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The CYP2D6 metaboliser status of patients prescribed risperidone for the treatment of psychosis

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Abstract

Aim To identify the distribution of CYP2D6 metaboliser status in patients who were being prescribed risperidone for the treatment of psychosis in a New Zealand-based clinical population.

Method 100 AmpliChip CYP450 Test® kits were made available by Roche Diagnostics. Clinicians in mental health services across three Auckland District Health Boards were instructed that the tests were being made available for use with patients who were being prescribed risperidone for the first time. Test results were fed back to the prescribing clinician. Data analysis was descriptive in nature; however, chi-square and independent sample t tests were employed to examine differences in age, gender, and ethnicity.

Results Data were obtained for 93 patients. Poor and intermediate metabolisers each constituted 10.6% of the sample. There were no ultra-rapid metabolisers. Statistical analysis revealed no significant between-group differences with respect to age or gender. The between-group difference in ethnicity status showed a trend towards statistical significance.

Conclusion Sample size limitations likely contributed to the finding that no statistically significant between-group differences were identified. In theory, though, for one in five patients a higher level of adverse effects might be predicted for a normal dose of risperidone, potentially leading to issues around treatment adherence or treatment failure.

Personalised prescription (the tailoring of medication type and dose to one's genetic make-up) has recognised potential to improve clinical outcomes across a range of common disorders.¹

Information on a patient's CYP2D6 genetic polymorphism offers one example of how personalised prescription might be employed in practice. CYP2D6—part of a group of liver-based enzymes that have a primary role in breaking down foreign or unwanted substances—is specifically involved in the metabolism of many medications, including commonly prescribed antiarrhythmics, antidepressants, antipsychotics, and antiemetics.²

The rate of metabolism of any CYP2D6-susceptible drug will vary according to phenotypic expression. Four phenotypic representations of CYP2D6 are currently recognised. These include: ultra-rapid metabolisers (UM) who have more than two copies of the relevant gene; extensive metabolisers (EM) who have two active copies; intermediate metabolisers (IM) who have one active copy; and poor metabolisers (PM) who have no active copies. Failure to account for this genetic variance may result in suboptimal clinical outcomes. For example, standard drug dose may not result in therapeutic plasma levels for UMs and may increase the risk of an adverse drug

reaction in PMs.³

Evidence suggests these scenarios have eventuated in clinical practice.^{4,5} Thus, knowledge of an individual's CYP2D6 status presents one means by which the risk of under- or over-prescribing CYP2D6-susceptible drugs may be avoided. Whilst the least problematic EM phenotype is dominant in most populations, the more problematic PM and UM phenotypes are not uncommon.^{3,6}

Evidence suggests the PM phenotype is highest amongst Western European populations and lowest amongst Asian populations (expressed in 10% and 1% of the population, respectively) whereas the UM phenotype is highest amongst African populations and lowest amongst Western European populations (expressed in 30% and 1% of the population, respectively).⁶

Few studies have explored the distribution of CYP2D6 phenotypes in New Zealand-based populations. Those studies that have been conducted, however, suggest substantial differences exist in the distribution of CYP2D6 phenotypes between New Zealanders of Māori and European descent,⁷ and that the distribution amongst the latter group is consistent with other populations of Western European origin.⁸

Given the potential benefits in adopting a personalised prescribing approach, this paper presents the results of a study that sought to identify the distribution of CYP2D6 metaboliser status among patients who were being prescribed risperidone for the first time for the treatment of psychosis in a New Zealand-based clinical population. This population presents as an ideal target for possible personalised prescription based on CYP2D6 status as risperidone is primarily metabolised by this enzyme group and a number of studies have noted an increase in adverse drug reactions amongst PMs prescribed antipsychotics.^{4,9,10}

In addition to reporting CYP2D6 distribution amongst this population, the paper also examines for age, sex and ethnic relationships that might predict the distribution and comments on health systems issues associated with CYP2D6 testing.

Method

Setting—This study was set in the Mental Health Services of the three District Health Boards (DHBs) serving the greater Auckland region: Auckland, Waitemata, and Counties Manukau. Records indicate that over 28,000 mental health clients access these services per annum.¹¹ Of these, Waitemata DHB serves half, while Auckland and Counties Manukau DHBs serve around a quarter each.

Māori are over-represented in mental health services across all three DHBs, forming 17% of the service user population,¹¹ compared with around 11% of the DHBs' catchment population.¹² However, Pacific and Asian peoples are under-represented, respectively comprising 8.5% and 5.2% of the service user population,¹¹ compared with 14.4% and 18.9% of the catchment population.¹²

Procedure—Ethical approval for the conduct of this study was obtained from the Northern X Regional Health Research Ethics Committee (Reference NTX/06/05/055). One hundred AmpliChip CYP450 Test® kits were made available at no cost by Roche Diagnostics for use between September 2006 and December 2007.

Information about these tests was provided to all clinicians occupying the positions of Senior Medical Officer, Registrar and House Officer (n=237.6 full time equivalent positions) in mental health services via a series of presentations and flyers distributed through existing networks within the three DHBs.

Email reminders were also sent to all clinicians throughout the study period. These included information on the potential benefits of the test, what was involved for clinicians and other process issues such as how the test was funded and the expected time frame for receiving results.

Clinicians were instructed that the tests were being made available specifically for use with patients who they believed were being prescribed the antipsychotic risperidone for the first time. Use of the test was not mandatory and compliance was not formally monitored; however, clinicians were encouraged to employ the test with all patients meeting the specified criteria, until December 2007 or until all 100 tests had been utilised (whichever came first).

Once appropriate patients were identified, the clinician was directed to prescribe 'as usual', then complete an AmpliChip CYP450 test order form which was given to the patient, who was required to visit a laboratory to have a blood sample taken. Testing was undertaken in a laboratory based in the South Island of New Zealand. Results were fed back to the prescribing clinician (in paper and electronic format) as per standard laboratory processes, so that results were available at subsequent patient visits.

Data were entered into an SPSS database (version 13). Much of the analysis was descriptive in nature; however, chi-square and independent sample t tests were employed to examine differences in age, gender

and ethnicity.

Results

Overall, 42 doctors ordered 95 AmpliChip CYP450 tests for 93 patients. Two patients were tested twice, one of these by the same doctor. Duplicate data were excluded from the analysis. The average number of tests used per clinician was 2.24 (range 1–8), with just over half of all clinicians ordering only one test. The majority of tests were conducted with Waitamata DHB patients (66.7%), while Auckland DHB patients constituted 25.8% of patients tested and Counties Manakau DHB patients comprised the final 7.5%. A breakdown of patient metaboliser status is shown in Table 1.

Table 1. Distribution of patients' metaboliser statuses (n=93)

| Metaboliser Status | n-(%) |
|--------------------|------------|
| Poor | 10·(10.6%) |
| Intermediate | 10·(10.6%) |
| Extensive | 68·(69%) |
| Ultra-rapid | Nil·(0%) |
| No-call* | 5·(5.3%) |

*No-call==could-not-be-determined-by-laboratory.

Table 2 presents selected demographic characteristics for the 88 patients whose metabolic status was identifiable.

Table 2. Demographic profile of patient participants by metabolic status†

| Variable | Poor/Intermediate-Metabolisers (n=20) | Extensive-Metabolisers (n=68) | Overall (n=88) |
|-----------------|---------------------------------------|-------------------------------|----------------|
| Mean age | 37.9+/-19.1 | 32.2+/-15.6 | 33.6+/-16.5 |
| %Female | 47.1 | 40.4 | 41.9 |
| Ethnicity | | | |
| %European | 75.0 | 52.9 | 58.2 |
| %Māori | 12.5 | 19.6 | 17.9 |
| %Pacific Nation | 6.3 | 11.8 | 10.4 |
| %Asian | 6.3 | 15.7 | 13.4 |

†Patients with 'poor' or 'intermediate' metabolic status were grouped into a single category in order to improve the power of statistical analysis. Patients whose metabolic status could not be determined ('no calls') were excluded from the analysis.

Statistical analysis revealed no significant between-group differences with respect to age ($t=1.17$, $df=87$, $p=0.247$), gender ($\chi^2=1.60$, $df=1$, $p=0.304$) or ethnicity (NZ European vs. other; $\chi^2=3.12$, $df=1$, $p=0.107$). Given the small sample size, the failure for statistically significant differences to emerge may be the result of Type II error.

The between-group difference in ethnicity status, in particular, showed a trend towards statistical significance and may have been obtained with a larger sample size. Further study in this area is therefore warranted with larger sample sizes, before firm conclusions can be drawn regarding the relationship between metaboliser status and demographic characteristics in the study population.

Discussion

This study sought to identify the prevalence of four recognised CYP2D6 phenotypes amongst

patients prescribed risperidone for the treatment of psychosis. As the EM phenotype is considered to be the 'norm',⁶ it was expected that the majority of participants would fall into this category. This proved to be the case as 77% of participants with an identifiable metaboliser status (n=88) were EM.

The distribution of PMs (10.6%) found by this study was also consistent with that reported in the literature⁶ and the absence of any UMs was not unexpected given that no people of Arabian or African descent were present in our sample (UMs are rare in non-Arabian or -African populations).^{3,13}

This study further sought to identify possible age, gender or ethnicity differences in the distribution of CYP2D6 phenotypes. No statistically significant differences were identified in any of these domains; however, sample size limitations likely contributed to this result, especially with regard to ethnicity.

Thus, whilst our findings concur with a study by Roberts et al where the prevalence of PMs among Māori was similar to that found in New Zealand Caucasians,⁸ caution should be taken not to over generalise this finding. On this note it is perhaps worth acknowledging that four of the five 'no call' subjects were of Māori or Pacific ethnicity, suggesting the question of different distribution for Māori and or Pacific remains a possibility that deserves exploration.

These data, alongside those of Lea et al, do suggest that a wider spread sampling of New Zealand Māori and Pacific people in New Zealand is warranted to see if these are racial differences which would have relevance for treatment planning. This would best be studied through an epidemiological based survey of the incidence of CYP2D6 polymorphisms in the New Zealand population.

The incidence of PMs (10.6%) and, to a lesser extent, IMs (10.6%) reported in this study is such that one could expect that knowing a patient's metaboliser status would be useful in the personalising of dose and possibly medication choice. These findings indicate that, in theory, for one in five patients, a higher level of adverse effects might be predicted for a normal dose of risperidone, potentially leading to issues around treatment adherence or treatment failure. It is well recognised in the literature about personalised prescription that the phenotype can never be the sole determinant of a clinician's dose choice.^{2,14} However, knowing this piece of information could reduce some of the intangibles.

Further exploration of the interaction between prescribing clinicians' knowledge of their patient's metaboliser status and dosing decisions is warranted. It is proposed that a randomised controlled trial would provide the most suitable methodology, where under one condition, clinicians receive the Amplichip test results and under the other, patients are untested. Data should be collected confirming receipt of test results and dosing decisions made subsequently. Test results should be ordered at first contact with the patient and received in accordance with standard laboratory turnaround times, for example within 24–48 hours.

To conclude this paper, it is worth noting a systemic issue identified during the data collection process. The Amplichip assay is a one-off test that provides clinical information relevant for the rest of the patient's life. This feature of the assay, however, presents a challenge for health record systems and especially the storing and accessing of laboratory test results. Standard laboratory information display systems, such as Concerto, display tests in chronological order, the latest first. For most purposes this is effective. For these one-off-enduring-tests it is a potential problem since this result becomes imbedded in a host of results and unless carefully looked for cannot assist the doctor in personalising drug/dose.

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