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Screening for genotypic and phenotypic variations in CYP450 activity in patients with therapeutic problems in a psychiatric setting, a retrospective study☆

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ABSTRACT

Objectives: This retrospective study aimed to assess to what extent an adverse drug reaction (ADR), an abnormal therapeutic drug monitoring (TDM) or a non-response, was attributable to an abnormal cytochrome P450 activity in a psychiatric setting.
Method: We collected the results of investigations performed in these situations related to psychotropic drugs between January 2005 and November 2014. Activities of different cytochrome P450 were assessed by genotyping and/or phenotyping. Two experienced clinical pharmacologists assessed independently the possible association between the event and the results of the investigations.
Results: One hundred and thirty eight clinical or biological situations had a complete assessment of all major metabolic pathways of the target drug. A majority of clinical or biological situations were observed with antidepressants (n = 93, 67.4%), followed by antipsychotics (n = 28, 20.3%), benzodiazepines and hypnotics (n = 13, 9.4%), and psychostimulants (n = 4, 2.9%). Genotype and/or phenotype determination was mainly performed because of ADRs (n = 68, 49.3%) or non-response (n = 46, 33.3%). Inter-rater reliability of the scoring system between the pharmacologists was excellent (kappa = 0.94). The probability of an association between ADR, TDM or non-response and metabolic status was rated as intermediate to high in 34.7% of all cases, with proportions of 30.4% and 36.7%, for non-response and ADR respectively.
Conclusion: When indicated by clinical pharmacologists, ADR, TDM or non-response may be attributable to a variation of the metabolic status with an intermediate to high probability in 34.7% of patients, based on the congruent assessment made by two clinical pharmacologists. Further studies assessing the clinical relevance of prospective explorations and clarifying the appropriate method according to the clinical context are needed.

1. Introduction

There is substantial unexplained interindividual variability in drug response in the management of psychiatric disorders [1]. This variability can lead to lack of improvement, adverse drug reactions (ADR) as well as variability in time to respond to treatment. Variability may bring a lack of adherence or put the patient at risk to be definitely considered as resistant or intolerant. This will further lead to the choice of another line of treatment, that is not always needed, thus delaying the overall benefit of the therapeutic regimen [2,3]. Predicting variability and using therapeutic individualization could increase the quality of care management [4,5]. Therefore, strategies able to identify the factors of variability and to select the appropriate drug or its adequate dosage represent promising tools in the care of psychiatric disorders.

Many factors may be involved in interindividual variability in drug response, in every step from drug prescription to drug effect (medications errors and lack of compliance to drug-receptor inter-

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action and desensitization, for example) [6]. Among them, the variability in drug metabolism, which can result in pronounced differences in steady-state plasma concentrations, may be predicted [7,8]. Hence, research has focused on the promise of individualized treatment in psychiatry. Different studies have supported a link between enzyme/transporter activity and the pharmacokinetic or pharmacodynamic parameters of antidepressant or antipsychotic agents, suggesting genotyped-based dose recommendations [4,5,7,9,10].

Hall-Flavin et al. recently demonstrated that the prospective use of a pharmacogenomic testing involving cytochrome P450 (CYP450) and an interpretive report was able to improve depression outcome, by allowing the physicians to select the appropriate drug in a small cohort of patients presenting with major depressive disorder. However, assessment of drug metabolism variability, e.g CYP450 activity, is not a part of the usual care in practice and psychiatrists mainly rely on clinical evaluation or therapeutic drug monitoring (TDM) when available, to start or adapt psychotropic medication.

To date, data are missing about the usefulness of prospective assessment of variability in drug metabolism in psychiatric settings. In the Geneva University Hospitals, clinical pharmacologists of the division of clinical pharmacology and toxicology daily answer to physicians' questions about adverse drug reactions (ADR), abnormal TDMs, non-response to treatment, or therapeutic management (choice of the drug, dose, route of administration), among other situations. After analysing the clinical situations and in order to clarify pharmacological abnormalities, genetic or phenotypic investigations may be proposed by the clinical pharmacologist, based on his clinical expertise, the clinical context, the nature of the ADR, TDM or non-response and the concomitant medications, potentially limiting the interpretation of the tests.

In order to better discuss the benefit of investigating patients' metabolic status during psychiatric therapeutic management and before engaging in a prospective study, this retrospective study aimed to assess to what extent an ADR, TDM or non-response was attributable to a variant of CYP450 activity when indicated by a clinical pharmacologist,

2. Methods

2.1. Patients and setting

The division of clinical pharmacology of Geneva University Hospitals give pharmacological advices to physicians on individual clinical situations, such as the appropriate drug in case of pregnancy or breastfeeding, in case of weight gain, in case of drug interactions, adverse effects or treatment failure, among others.

Questions come from hospitals physicians as well as from private practices, and this for all medical specialities. Individual propositions are summarized in a report and when considered appropriate by a senior clinical pharmacologist, genetic and/or phenotypic investigations are proposed. If the tests are performed, their results are analysed according to the clinical context and summarized in a second report. We retrospectively collected results of genetic and/or phenotypic investigations performed between January 2005 and November 2014 and selected all data related to psychotropic drugs (N = 250). The study was approved by the local ethics committee (Reference: 14–244). Data were excluded if investigations did not assess all major metabolic pathways of the involved drug, according to the table of cytochrome substrates (http://www.hug-ge.ch/sites/interhug/files/structures/pharmacologie_et_toxicologie_cliniques/documents/substrats_et_inhibiteurs_a5.pdf) [11]. For example, an investigation related to citalopram was only included if CYP2C19 and CYP3A4 activities were studied, CYP1A2 and CYP2D6 for duloxetine, CYP2D6 and CYP3A4 for haloperidol etc. The flowchart of data inclusion is illustrated in Fig. 1: 138 therapeutic situations were analysed, which referred to 89 patients and 34 drugs.

2.2. Evaluation criteria

All clinical pharmacology reports were carefully reviewed and classified into different categories according to clinical events, such as ADR and lack of response to the prescribed drug. Two experienced clinical pharmacologists assessed the possible association between these clinical events and the genetic and phenotypic results independently according to a semi-quantitative scale and their clinical judgment (Appendix A). The semi-quantitative scale was mainly built on scientific databases (e.g. http://www.hugge.ch/sites/interhug/files/structures/pharmacologie_et_toxicologie_cliniques/documents/substrats_et_inhibiteurs_a5; DrugBank, http://www.drugbank.ca/; 'The Human Cytochrome P450 (CYP) Allele Nomenclature Database', http://cypalleles.ki.se). For a given drug, each relevant metabolic pathway, whether major or minor, was considered and a global rating was made according to a 3-point scale: 0 = no or low probability of genetic and phenotypic results being linked with a clinical or biological problem; 1 = intermediate probability; 2 = high probability. In case of drugs with active metabolites, the use of the table was completed by the available literature on the respective clinical relevance of the metabolite and the parent compound. In case of disagreement, the opinion of a third expert in clinical pharmacology was sought and retained as the final score. The patient's treatment at the time of the phenotypic and/or genetic investigation was recorded and taken into account when rating the association between metabolic status and event.

2.3. Metabolic status

Activities of CYP2D6, 2C9 and 2C19 were assessed by genotyping and/or phenotyping, whereas activities of CYP1A2 and 3A4 were only determined by phenotyping.

2.3.1. Genotyping

The following variants of the *CYP2D6* gene were genotyped: CYP2D6*3, *4, *5, *6, *35, *41 and duplications, until 2007, when the AmpliChip CYP450 test allowed the simultaneous analysis of 33 CYP2D6 alleles. For the *CYP2C9* and *CYP2C19* genes, the following variants were genotyped: CYP2C9 *2 and *3, CYP2C19*2 and *17 (since 2009).

The predicted phenotypes were based on enzyme activities of these alleles, as listed in 'The Human Cytochrome P450 (CYP) Allele Nomenclature Database' (http://cypalleles.ki.se) or the PharmGKB database (http://www.pharmgkb.org/index.jsp), or in the AmpliChip CYP450 2D6 test. Patients were classified as poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM) and ultra-rapid metabolizer (UM) for CYP2C19 and CYP2D6 and as induced, normal or reduced activity for CYP2C9.

2.3.2. Phenotyping

Phenotyping consists in the administration of probe substrates metabolised by specific CYPs and determination of plasma, blood, or urine metabolic ratios. Probe substrates were caffeine for CYP1A2, flurbiprofen for CYP2C9, omeprazole for CYP2C19, dextromethorphan for CYP2D6 and midazolam for CYP3A4. Individual phenotyping corresponded to the administration of the CYP2D6-specific probe, dextromethorphan. Dextrorphan/dextromethorphan ratio was measured in urinary samples during several years based on cut-off data from previous studies [12,13]. Lately, with the development of dried blood spots