regulated by the CYP3A4 (low affinity). The NT/10-OH-NT ratio during NT treatment is an expression of the CYP2D6 phenotype.

NT and 10-OH-NT interact as to the antidepressant effect. A therapeutic window has been defined by a plasma concentration of 358–728 nmol/l för NT and 428–688 nmol/L for 10-OH-NT. In the CSF, NT and 10-OH-NT reduce HMPG. NT also reduces CSF 5-HIAA, while CSF HVA is increased by NT but decreased by 10-OH-NT. During NT treatment the regression line for HVA and 5-HIAA is shifted anticlockwise in responders but clockwise in non-responders.

There is evidence for a better clinical outcome with increasing plasma concentrations of Z-10-OH-NT, while the opposite is the case with E-10-OH-NT. Given alone E-10-OH-NT seems to be antidepressant along with a favourable side-effect profile.

SES04.2

Drug metabolism of antipsychotics and clinical consequences

P. Baumann*, D. Zullino, C.B. Eap. *Unité de Biochimie et Psychopharmacologie Clinique, University Department Adult Psychiatry, Prilly-Lausanne, Switzerland*

The recent atypical antipsychotics amisulpride, aripiprazol, clozapine, olanzapine, quetiapine, risperidone, sertindol, ziprasidone and zotepine differ widely in their chemical structure and therefore also in their metabolism by cytochrome P-450. While their pharmacokinetic interaction potential with other drugs is relatively low, many psychotropic and somatic drugs interfere with the metabolism of these atypical antipsychotics. For clozapine and olanzapine, several studies show evidence for the existence of a plasma level–clinical effectiveness relationship. Therefore, therapeutic drug monitoring (TDM) of these antipsychotics may be a useful clinical tool in order to optimize treatment in psychotic patients. These findings suggest that for other atypical antipsychotics, such studies should also be systematically performed.

SES04.3

Clinical pharmacogenetic aspects of thymo- and neuroleptic drug treatment

M.-L. Dahl*. *Uppsala University, Department of Medical Sciences, Clinical Pharmacology, Sweden*

Large interindividual differences in drug response and dose requirement are well-known during treatment with thymo- and neuroleptic drugs. This variability is due to genetic, environmental and physiological/pathophysiological factors influencing the pharmacokinetics and pharmacodynamics of drugs. The pharmacokinetic variability is largely due to differences in the activity of cytochrome P450 (CYP) enzymes catalyzing their metabolism. The activity of the polymorphic CYPs (CYP2D6, CYP2C19 and CYP2C9) is under genetic control while for example CYP1A2 and CYP3A4 are more prone to environmental and hormonal regulation. Many thymo- and neuroleptic drugs are substrates of the polymorphic CYP2D6. Genotyping allows identification of poor and extensive metabolisers as well as ultrarapid metabolisers with CYP2D6 gene duplication/multiduplication. Numerous studies suggest a relationship between the CYP2D6 pheno- or genotype and adverse reactions to thymo- and neuroleptic drugs. Prospective individualization of dosage, based on drug metabolic pheno- or genotype, has been suggested but not evaluated so far. Identification of new functionally important SNPs in the genes coding for drug metabolising enzymes, transporters and targets can be expected to open new strategies for improved pharmacotherapy of psychiatric disorders.

SES04.4

Pharmacogenomics, pharmacogenetics and drug response

T. Lewander*. *Department of Neuroscience, Psychiatry, Uppsala University, Sweden*

Non-responders, treatment resistance and side effects are disturbing problems in clinical psychopharmacology. With the advent of pharmacogenomics and pharmacogenetics as new disciplines, individualized drug treatment (personalized medicine) has come within reach. Huge research and educational efforts are needed, however. Polymorphisms in drug metabolizing enzymes are known to explain interindividual variability in drug metabolism permitting individualization of dosage based on genetic information. A next step is to discover DNA tests predicting response to drugs based on genes relevant for their mechanisms of action. Published tests predicting response to antidepressants, antipsychotics and antidementia drugs will be discussed. Another next step is to discover genetic variability explaining the etiology or pathogenesis of disease. Genetic tests defining subtypes within the present diagnostic entities (such as schizophrenia) that are not responding to available drugs are possible. Such knowledge will steer the pharmaceutical industry to develop novel drugs to the benefit of patients presently not treated adequately. In summary, genetic tests for diagnosis, choice of drug and choice of dose will most probably be parts of the future in medicine.

SES04.5

Pharmacokinetic drug interactions of new psychotropic agents

E. Spina*. *University of Messina, Department of Clinical & Experimental Medicine & Pharmacology, Italy*

During the last decade, new psychotropic agents have been introduced in psychiatric practice. Among newer antidepressants, selective serotonin reuptake inhibitors are involved in clinically relevant pharmacokinetic drug interactions due to their inhibitory effects on CYP enzymes. Fluoxetine and paroxetine are potent inhibitors of CYP2D6 and fluvoxamine of CYP1A2. Both fluoxetine and fluvoxamine are also moderate inhibitors of CYP2C9, CYP2C19 and CYP3A4. Fluvoxamine may cause a significant increase in plasma concentrations of clozapine. It has recently demonstrated that fluoxetine and paroxetine may increase total plasma concentrations of risperidone. Other newer antidepressants including venlafaxine and reboxetine have a more favorable drug interaction profile as they do not affect CYP activity. On the other hand, nefazodone is a potent inhibitor of CYP3A4 and may interfere with the elimination of carbamazepine. While novel atypical antipsychotics, notably clozapine, risperidone, olanzapine, quetiapine and ziprasidone, are unlikely to interfere with the elimination of other drugs, coadministration of inhibitors or inducers of the CYP enzymes responsible for their metabolism may modify plasma antipsychotic concentrations, leading to potentially significant effects.

https://doi.org/10.1016/S0924-9338(02)80072-4 Published online by Cambridge University Press