of thiosemicarbazones, it appeared that synthesizing the thiosemicarbazone of isonicotinaldehyde would be a promising approach. This synthesis started from the methyl esther of isonicotinic acid and the first intermediate of the process was isonicotinylhydrazine (isoniazid). While the thiosemicarbazone of isonicotinaldehyde remained generally ineffective, isoniazid was found to be a potent antituberculous agent and its isopropyl derivative, iproniazid, was noted by Selikoff in 1952 to have mood elevating properties when administered to tuberculous patients.

The recognition of the MAOI inhibiting effect of iproniazid was the result of the pioneering work of Zeller et al. (1952) which was concluded by demonstration of an actual increase in brain monoamines after the administration of various MAOI drugs by Brodie et al. in 1956. However, only after the independent verification of the potent antidepressant action of iproniazid by Kline, Loomis and Sanders, Crane, and Scherbel and co - workers in 1957, was a possible relationship between the biochemical increase in brain monoamines and the clinical antidepressant effect of the monoamine oxidase inhibitors suggested.

Tricyclic Antidepressants

The first clinical report of Kuhn on the specific therapeutic value of imipramine in the treatment of depressive states was published in the Swiss Medical Weekly in 1957. Consequently, the first tricyclic antidepressant (imipramine) and the first MAOI with recognized antidepressant properties (iproniazid) were introduced to medical practice about the same time.

Imipramine (Tofranil®) is an iminodibenzyl (dihydrodibenzazepine) derivative with a structural resemblance to chlorpromazine. The substitution of an ethyl-linkage for sulfur in the phenothiazine ring results in the iminodibenzyl structure. This substitution, the chemical synthesis of iminodibenzyl, was performed by Thiele and Holzinger in 1899. However, no further work with the iminodibenzyl structure was done until the early 1950's when Haefliger and Schindler synthesized a series of its aminoalkyl derivatives (1951).

The renewal of work with the iminodibenzyl structure was due to the interest in the then still recent discovery of the antihistaminic and sedative properties of the chemically-related phenothiazines. The search.

which was directed towards finding iminodibenzyls with similar characteristics, seemed to hold promise of success. In addition to the antihistaminic, sedative, analgesic properties of these compounds, the search also revealed an anticholinergic effect in some of the synthesized drugs, suggesting their possible use in the treatment of Parkinson's disease. Further impetus was given to the investigation when the tranquilizing properties of chlorpromazine and its usefulness in the treatment of psychotic, particularly schizophrenic and manic, disorders were recognized. Special emphasis was laid on the investigation of the iminodibenzyl analogue of chlorpromazine, imipramine, which was tested extensively in the treatment of different psychiatric, primarily psychotic, patients. Although imipramine was ineffective in schizophrenics, the skillful clinical observations of Kuhn in Europe (1957) recognized, and those of Lehmann in Canada (1958), confirmed, the antidepressant property of this compound.

Butyrophenones

The search for psychoactive drugs with more specific therapeutic effects led to the butyrophenones. The first clinically important representative of this series was haloperidol synthesized in Janssen's laboratories (Beerse, Belgium) in 1956.

The basic structure of this group of compounds is the butyrophenone moiety which consists of a ketonic phenyl ring with a straight propylene chain with a piperidine nucleus. In paraposition the ketonic phenyl ring has a fluorine substituent and the piperidine nucleus is substituted in position four with a tertiary alcohol group and with a phenyl ring. In haloperidol this phenyl ring is parasubstituted with a chlorine.

Janssen and collaborators, in pharmacological studies, soon established (1956-57) the potent cataleptic effect of this group of drugs, their effectiveness in antagonizing psychostimulants, in potentiating barbiturates and their relatively low autonomic-sympatholytic property. On the basis of information collected in animal studies they anticipated a strong neuroleptic-antipsychotic effect and suggested therapeutic trials with manic and schizophrenic psychiatric patients.

The therapeutic expectations were fulfilled. In 1958, Divry, Bobon and Collard published the results of their first clinical trial in which they were able to control successfully psychomotor agitation with haloperidol. While in later clinical trials no differential therapeutic effect of haloperidol when compared to other neuroleptic-antipsychotic drugs was revealed, a relatively low incidence of autonomic side effects of the drug have been noted during clinical administrations.

Benzodiazepines

The reaction of chlormethylquinazoline N-oxide with methylamine, attempted first by Sternbach and his collaborators in 1959, resulted in chlordiazepoxide (Librium®), a compound with interesting sedative, muscle relaxant and anticonvulsive properties in animals.

Chlordiazepoxide (7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide) was the result of a systematic search for new types of pharmacologically active compounds by investigation of the biological properties of known, but unexplored, molecular structures and their synthetic analogues and derivatives. The investigation started with the group of benzoxadiazepines of which the first member was described by Auwers and Von Meyenburg in 1891. Further benzoxadiazepines were described by Bischler (1893), Meisenheimer and Diedrich (1924), Auwers (1924), and Dziewonski and Sternbach (1935). After a number of years of further study Sternbach in 1957 prepared the first active compound of the benzodiazepine series and his continuous work led to the discovery of chlordiazepoxide (1959), the first therapeutically used benzodiazepine in the treatment of a variety of psychiatric disorders.

The first promising findings with the new drug were those of Tobin et al. who called attention, as early as 1960, to the particular value of chlordiazepoxide against anxiety and tension. In the same year, three other independent workers (Farb, Ticktin and Schultz, Kinross-Wright) revealed the effectiveness of the drug in alcoholism, both in the immediate withdrawal period and in subsequent long-term rehabilitation. Since that time chlordiazepoxide has been successfully employed in different neuroses but remains ineffective in psychoses.

Classification

Different chemical groups of psychotropic drugs may share some common characteristics. On the basis of these common characteristics psychoactive groups are assigned to *classes*. The purpose of these classifications is to indicate the characteristic effects of the drugs on factors which differentiate them from each other.

The three most widely accepted clinical groups of psychoactive drugs are Kline's pragmatic, Delay's phenomenological, and Lehmann's psychophysiological classification. Kline distinguishes among psychic inhibitor, psychic activator, and psychotomimetic groups of drugs. Psychic inhibitors are the hypnotics (i.e. barbiturates), ataraxics, or drugs which produce emotional equilibrium (i.e. phenothiazines) and sedatives (i.e. propanediols). Psychic activators are the psychomotor stimulants (i.e. amphetamines), psychic stimulants (i.e. tricyclic antidepressants) and psychic energizers or drugs with a dominant antidepressant effect (i.e. MAOI's). Psychotomimetics are defined as drugs which produce the so-called *model psychoses* and which have hallucinogenic and mildly stimulating properties.

Psycholeptics or sedatives, according to Delay, are the hypnotics (i.e. barbiturates), the neuroleptics (i.e. Rauwolfias, phenothiazines, butyrophenones) and tranquilizers (i.e. propanediols and benzodiazepines). Psychoanaleptics are divided into stimulants of vigilance (i.e. amphetamines) and stimulants of mood (i.e. tricyclic antidepressants). Delay defined

neuroleptic drugs as compounds which induce a neurological syndrome composed of psychomotor inhibition, autonomic changes, disturbance of tonus and extrapyramidal signs with a reduction of psychopathological manifestations. On the other hand, he called tranquilizers those drugs which have a sedative action, alleviate anxiety and reduce agitation to some extent without producing the neurological syndrome and without having a strongly beneficial effect on psychotic manifestations.

In Lehmann's model, drug action is clinically characterized by the effects of the psychoactive compounds on the *psychological parameters* of arousal, affect and mental integration. Drugs that primarily influence manifestations of the psychological parameter of arousal are the stimulants (amphetamines, piperidyl derivatives) and the sedatives (barbiturates). Drugs that have an effect on the psychological parameter of affectivity are the antidepressants (tricyclic antidepressants and MAOI's). On the other side of this psychological parameter are drugs with inhibitory properties: the minor tranquilizers (propanediols and benzodiazepines) and the major tranquilizers (phenothiazines, Rauwolfias). Drugs whose clinical action is primarily upon mental integration are the psychotomimetics and the antipsychotic drugs. Psychotomimetics are chemicals that induce mental derangement with a concomitant state resembling the psychoses. On the other hand antipsychotics are drugs (phenothiazines, Rauwolfias, butyrophenones) that counteract specific psychotic symptoms resulting from mental disintegration or pathological integration such as delusions and hallucinations.

In the following sections, the clinical pharmacology of the ten most widely used groups of psychotropic drugs will be discussed in the order presented in the historical introduction.

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