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Pharmacokinetic Optimisation of the Treatment of Psychosis

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Summary Psychosis is a generic term covering (for the purposes of the present article)) schizophrenia, brief reactive psychoses and manic episodes. Traditionally, research has focused on the effect of antipsychotic agents on positive or productive symptoms such as hallucinations or delusions. More recently, attention has been focused on negative symptoms such as emotional withdrawal or impairment of social participation. Typical antipsychotic medications such as phenothiazines have little effect on these clinical manifestations. This has raised interest in atypical antipsychotics such as clozapine.

Acute psychotic episodes are less difficult to treat than long term schizophrenic manifestations. Current research indicates that antipsychotics are effective only if a threshold concentration is reached, but that above a certain level, dose escalation is of no benefit to the patient. This implies the existence of an optimal therapeutic concentration range. Due to interindividual variability caused by age, genetic and interethnic factors or drug-drug interactions, antipsychotic plasma concentrations show a wide range of values for the same dosage regimen. This is why clinical pharmacokinetic principles and therapeutic drug monitoring are essential tools for dosage individualisation.

Clinical pharmacokinetics in therapeutics implies that the pharmacokinetic parameters of the medication under scrutiny are known. This is, however, not always the case with antipsychotics since, due to the difficulties encountered in conducting phase I studies in healthy volunteers with these substances, published data are not always complete.

1. Historical Background

In the early 1950s, chlorpromazine was studied as an anti-autonomic substance to protect the body against its own excessive compensatory reactions during major surgery (Laborit 1952). It spread into psychiatry from the field of anaesthesia when Delay and Deniker (1952) demonstrated the efficacy of this drug in the treatment of acute psychosis. After the initial enthusiasm with these drugs, it became evident that their use was associated with a variety of adverse effects including the extrapyramidal disorders such as acute dystonia, Parkinsonism, akathisia, tardive dyskinesia, tardive dystonia and tardive akathisia. This fostered numerous studies of the pharmacology, pharmacokinetics and clinical effects of antipsychotics and the enhancement of our understanding of the mechanisms of both clinical improvement and adverse reactions (Verghese et al. 1991). This subject has recently been reviewed by Schwartz and Brotman (1992).

Despite the enormous amount of work in the field of psychoses, very little is known about the basic mechanisms responsible for the appearance of the disease and its clinical manifestations and, as a consequence, about the mode of action of antipsychotic medication. Despite this lack of knowledge, the measurement of plasma concentrations of the active principles and the use of this information in the frame of dosage regimen design and individualisation can be considered as a major improvement of pharmacotherapy in the field of psychoses. As a result, clinicians are beginning to adopt more conservative dosage strategies, and there is increased interest in the concepts of concentration thresholds and therapeutic margins for these agents. However, therapeutic drug monitoring of antipsychotics has not yet gained the official acceptance received by such authorities as the American Psychiatric Association (APA Task Force 1985) for monitoring of tricyclic antidepressants.

The present review concentrates on the clinical pharmacokinetic progress that led to the present situation. For more details on analytical methods and the clinical pharmacokinetics of antipsychotics, reviews are available (Balant-Gorgia & Balant 1987a; Dahl 1986; Jørgensen 1986; Simpson & Yadalam 1985). Accordingly, the bibliography in the present article is restricted to a minimum.

2. Definitions of Psychoses and Psychotic Symptoms

2.1 Psychoses

Psychosis is a generic term which has been used with a variety of meanings. Recently, more precise diagnostic criteria have been established and, thus, for the specific purpose of this review, only 3 types of disorders will be considered: (a) schizophrenia (strictly speaking); (b) brief reactive psychoses; and (c) manic episodes.

According to DSM-III-R (American Psychiatric Association 1987), schizophrenia is defined by the presence of characteristic psychotic symptoms (e.g. delusions, hallucinations, inappropriate affects, etc.) during the active phase of the illness and social or familial functioning below the highest level previously achieved. The duration of the disease should be at least 6 months, including characteristic prodromal or residual symptoms. Thus, 2 situations must be distinguished: an active phase (or active phases), followed by a residual phase. This is an important distinction, since treatment strategies are not identical in the 2 phases.

A brief reactive psychosis is defined as a sudden onset of psychotic symptoms of at least a few hours' duration, but no more than 1 month's duration, with eventual full return to premorbid level of functioning.

The essential feature of a manic episode is a distinct period during which the predominant mood is either elevated, expansive, or irritable, and there are associated symptoms of the manic syndrome (e.g. inflated self-esteem, flight of ideas, marked impairment of functioning and possibly a short period of delusions or hallucinations).

It is, however, mandatory to remember that these classifications represent, by obligation, an overall simplification of the clinical pictures encountered in psychiatric practice. Patients are individuals and the clinical symptoms reflect these individualities. As a consequence, treatment strategies must imperatively be individualised even if, as presented in this article, some generalisations are necessary for the sake of simplicity and teaching. As experienced in the Psychiatric University Institutions of Geneva, among possible methods of treatment individualisation, therapeutic drug monitoring represents one of the more promising approaches.

2.2 Symptoms and Rating Scales

It is now customary to separate psychotic symptoms, as observed in schizophrenia, into 2 major groups: positive or productive symptoms *vs* negative symptoms. Broadly defined, positive symptoms refer to abnormal productions of the patient, including hallucinations, delusions and some aspects of thought disorder. Negative symptoms generally identify deficits in the patient's behaviour such as blunted affect (e.g. poverty of thought and speech content), emotional withdrawal and impaired social participation. In the past several years, increasing interest has been raised in subtyping schizophrenic symptoms. Research has attempted to link these symptoms to such variables as cerebrospinal fluid (CSF) neurochemistry, brain neuroanatomy, cognitive functioning or movement disorders such as tardive dyskinesia.

Besides the potential effects of such investigations in achieving a better understanding of schizophrenia, they are also of great importance in the field of clinical psychopharmacology, particularly in light of the realisation that antipsychotics such as clozapine may have an effect on negative symptoms. This is of potential importance since it is now well known that 'typical' antipsychotic agents are usually more efficacious in the reduction of positive than negative symptoms.

Traditionally, the Brief Psychiatric Rating Scale or BPRS (Overall & Gorham 1962) is used to evaluate psychotic symptoms. It is a widely studied and well validated instrument for positive symptoms, but it also assesses negative symptoms. In order to overcome its potential limitations in the latter area, specific scales have been developed; among them the Scale for the Assessment of Negative Symptoms or SANS (Andreasen 1982; Andreasen & Olsen 1982).

Note that positive symptoms are usually associated with acute exacerbations of schizophrenia,

brief reactive psychoses and manic episodes. On the other hand, negative symptoms are a specific feature of the residual phases of schizophrenia, since, by definition, brief reactive psychoses imply a full return to premorbid level of functioning. Manic episodes in mixed bipolar disorders, if followed by a morbid phase, turn into depressive states. The distinction between negative symptoms and depressive states is important, since depression in schizophrenic or bipolar disorders necessitates the intervention of antidepressive medication which is of no use in treating negative symptoms in schizophrenic patients.

Open issues in the area of treatment of schizophrenia include the assessment of the overall relevance of quality of life and social adjustment. These problems are presently the subject of extensive clinical research and it is thus possible that, in the future, results of these investigations will modulate our approach to the pharmacological treatment of these diseases. Pharmacokinetic/pharmacodynamic issues such as minimum effective concentrations are, as stated below, of crucial importance in this context.

3. Drugs Used to Treat Psychoses

3.1 Schizophrenia

Schizophrenic patients often receive different types of psychotropic drugs such as benzodiazepines and antidepressants in addition to their antipsychotic medication. In some cases, drug-drug interactions may occur. In the following paragraphs only antipsychotics used in acute schizophrenic episodes or for long term treatment are presented. For the purpose of the present review, antipsychotics are classified in 3 categories:

- 'Typical' low potency (i.e. on a mg/day basis) medications (e.g. chlorpromazine),
- 'Typical' high potency medications (e.g. haloperidol, fluphenazine),
- 'Atypical' medications (e.g. clozapine).

It is not clear if typical low potency and high potency antipsychotics show different overall clinical efficacy. However, there is 1 major difference between these 2 types of compounds in that only drugs given at low doses (i.e. high potency antipsychotics) can be formulated as depot preparations to be administered once or twice per month.

The term 'atypical' antipsychotic broadly describes antipsychotic medications that produce few or no extrapyramidal adverse effects. As an example, clozapine is relatively weak among antipsychotics as a dopamine antagonist and shows similar binding affinities for both the D_1 and D_2 receptors. This classification includes a heterogeneous group of substances in terms of chemical structure, as well as pharmacological profile. Classical or typical antipsychotics characteristically show greater D_2 than D_1 affinity. They also differ widely in chemical structures.

As stated above, an important characteristic of a drug product is the potential existence of more than 1 pharmaceutical form (e.g. oral and depot). Table I indicates the most commonly used antipsychotics, available formulations and average daily doses and suggested range of therapeutic concentrations. All these drugs are used both in active and residual phases of the illness, although, as discussed below, pharmaceutical formulations and dosages may be different. It is also important to remember that some patients will find one antipsychotic agent more tolerable than others. Presently there are no rules except careful clinical observation to detect these particularities.

3.2 Brief Reactive Psychoses

As the definition of this illness implies (see section 2.1), a single acute episode needs pharmacotherapy. The medications used are usually the same as those of the active phases of schizophrenia.

During the acute phase, antipsychotic dosages are the same as are used during exacerbation states of schizophrenia. However, it seems that after 2 or 3 days, patients usually benefit from lower dosages of typical antipsychotics than do relapsing schizophrenic patients (Balant-Gorgia, personal observation). It can, thus, be speculated that careful clinical observation of the early response to antipsychotic therapy might be used as a predictor of

Table I. Available formulations, average daily doses and suggested therapeutic ranges for the most commonly used antipsychotic agents. This table is not exhaustive. It contains only some of the better known drugs

Medication (proprietary name)	Dosage form				Usual daily dose (mg)	Suggested therapeutic concentration range (μg/L)
	IV	IM	PO	depot		
Typical low potency antipsychotics						
Chlorpromazine	✓	✓	✓		25-150	50-300
Levomepromazine		✓	✓		150-250	
Thioridazine			✓		100-600	
Typical high potency antipsychotics						
Flupenthixol			✓	✓[a]	3-15	2-5
Fluphenazine		✓	✓		2.5-10	0.5-2.5
Haloperidol			✓	✓[b]	5-20	5-15
Perphenazine		✓	✓		5-20	0.8-2.4
Pimozide			✓		2-6	
Zuclopenthixol		✓[c]	✓	✓[d]	10-50	6-30[e]
Atypical antipsychotics						
Clozapine		✓	✓		200-600	450-?[f]
Sulpiride			✓		800-1600	

a Usually 1 injection every 2 weeks.
b Usually 1 injection every 4 weeks (rarely every 2 to 3 weeks).
c An acetate ester, allowing injections every 3 days, is also available in some countries.
d Usually 1 injection every 2 to 3 weeks.
e Upper limit not determined.
f The upper limit has not been determined, but above 1000 μg/L, seizures have been observed.
Abbreviations: IV = intravenous; IM = intramuscular; PO = oral.

the course of the disease, particularly in patients suffering from a first psychotic episode. To test this hypothesis requires careful prospective and long term clinical trials in patients admitted for the first time in a psychiatric setting.

3.3 Manic Episodes

Manic episodes represent a particular moment of a mood disorder which can also comprise major depressive episodes or hypomanic phases. As a consequence, patients who suffer from this disease often receive preventive medication such as lithium or carbamazepine, antidepressant therapy during depressive episodes and antipsychotic medication during manic episodes. In the present review, only the latter situation is discussed.

Essentially, these drugs are the same as those listed in table I, but therapy is usually limited in duration. If a patient is receiving lithium therapy, it does not need to be interrupted during antipsychotic administration. It has also been advocated, in the case of a clearcut diagnosis, to start lithium during the manic episode in parallel to the antipsychotic agent. However, this approach has the disadvantage of combining 2 drugs which are already difficult to handle when administered alone, and which when combined have no clear advantage in the majority of patients.

3.4 Pharmacokinetic Profile of Antipsychotics

Human pharmacokinetics of the antipsychotics under review have been studied only partially for some drugs and in more detail for others. It is thus often difficult to obtain more than minimal information from the published results.

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