Delayed Adverse Effects of Drugs and Toxicological Risk Assessment (T. Fujii and T. Yanagita, eds.)
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TARDIVE ADVERSE EFFECTS OF DRUGS

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Introduction
Since animal experiments have begun to be used for appraisal of drug safety in human, the extrapolation of animal data to human became an important scientific as well as practical issues in the development of new drugs because of the problems of species differences between animals and human. Therefore, methodological issues concerning the prediction of human responses from animal data and the relevancy of animal data to human have been repeatedly discussed in the fields of pharmacology, toxicology, and clinical pharmacology. By now, plenty of knowledge and experience have been accumulated in this regard, and the species differences are known to be attributable to differences in such aspects as 1) pharmacokinetics, 2) pharmacodynamics, 3) organ structures and functions, 4) physical characteristics, 5) dosing conditions, 6) living environments, and 7) disease states. As a result, in recent years, the methods of predicting drug safety in human have greatly advanced although they are still far from satisfactory. Particularly, to predict adverse reactions with delayed onset (tardive adverse reaction) from animal experiments is a difficult issue because of uncertainty in the occurrence and complexity of the mechanisms of onset.

1. Modes of drugs to produce adverse reactions
The modes of developing adverse reactions can be categorized as follows.
1) Adverse reactions caused by main effects of drugs
The modes of developing adverse reaction with drugs are shown in Table 1. The first category is adverse reactions that are caused by the main effects of a drug. Adverse reactions such as a respiratory arrest with anesthetics or hypnotics, hypotension with antihypertensive drugs, and hypoglycemia with antidiabetic drugs are attributable to the main effects of the drugs. Extrapyramidal disorders with neuroleptics, inflammatory changes with inflammatory cytokines, and serious adverse reactions with adrenal and gonad hormones can be regarded as the tardive adverse reactions that are caused by the main effects of the drugs.
2) Adverse reactions caused by side effects of drugs
The second case is adverse reactions that are caused by side effects of drugs. Many tardive

Table 1. Modes of drug effects to produce adverse reactions.

| 1. Attributable to main effects of drugs          |
| 2. Attributable to side effects of drugs        |
| 1) Pharmacodynamic side effects                 |
| 2) General toxic effects                        |
| 3) Specific toxic effects                       |
| 4) Dependence-producing and psychotoxic effects |
| 3. Attributable to pharmacokinetic mode         |
| 4. Attributable to allergic mode                 |
| 5. Attributable to interactive mode             |
adverse reactions are known to be produced by this mode. Side effects can be classified into four categories: a) pharmacodynamic action of drugs (such as impairment of cognitive function by chronic use of benzodiazepines, paradoxical arrhythmia by antiarrhythmic drugs, and hyperglycemia by, Ca-antagonists); b) general toxic effects of drugs (such as liver, kidney, and tissue damages); c) specific toxic effects of drugs (such as carcinogenicity and teratogenicity); and d) dependence-producing and psychotoxic effects of drugs (such as compulsive drug-seeking, withdrawal manifestations, and psychotic manifestations).

3) Adverse reactions caused by pharmacokinetic mechanisms

Many adverse effects can be attributable to pharmacokinetic aspects of drugs. One well-known instance of tardive adverse reactions that are caused by a pharmacokinetic mode is the case of liver injury produced by “coralidil”, an antianginal DH preparation. The outline of this example is summarized in Table 2. At an early stage of the incident the injury was thought to be phospholipidosis, but further studies revealed that the pathogenesis was due to an unrecoverable hepatic deposition of a combination substance consisting of the drug with cholesterol.

4) Adverse reactions caused by allergic mechanisms

Many adverse reactions including the tardive adverse reactions are known to be developed as a result of allergic reactions. The latter include delayed allergic reactions such as allergic hepatitis, agranulocytosis, and autoimmune disorders with various types of drugs including contrast agents.

5) Adverse reactions caused by interactions of drugs

Adverse reactions can be developed as the result of drug interactions. The case of the adverse reaction caused by the interaction of nialamide, a MAO inhibitor, with cheese is the case that is frequently cited as a classic example of drug interaction, although technically this is not an interaction between drugs. Recently the interaction between the quinolone antibacterials and non-steroidal antiinflammatory drugs and the interaction between an antiviral drug (soribudin) and an anticancer drug (5-FU) attracted special attention in the medical and pharmaceutical professions.

2. Predictability of tardive adverse effects from preclinical studies

To what extent will it be possible to predict the tardive adverse effects from preclinical studies? Let us consider this issue point-by-point along the categories described above.

1) Prediction of adverse effects attributable to the main effects of drugs

Prediction of the adverse effects that are attributable to the main effects of a drug appears to be relatively easy within a limited range compared to those attributable to the other modes. For example, tardive dyskinesia is reproducible in monkeys by repeated administration of haloperidol for several months. This prediction does not necessarily require reproduction of a manifestation similar to that of human, but can be based on observing the supersensitivity of the brain dopaminergic nerve system at the striatum in other species of animals, such as rats, which is developed as the result of the continuous receptor blocking effect of neuroleptics.

With adrenal corticosteroid hormones, the

<table>
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<th>Table 2. A case of hepatic injury caused by a DH drug.</th>
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<td>1. Clinical use: Anti-anginal drug, anti-hypercholesteremia drug</td>
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<td>2. Onset of injury: After repeated use for longer than 4 months</td>
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<td>3. Clinical signs: Loss of body weight, fever, swelling of liver and spleen, and occasionally ascites</td>
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<td>4. Hematochemistry: Accelerated sedimentation, increase of white cells, hyper-cholesteremia, vacuolization in white cells and bone marrow</td>
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<td>5. Histopathology: Fat liver, and deposit of phospholipid-like substance with myelin-like structure in the liver</td>
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<td>6. Deposit: DH-cholesterol combined substance</td>
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withdrawal adverse effects can be easily predicted by observing atrophy of the gland following repeated administration of the hormones. In fact, the atrophy will be developed within a short term even by dermal application of relatively small dose of the drug in any species of animals, although adverse reactions other than those based on the withdrawal phenomenon and infection (such as dermatitis and bone necrosis) are generally hard to reproduce in animals.

The carcinogenicity of gonad hormones can be predicted from the carcinogenicity studies in animals, although the results may not always be reliable.

Concerning cytokines, it is very difficult to predict what effects are likely to be adverse since cytokines possess a range of effects in animals. For example, in our 13-week toxicity study on an inflammatory cytokine in crab-eating monkeys, the many changes shown in Table 3 were observed in hematological, hematochemical, and pathological examinations. These include increase of white cells and platelets, skin ulcer, swelling of the spleen and liver, inflammatory changes of various tissues and organs, and extramedullary hematopoiesis. Any of these changes can be adverse effects if they are manifested to the extent of becoming clinically problematic. In fact, recent case reports on the adverse effects of interferons indicate a high possibility that the effects observed in the above experiment can be adverse drug effects in human.

2) Adverse reactions caused by side effects of drugs

One good example of tardive adverse reactions that occur due to side effects of drugs developed by the pharmacodynamic mode is impairment of cognitive functions such as dementia produced by a chronic use of benzodiazepines. Although acute impairment of the function can be produced by the benzodiazepines and irreversible impairment can be produced by chronic administration of ethanol in rats, the irreversible impairment that occurs only after chronic administration of benzodiazepines in human is not known in animals. Therefore, at present, the prediction of such impairment from animal experiments will be very difficult. The tardive adverse reactions that occur due to pharmacodynamic side effects are generally difficult to predict from animal experiments. The paradoxical arrhythmia produced by disopyramide, and the swelling of the gingiva produced by nifedipine are difficult to observe in animals.

Contrary to the above, the tardive adverse reactions that occur with organ toxicity of drugs are predictable from animal experiments within a certain limit. Such toxicity may be called delayed toxicity, prolonged toxicity, or chronic toxicity, and can be observed in general toxicity studies in animals.

Similar to the above, the reactions that occur due to special toxicity of drugs such as teratogenicity and carcinogenicity can be predicted from animal experiments.

Some tardive adverse reactions such as compulsive drug-seeking, severe withdrawal manifestation, and psychotic manifestation will be produced as a result of developing dependence on a particular drug and from its psychotoxic effects.

Table 3. Immunological examinations on sera obtained from phase I subjects.

| Test serum | Obtained from subjects of a phase I study who manifested skin rash after single dose intravenous administration of a test drug. |
| Time of sampling | Before and 7 days after administration |
| Test drug | A protease with human protein |
| Skin rash | Erupted shortly after drug administration and disappeared within 1 hr Urticaria-like on a whole body in one subject and several spots on the breast area in the other. |
| Examinations | 1) HA reaction test (hapten-coated red cells of sheeps) 2) PCA reaction in the guinea pig 3) PCA reaction in the rhesus monkeys 4) lymphocyte stimulation test |
| Results | Negative in all examinations. |
The effects to produce such reactions can be predicted from drug dependence studies in animals with considerably high reliability.

3) **Adverse reactions caused by pharmacokinetic mechanisms**

The incidence of the tardive adverse reaction that is summarized in Table 2, was confirmed to be predictable from animal experiments. The irreversible deposit of the drug-cholesterol combined substance in the liver was easily reproduced in a rat experiment. However, generally speaking, the reactions caused by this mode may be difficult to predict from animal experiments unless the animal species used in the experiment shares pharmacokinetic similarity to human.

4) **Adverse reactions caused by allergic mechanisms**

The adverse reaction caused by allergic mechanisms is one of the most difficult issues in prediction of adverse reactions from animal experiments, since many reactions caused by this mechanism are not reproducible in animal experiments. A case of allergic hepatitis caused by a nonsteroidal antiinflammatory drug is summarized in Table 4. Repeated performance of toxicity studies up to 6-month administration of the drug in rats and monkeys did not reveal any hepatic disorder. In addition, the lymphocyte stimulation test on the serum of the monkeys did not indicate any possible allergic phenomenon. Thus, the immunogenicity of the drug was not predictable from the animal experiments.

Although this is not a case of tardive adverse reactions, another case of adverse reactions with a protein enzyme is shown in Table 5. The serum of subjects who manifested skin rash was obtained and the possibility of an allergic reaction was indicated by the clinical findings. Therefore, the four immunological tests shown in the table were conducted in our laboratory, but none of them showed a positive result. Thus, we failed to identify the cause.

5) **Adverse reactions caused by interaction of drugs**

Many tardive adverse reaction can be produced as the consequence of slow or delayed interaction of drugs. One good example that recently came to light is the case of interaction between antiviral and anticancer drugs (soribdin and 5-FU) which resulted in several deaths. The cause soon became clear. The antiviral drug interacts with the anticancer drug and unusually

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**Table 4. Incidence of allergic hepatitis caused by a NSAID.**

1. Onset of hepatitis: After a certain latent period
2. Manifestations: 1) Hyperthermia, eruption, pruitis
   2) Abnormal hepatic functions
   3) Eosinophilia
   4) Provocation test positive
3. Results of toxicity studies: No unusual findings in 6-months studies in rats and rhesus monkeys. Lymphocyte stimulation test on monkey's serum also negative

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**Table 5. Toxicity study on inflammatory cytokine in crab-eating monkeys.**

1. Administration: Intravenous once daily for 13 weeks
2. Doses: 10, 30, and 90 μg/kg
3. Changes observed: 1) Increases of white cells and platelets
   2) Skin ulcer
   3) Swellings of spleen and liver
   4) Inflammatory changes of tissues
   5) Extramedullar hematopoiesis
   6) Osteomyelitis
elevates the blood concentration of the latter up to a fatal level. This interaction was known before the drug was marketed and predicted from animal experiments. The interaction between the quinolone antibacterials and non-steroidal antiinflammatory drugs that produces convulsive disorders was found to be reproducible in laboratory animals. Therefore, it is predictable, but this type of study is not routinely conducted in laboratories and this combination would not have been tested if the clinical incident had gone unnoticed. In this sense, prediction can be said to be difficult.

The third example of the interaction is the case of an OTC cough syrup which contains four active ingredients such as dihydrocodeine, caffeine, methylephedrine, and chlorpheniramine. The syrup was and still is frequently abused by teenagers. Animal studies on the reinforcing efficacy of the preparation by self-administration experiments in rhesus monkeys revealed that the reinforcing efficacy of dihydrocodeine is substantially enhanced by combination with other three ingredients although the combinations with any one of these three ingredients did not enhance the reinforcing effect of dihydrocodeine. Therefore, a high abuse potential of the combination preparation was predictable from the animal experiments, although, similarly to the previous case, dependence studies on combination preparations are not routinely conducted at present time. Thus, prediction of this type of adverse effects may be regarded as one of the difficult areas.