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Understanding pharmacogenetics and drug interactions through case-based examples

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INTRODUCTION

Pharmacogenetics of drug metabolism is progressing in community and primary care settings, presenting a challenge to integrate applied aspects in pharmacy curricula. Phenoconversion, where the metaboliser status predicted by genotype is altered through drug interactions, is often overlooked[1], and warrants further consideration within programmes of study.

METHOD

Case studies from 44 patients on amitriptyline, an established medicine with pharmacogenetic connotations, were selected as pedagogical resources to explain drug-gene, drug-drug, and drug-drug-gene interactions. Data included results of analytical (genetic/chemical) and clinical investigations for the patients who were recruited from Mater Dei Hospital, Malta, following ethics approval and written informed consent. An interactive exercise on three case-based scenarios was integrated in a two-hour seminar delivered to second-year pharmacy students. The teaching model included presentation of applied biochemistry basics followed by hands-on understanding of pharmaco-therapeutic implications.

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Example of interactive cases presented to students

This scenario illustrates how the serum levels of amitriptyline and its active metabolite nortiptyline, as measured through an LC-MS/MS method developed in-house[2], vary between two individual patients with the same CYP2C19/CYP2D6 genotypes, who have been on the same daily dose of amitriptyline for over 20 years. Divergence from the expected blood levels is evident in the patient being co-administered paroxetine, a strong CYP2D6 inhibitor.

Genotype	*CYP2C19 *1/*17*	*CYP2D6 *1/*4*
Metaboliser Status	Rapid	Intermediate
Genotype-guided dosing recommendation as per Clinical Pharmacogenetics Implementation Consortium (CPIC) annotation	*Consider alternative drug not metabolised by CYP2C19* If amitriptyline is warranted, utilize therapeutic drug monitoring to guide dose adjustment	
Amitriptyline Summary of Product Characteristics (SmPC)	*No recommendation specific to metaboliser status* Lower dose to be considered in case of concomitant strong CYP2D6 inhibitor	

Male
61 yrs
Weight: 70 Kg
Side-effects reported: 0
On amitriptyline
+ chlorpromazine

Amitriptyline + Nortriptyline 40 ng/mL

Female
51 yrs
Weight: 100 Kg
Side-effects reported: 10
On amitriptyline
+ chlorpromazine and paroxetine

Amitriptyline + Nortriptyline 260 ng/mL

Measured Levels

Dosage regimen	50mg amitriptyline daily
Therapeutic drug monitoring	Blood withdrawn 15 hours post-dose
Expected levels	Amitriptyline + Nortriptyline 30 – 60 ng/mL

RESULTS

In the cases presented, CYP2D6 inhibition by concomitant drugs (particularly paroxetine) was linked to higher-than-expected serum concentrations of amitriptyline and its active metabolite nortriptyline in the recruited subjects, explaining almost 50% of variation ($P<0.01$). Through the selected case studies, students could identify the impact of genetic variants and the co-administration of CYP inhibitors, on drug-metabolising enzyme activity and individual patient outcomes. The seminar evaluation highlighted that the real-case scenarios helped students understand not only the applied aspects but also the fundamental principles of pharmacogenetics.

CONCLUSION

As the genomics era endures, it is crucial to impart a practical grasp of how clinical pharmacology, embracing real-world patients and the polypharmacy challenge, should complement pharmacogenetics in making precision medicine a working reality. Leveraging research findings from local investigations provides an opportunity for students to learn from examples having familiar therapeutic regimes and clinical settings. A case-based learning experience enables future pharmacists to comprehend the translational value, appreciating their prospective role in spearheading effective implementation for patient care.

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