Safe and Effective Use of Psychotropic Drugs

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Abstract: This paper outlines the safe and effective use of psychotropic drugs commonly employed in primary care practice. If a patient undergoing primary care develops psychiatric symptoms that necessitate the administration of psychotropic drugs, one needs to be aware of the possibility that the underlying physical disease may have altered the patient's pharmacokinetics and pharmacodynamics. Changes in pharmacokinetics may cause delays in absorption, distribution, metabolism, and excretion of the drug, leading to high blood concentrations that can result in unexpected adverse reactions. It is also important to consider possible interactions with therapeutic drugs prescribed for the patient's physical condition. In Japan, recently developed psychotropic drugs, particularly selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs) among the antidepressants and serotonin-dopamine antagonists (SDAs) among the antipsychotic drugs, are associated with greater safety and fewer adverse reactions than conventional psychotropic drugs. Thus, they appear to be appropriate for patients who have both physical and psychiatric disorders and who have visited a primary care clinic.

Key words: Antipsychotics; Pharmacokinetics; Pharmacodynamics; SDA; SSRI; SNRI

Introduction

The safe and effective use of psychotropic drugs in primary care practice will be discussed on the basis of recent findings in Japan. Along with the aging of society as well as changes in the social and economic climate that are apt to increase stress, basic and marginal symptoms of dementia, depressive state, panic disorder (anxiety neurosis), and hypochondria appear to be increasing among patients who visit primary care clinics. In other words, patients with mental disorders such as psychosomatic disease and depression may be included among
multiple diseases may cause serious toxic effects from interactions among the drugs. To avoid these issues of drug treatment, it is necessary to choose appropriate drugs and dosage regimens, on the basis of a clear understanding of the mechanisms of change occurring in the patient as a result of aging and drug combinations.

Changes in Metabolic Fate and Pharmacodynamics of Drugs

The pharmacologic action of a drug is determined by two characteristics: (1) its pharmacokinetics, the process by which it reaches the site of action, and (2) its pharmacodynamics, the reaction between the drug and the living body (Fig. 1).1

Any change in these processes causes variation in the pharmacologic action of the drug. Such changes may be either pharmacokinetic or pharmacodynamic, or both.

1. Pharmacokinetic changes in ill or elderly patients

Changes occurring in elderly patients or those with physical complications may be related to
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Fig. 2 Aging-related changes in various indices of absorption, distribution, metabolism and excretion of drugs

several factors, shown in Fig. 2. For example, drug absorption is decreased with declining gastric secretion, gastrointestinal blood flow, or motility of the gastrointestinal tract resulting from aging or physical illness. Decreased hepatic blood flow and a decline in the drug-metabolizing enzyme cytochrome P-450 cause delays in drug metabolism. In addition, when the intracellular water content or serum albumin is decreased, and body lipid content is increased, the volume of distribution of watersoluble drugs lessens, resulting in elevated drug concentrations in blood. In contrast, under these conditions, most psychotropic drugs, which are lipophilic to facilitate their passage through the blood-brain barrier, have an increased volume of distribution. As a result, their elimination half-lives are prolonged, while blood concentrations are decreased.

For example, it has been reported that the volume of distribution of diazepam increases with aging, reaching a four- to fivefold difference between the elderly and younger individuals. When the serum albumin level is decreased by aging or the presence of physical disease, the protein binding rates of drugs that have a high albumin-binding capacity decline, and free drug concentrations rise, occasionally leading to a strong pharmacologic effect. Therefore, measurement of blood drug concentrations has no meaning unless free drug concentrations are determined.

Most drugs are metabolized mainly in the liver. Aging and hepatic disease lower the number of parenchymal cells, resulting in reduced liver weight. In addition, hepatic blood flow, by which the drug is delivered to the liver; activity of the drug-metabolizing enzyme cytochrome P-450; and the bile flow required for excretion of the drug also decline, inducing hepatic dysfunction. Therefore, complications and aging may cause high blood concentrations of drugs that are ordinarily metabolized in the liver, leading to a strong pharmacologic effect and strong adverse reactions.

Hypofunction of the kidney, the organ respon-
sible for the excretion of drugs, delays their urinary excretion. Aging alone is associated with a linear decrease in creatinine clearance, an index of drug excretion. Therefore, the blood concentrations of drugs normally excreted through the kidneys may be increased in the presence of renal hypofunction, creating a strong pharmacologic effect, adverse reactions, or toxicities. Although renal function is assessed in terms of creatinine clearance, it should be kept in mind that the serum creatinine level may not be elevated even under decreased renal function if muscle mass is decreased because of chronic disease or aging.

In summary, when prescribing psychotropic drugs in primary care clinics, it is necessary for the physician to be aware in advance of the drug’s metabolism, excretion, and protein binding and to take into account interactions with other drugs prescribed for the treatment of concomitant physical disease.

2. Influence of psychotropic drugs on biofunction

Unlike drugs used for the treatment of physical diseases, psychotropic drugs are fat-soluble and usually act to depress the central nervous system. Therefore, when the effect of the drug is too strong, fatal reactions such as inhibited respiratory function and decreased blood pressure may be elicited.

The use of psychotropic drugs, particularly the antipsychotics, may cause adverse reactions like supraduction of eyeballs, akathisia, and dystonia in the acute stage, owing to dopamine (D2) receptor blocking in the central nervous system. In the chronic stage, extrapyramidal symptoms such as tardive dyskinesia, parkinsonism, amenorrhea, lactation due to hyperprolactinemia, thirst, constipation, ileus, urinary disturbance, and delirium caused by the anticholinergic action also may occur. Anticholinergic side effects are another problem related to the use of antidepressants.

The mental status of the patient may decline as a result of oversedation in cases of psychotropic drug overdose.

Development of Safe Psychotropic Drugs

It would not be much of an exaggeration to say that the entire history of psychotropic drug development has been a struggle to reduce side effects. Problems that need to be solved include reduction of the muscle relaxant effect and dyskinesia associated with hypnotics, reduction of anticholinergic side effects associated with antidepressants, and inhibition of the occurrence of extrapyramidal symptoms associated with antipsychotics. Various new psychotropic drugs have been developed recently and applied to clinical practice.

1. Benzodiazepines (BZ)

A new drug for insomnia, zolpidem (Myslee®), which has higher selectivity for BZ/H9275 receptors, has recently been developed. This drug has a shorter half-life, the same as triazolam (Halcion®). In comparison with conventional drugs used to induce sleep, there is hardly any antianxiety effect, muscle relaxation, movement disturbance, or enhancement by alcohol, whereas it has sedative, amnestic, and anti-convulsant actions. Therefore, it is expected to reduce the incidence of fractures resulting from “wooziness” caused by the overdosing of sleep-inducing drugs.

Although lormetazepam (Loramet®, Evamyl®) is a sleep-inducing drug of the BZ group, it can be used for patients with liver injury because it is metabolized in the liver by simple glucuronic acid conjugation, unlike other drugs used to induce sleep.

Japan has been criticized by other countries for its overuse of BZ drugs. Prudence is necessary in prescribing these drugs because there is a risk of amnesia with prolonged use, dependence at the usual dose, and rebound insomnia/anxiety after abrupt withdrawal. In this connection, the use of selective serotonin reuptake inhibitors (SSRIs) has been tried.
2. Antidepressants

Tricyclic and tetracyclic antidepressants have a long history of clinical use, and therefore their clinical efficacy has been relatively well established. However, as mentioned previously, these drugs are often associated with low compliance owing to anticholinergic side effects and resultant recrudescence.

In this regard, new drugs with higher sensitivity to serotonin (5-HT2) or noradrenaline receptors have been developed in conjunction with the pathological hypothesis of depression. Such drugs include SSRIs and serotonin-noradrenaline reuptake inhibitors (SNRIs). The major pharmacologic actions of these drugs are to inhibit 5-HT2 or 5-HT2 and noradrenaline, respectively, targeting transporters in the presynaptic region.

These antidepressants cause far fewer adverse events, although nausea and vomiting may occur as a result of 5-HT2 stimulation in the intestinal tract. When used with other drugs, some SSRIs may be associated with high blood concentrations owing to competition with several cytochrome P-450 molecular species or, conversely, low blood concentrations as a result of enzyme induction.

In Japan, the SSRIs available are fluvoxamine (Depromel®, Luvox®) and paroxetine (Paxil®). Milnacipran (Toledomin®), an SNRI, is available in clinics. Among the SSRIs, fluvoxamine is indicated for obsessive-compulsive disorder as well as depression, and paroxetine, which has a potent antianxiety effect in addition to its antidepressant effect, is also indicated for panic disorder. On the other hand, milnacipran inhibits the noradrenaline transporter in addition to 5-HT2 reuptake inhibition, and is therefore expected to be effective for more serious depressive disorders.

3. Antipsychotics

Risperidone (Risperdal®), whose 5-HT2 receptor inhibitory action predominates over its D2 receptor inhibitory action, has been clinically available in Japan since 1996. Conventional antipsychotic drugs such as chlorpromazine and haloperidol are called typical antipsychotic drugs, whereas new drugs such as risperidone, i.e., serotonin-dopamine antagonists (SDAs), are called atypical antipsychotic drugs. Drugs of this class on the market include quetiapine (Seroquel®), olanzapine (Zyprexa®), and perospirone (Lullan®), the first SDA developed in Japan based on the concept of serotonin-dopamine antagonism.

All these drugs have proved effective for negative symptoms and cognitive disorders, for which conventional typical antipsychotic drugs are much less effective, and are associated with lower frequencies of extrapyramidal side effects. Therefore, they are expected to be effective for schizophrenia, including the long-term prognosis of the disease.

Because of their lower frequencies of chronic adverse reactions, atypical antipsychotic drugs are considered to be associated with better compliance and thus better quality of life for patients. However, our 4-year clinical experience with risperidone indicated that extrapyramidal side effects occurred more frequently than expected at doses above 4 mg. Olanzapine and quetiapine are expected to be effective for refractory schizophrenia, but are contraindicated for patients who have a high probability of developing diabetes mellitus because of the reported risk these drugs have of causing diabetes mellitus. The use of quetiapine may reduce the problems of various adverse reactions common to typical antipsychotic drugs.

Although antipsychotic drug use is infrequent in primary care practice, atypical rather than typical antipsychotic drugs should be prescribed for psychotic conditions for which the use of conventional typical antipsychotic drugs had been the treatment of choice. In patients with serious complications in whom irritability and anxiety associated with insomnia and restlessness just after surgery develops into rambling conversation, unusual behavior, and, eventually, psychomotor excitability or delirium, haloperidol commonly has been employed.
However, given the adverse reactions to long-term use of this drug, an atypical antipsychotic drug would be a better choice.

**Conclusion**

It is currently more common to see patients visiting a primary care clinic because of poor mental health. However, patients seen in primary care clinics often have physical complications and may have been on multiple drug therapy before psychotropic drugs are prescribed. Therefore, psychotropic drug treatment should be given as monotherapy as a rule and be based on a good understanding of the pharmacologic action of the drug. Although recent psychotropic drugs are associated with reduced side effects, it is necessary to prescribe a proper dose, exercising due caution with regard to the possible development of adverse reactions.

In addition to drug administration, because many patients have psychosocial stress as a background to their pathologic condition, it is vital to allow patients to talk about their stress and to offer supportive psychotherapy.

**REFERENCES**
