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Structure Side-Effect Sorting of Drugs I: Extrapyramidal Syndrome

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Abstract □ A computer program using PL/I language was developed to sort the side effects of 540 clinically useful drugs. The common structural features of the drugs that produce the extrapyramidal syndrome are: (*a*) the drug contains at least one tertiary amino group separated by three carbon atoms from a coplanar hydrophobic region, and (*b*) the coplanar hydrophobic region can be a phenothiazine ring, its isosteres, or two benzene rings held close together (*e.g.*, trimethobenzamide and haloperidol). Other tranquilizers and anticonvulsants such as diazepam and diphenylhydantoin are shown to have entirely different structural features.

Keyphrases □ Side effects, computer sorting of 540 drugs—extrapyramidal syndrome related to structure □ Computer sorting of side effects of 540 drugs—extrapyramidal syndrome related to structure □ Structure-activity relationships—features related to extrapyramidal side effects, result of computer sorting of 540 drugs □ Extrapyramidal syndrome—related to structural features, result of computer sorting of side effects of 540 drugs □ Drug sorting by side effects—structure-activity relationships

In recent years, numerous publications on chemical structure-pharmacological activity have appeared in various journals (1–13). However, due to several reasons, little systematic work has been done in sorting and correlating undesirable side effects of various drugs with their chemical structures. One reason is that side effects are usually more variable and more difficult to measure than the major pharmacological effect. In addition, when several drugs are concurrently administered to a patient, it is not easy to pinpoint the agent causing the most undesirable side effect or to detect the presence of drug interactions.

Many potentially useful drugs are not used primarily because of the severity of their side effects, not because of the lack of efficacy. On the other hand, there are many instances of an annoying side effect promoted later to be an appreciated therapeutic effect, such as the development of oral antidiabetic drugs from the observation of hypoglycemia in patients treated with certain sulfonamides. Therefore, it was considered worthwhile to employ a computerized program to sort the side effects of all clinically useful drugs and to correlate these effects with the chemical structure. It is believed that any effect of a drug, desired or undesired, direct or indirect, is determined by its physicochemical properties which are, in turn, governed by its structure.

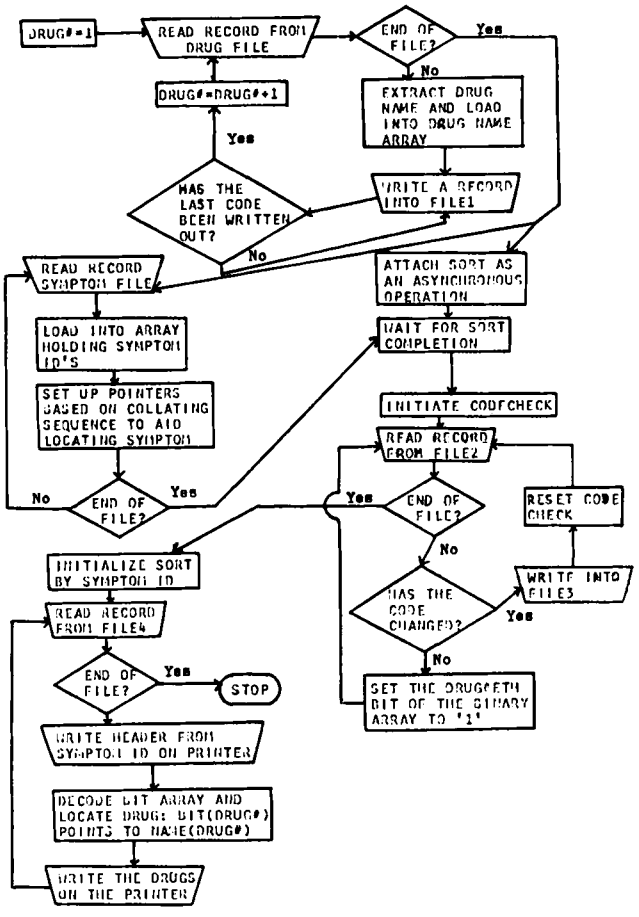
This report discusses the structural features of the drugs known to cause extrapyramidal syndrome and why other tranquilizers (*e.g.*, diazepam) do not cause this side effect. Extrapyramidal syndrome consists of parkinsonian-like symptoms (*e.g.*, tremors, rigidity, and salivation), akathisia (a psychosis marked by an inability to sit still or to remain seated), and akinesia (loss of the power of voluntary motion).

METHOD

A data bank consisting of 540 clinically useful drugs (14–17) was established, and each side effect is represented by a unique three-digit hexadecimal code. The name of the side effect associated with each code is stored separately in another file, the symptom file. The code is also the key for each record, allowing direct retrieval of the name.

A program was developed[1], using the PL/I language (18, 19), which allows the data bank to be sorted by individual side effect

[1] A listing of the program is available upon request.



DRUG FILE—a sequential input file, with each record organized as follows: NAME, CODE 1, CODE 2, CODE 3, . . ., CODE n, where NAME is the name of the drug, and CODE n represents a three-digit hexadecimal code for each side effect associated with the drug.

SYMPTOM FILE—a sequential input file, with each record organized as follows: CODE n, SYMPTOM-ID, WORD, where CODE n is the three-digit hexadecimal code for the symptom, SYMPTOM-ID is the name of the symptom, and WORD is a binary string of length 20 categorizing the symptom by anatomical region.

FILE 1, FILE 2, FILE 3, FILE 4—sequential input and output files used by the sort routine.

FILE 1 organization: CODE n, DRUG #; CODE n is the three-digit hexadecimal number code, and DRUG # is the relative position of the drug in the drug bank.

FILE 2—sorted output of FILE 1.

FILE 3—a sequential input file which is organized: SYMPTOM -ID, BINARY (504); BINARY (DRUG #) = '1' if the drug #eth drug has the side effect, otherwise it is = to '0'.

FILE 4—sorted output of FILE 3 alphabetically.

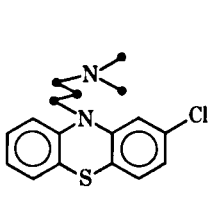
Scheme I—Flow chart of sorting program

and lists the drugs that have been reported to cause it. The program consists of three steps (Scheme I):

1. A procedure that creates records in a new file comprised of the code followed by the sequence number of the drug. For example, if the side effect code is 123 and it is associated with drug A, the 50th drug, the record will be "12350." This is done for the entire data bank, the output being stored on a temporary data set.

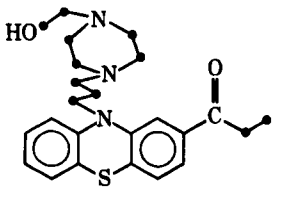
2. A link with the IBM Sorting Program, through the facilities of PL/I, that initiates sorting of the temporary data set based on the first three characters of each record. Output of 12301, 12338, 12345, and 12350 would then indicate that drugs 01, 38, 45, and 50 have the side effect corresponding to code 123.

3. A procedure that examines the output of the sort routine, retrieving the name of the side effect from the symptom bank based on the code and retrieving the names of the drugs based on their sequence number. The printout would have the following format: "THE FOLLOWING DRUGS HAVE THE SIDE EFFECT OF XYZ: A, B, C, D, E."



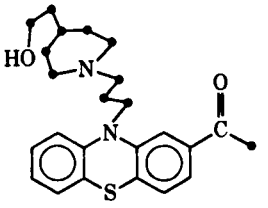
I

chlorpromazine



II

carphenazine



III

piperacetazine

RESULTS AND DISCUSSION

By sorting the data bank of 540 drugs, the following striking common features were found for the drugs that produce the extrapyramidal syndrome:

1. A phenothiazine derivative with a tertiary amino group which is separated from the ring by three carbon atoms [chlorpromazine (I), promazine, trifluoperazine, fluphenazine, mesoridazine, thioridazine, thiopropazate, acetophenazine, carphenazine (II), piperacetazine (III), *etc.*]. (In the structures illustrated here, the hydrogens on the carbon atoms are not shown.)

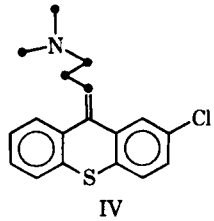
2. Isosteres of phenothiazine, such as chlorprothixene (IV), doxepin (V), and thiothixine, cause the same type of side effect (16–19).

3. Two compounds, trimethobenzamide (VI) and haloperidol (VII), are structurally quite different from phenothiazines and yet produce the extrapyramidal syndrome. By making Corey–Pauling–Kaltun (CPK) molecular models, it was noticed that these molecules could assume many different conformations, ranging from a more or less linear to a phenothiazine-like shape. When these molecules assumed the phenothiazine-like conformation, the tertiary amino group occupied the apex of a triangle, with two benzene rings occupying the baseline.

Since the pKa value of a tertiary amino group is approximately 10–11, it would be protonated under a physiological condition. If one assumes that the phenothiazine-like conformation is necessary for production of the extrapyramidal syndrome, then it appears that the protonated tertiary amino group would bind to a negatively charged site on the receptor while the coplanar ring system would occupy a flat nonpolar region by hydrophobic interactions.

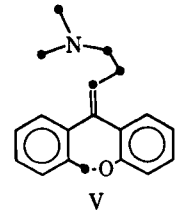
The distance between the tertiary amino group and the ring system of three carbon atoms appears to be very critical. It is known that phenothiazines with a two-carbon side chain show antiparkinsonian and antihistamine effects (20).

Since the drugs were not administered on an equimolar basis, no attempt was made to correlate the frequency of occurrence or the



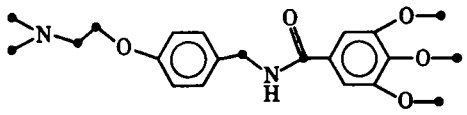
IV

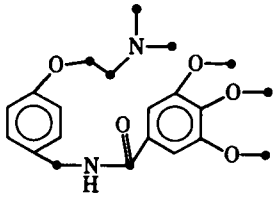
chlorprothixene



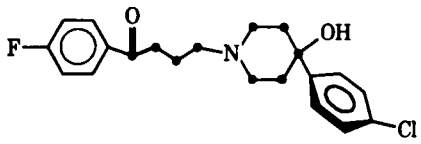
V

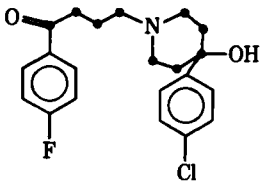
doxepin



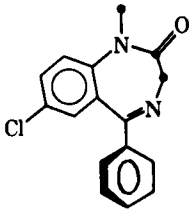


VI
trimethobenzamide

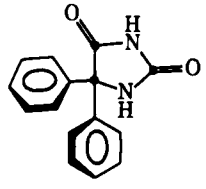




VII
haloperidol



VIII
diazepam



IX
diphenylhydantoin

degree of severity of the extrapyramidal syndrome with the structure. However, it is generally known that extrapyramidal effects are most commonly associated with the piperazine derivatives (21).

In clinical applications, it is known that tranquilizers like diazepam do not give extrapyramidal effects. Comparison of the CPK model of diazepam with those of phenothiazines revealed significant differences. An X-ray crystallographic study (22) showed that the phenyl group in diazepam (VIII) made an angle of 124° with the chlorophenyl ring. In the same study it was found that diphenylhydantoin (IX), a potent anticonvulsant, exhibited very similar structural features with diazepam, which is a tranquilizer and a muscle relaxant and is also used in treating emergency cases of status epilepticus (23). The two phenyl groups of diphenylhydantoin lie at angles of 114 and 113° to the hydantoin ring and at an angle of 90° to each other. These are, of course, quite different from the phenothiazines where the two benzene rings are essentially coplanar. Furthermore, neither of these two anticonvulsant drugs possesses a tertiary amino group.

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