Clinical Pharmacology in Psychiatry

Neuroleptic and Antidepressant Research

Edited by

Earl Usdin, Svein G. Dahl, Lars F. Gram and Odd Lingjærde

CLINICAL PHARMACOLOGY IN PSYCHIATRY

NEUROLEPTIC AND ANTIDEPRESSANT RESEARCH

Edited by

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Preface

The second International Meeting on Clinical Pharmacology in Psychiatry was held on June 20–21, 1980 at the northernmost university in the world: the University of Tromsø. The 24 hours per day of sunlight allowed for long, pleasant and productive sessions. Confining the coverage of this meeting to areas of neuroleptic and antidepressant research allowed greater in-depth coverage. The rapidity of developments in the field of clinical pharmacology in psychiatry is evidenced by the relatively short interval between the first and second international meetings. The common objectives of the experimental pharmacologists, the clinical pharmacologists, and the clinicians who contributed to the meeting and to this volume are improvements in the utilization of neuroleptic and antidepressant drugs and, ultimately, the better management of psychiatric patients.

Rockville, Tromsø and Odense, 1981

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S.G.D.
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Abbreviations

AAG	α_1-acid glycoprotein
ADTN	2-amino-6, 7-dihydroxy-1,2,3,4-tetrahydroxy-naphthalene
AMI	amitriptyline
AMP	adenosine monophosphate
AMPT	α-methyl-*p*-tyrosine
AUC	area under the curve
BP	blood pressure
BPRS	Brief Psychiatric Rating Scale
cAMP	cyclic AMP
CI	chlorimipramine
CNS	central nervous system
CPRS	Comprehensive Psychiatric Rating Scale
CPZ	chlorpromazine
CPZ-NO	CPZ-*N*-oxide
CPZ-SO	CPZ-*S*-oxide
CSF	cerebrospinal fluid
DA	dopamine
DMCI	demethylchlor-imipramine
DMI	desmethylimipramine
Dopa	dihydroxyphenylalanine
DOPAC	3,4-dihydroxyphenyl-acetic acid
DTγE	destyrosine-γ-endorphin
ECD	electron capture detector
ECG	electrocardiogram
EDTA	ethylene diamine tetraacetic acid
EEG	electroencephalogram
Eq	equivalents
FAD	flavin adenine dinucleotide
FNM	flunitrazepam
FPZ	fluphenazine
GABA	γ-aminobutyric acid
GABA-T	GABA transaminase
GAG	γ-acetylenic GABA
GLC	gas–liquid chromatography
HBE	His bundle electrocardiography
HDRS	Hamilton Depression Rating Scale
5-HIAA	5-hydroxyindole acetic acid
HPLC	high performance liquid chromatography
HRS	Hamilton Rating Scale
HSA	human serum albumin
5-HT	serotonin
HVA	homovanillic acid
IMI	imipramine
IU	International Units
Li	lithium (salts)
LPH	lipotropin = lipoprotein hormone
LSD	lysergic acid diethylamide
LVET	left ventricular ejection time
MAO	monoamine oxidase
MAOI	MAO inhibitor(s)
MF	mass fragmentography
MHPG	3-methoxy-4-hydroxyphenylene glycol
MOPEG	MHPG
MS	mass spectrometry
NaP	sodium phosphate buffer
NE	norepinephrine

NIAMDD	National Institute of Arthritis, Metabolism, and Digestive Disorders
NIMH	National Institute of Mental Health
NPA	*N*-*n*-propylnorapomorphine
NT	nortriptyline
OH-CPZ	hydroxy-CPZ
OH-DA	hydroxy-DA
OH-DMI	hydroxy-DMI
OH-IMI	hydroxy-IMI
OH-NT	hydroxy-NT
PEP	pre-ejection period
P/M	parent drug/metabolite (ratio)
PRL	prolactin
PRP	platelet-rich plasma
PSE	Present State Examination
RBC	erythrocyte
REM	rapid eye movement (sleep)
RIA	radioimmunoassay
RRA	radioreceptor assay
S.A.	specific activity
S.D.	standard deviation
SHAM	slopes, heights, area, first moment (of curves)
STI	systolic time intervals
$t_{1/2}$	half-life
TBEP	tris (2-butoxyethyl) phosphate
TCA	tricyclic antidepressant drug(s)
TD	tardive dyskinesia
TLC	thin layer chromatography
VMA	vanillylmandelic acid
VPD	ventricular premature depolarization

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Section One
Recent Developments in Analytical Procedures of Psychoactive Drugs

Evaluation of existing methods for quantitation of neuroleptics in relation to clinical use

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INTRODUCTION

When Curry in 1968 published his first gas chromatographic method for the determination of chlorpromazine (Curry, 1968) many expected therapeutic monitoring of this drug to be just around the corner. Since then 12 years have elapsed, characterized by an enormous advance in analytical possibilities, but without much progress when evaluated from a clinical aspect (Cooper, 1978; May and Van Putten, 1978); some possible reasons for this will be sought. The present paper is divided into two main parts: first, general considerations concerning some practical and pharmacokinetic items; second, a review of six different analytical methods, including both their advantages and problems, evaluated from a clinical point of view.

GENERAL CONSIDERATIONS

Most assays for neuroleptics have been created by chemists lacking a background in psychiatry. As I see it, this problem is of particular significance, realizing that our efforts are to give patients the best possible medical care. This can, in my mind, be fully achieved only if the chemist and the psychiatrist work close together in monitoring therapeutic drugs and related investigations.

Clinical pharmacological investigations often start with estimating basic pharmacokinetic parameters, such as the elimination half-life, the total clearance and the distribution volume of the parent compound. A further step is a determination of the dose interval and a determination of the plasma concentration profile during constant medication in order to get an