Letter to the Editors

CYP2D6 deficiency, a factor in ecstasy related deaths?

Ecstasy related drug deaths are infrequent but tragic events, which are difficult to study due to their relative rarity and the multiple modes of death. Serotonin syndrome, hepatic failure, hyponatraemia, and cerebral haemorrhage all having been identified as causes of death [1]. The group of drugs known as 'ecstasy' includes a range of ring substituted amphetamines, the most common ones being methylenedioxymethamphetamine [MDMA], methlylenedioxyamphetamine [MDA] and methylenedioxyethylamphetamine [MDEA]. Widespread polydrug use and changing patterns among the users of ecstasy is common, adding to the complexity [2]. Tucker *et al*. raised the possibility that genetically determined poor metabolism of ecstasy may be a predisposing factor for acute toxicity (serotonin syndrome) and ecstasy related deaths [3]. This hypothesis was examined by Schwab *et al*. [4] and by O'Donohoe *et al*. [5] who found no evidence for such a link, although the authors conceded that a larger study was required.

CYP2D6 [debrisoquine hydroxylase], one of the cytochrome P450 enzymes, is involved in the metabolism of MDMA. CYP2D6 activity is lacking in 5% to 10% of Caucasians, known as poor metabolizers [PM] [3]. These individuals can be distinguished from individuals with levels of enzyme in the normal range [extensive metabolizers [EM]] using a polymerase chain reaction [PCR] based genotyping assay.

We have compared the prevalence of the *CYP2D6* PM genotype with that in the general population, using a PCR assay to analyse post mortem samples from individuals believed to have died from ecstasy related toxicity (defined by the pathologist as the presence of MDMA, MDA or MDEA at post mortem toxicological examination).

Samples of post mortem material from 15 individuals who had tested positive for MDMA, MDA or MDEA were obtained from various U.K. pathology departments. In 14 cases liver tissue specimens were used and DNA was extracted from the paraffin embedded tissue by dewaxing with xylene followed by proteinase K digestion [6]. In one case a blood sample had been obtained prior to death and used for DNA preparation by the standard methods. Biological material was screened for the non functional *CYP2D6*3* and *CYP2D6*4* alleles by two separate PCR reactions which involved amplifications of exons 4 and 5 followed by digestion of the products with the restriction enzymes *Bst*NI and *Msp*I, respectively [7, 8].

Thirteen samples could be genotyped for both the defective alleles *CYP2D6*3* and *CYP2D6*4*, one for the *CYP2D6*4* allele only, and in one no PCR product was obtained. None of the 13 samples genotyped for both *CYP2D6* alleles was homozygous for *CYP2D6*3, CYP2D6*4* or a combination of the two, and therefore was not predicted to be PM. Five of the subjects were heterozygous and the remainder were homozygous wild type [Table 1].

The frequency of the *CYP2D6*3* plus the *CYP2D6*4* allele was 0.18, which is close to the value of 0.25 previously reported for a group of 662 British controls [9]. The heterozygote frequency in the ecstasy-related deaths patients was 35.7% which was not significantly different from that control group in the previous study [40.3%, $P > 0.05$]. The genotyping procedure used detects 88% of phenotypic CYP2D6 poor metabolizers [10].

Ecstasy related deaths are rare and complex events, which have so far defied adequate explanation. Of the 14 post mortem samples that could be genotyped in this study, none was genotyped as PM of *CYP2D6* and, therefore, would not be expected to show deficient metabolism of MDMA. Our study is small which limits its power and fails to demonstrate statistical significance but our findings do support those of O'Donohoe that poor metabolizers of *CYP2D6* are not at greater risk of ecstasy-related death. There appear to be other metabolic mechanisms which compensate for the poor metabolism of these drugs by CYP2D6 [11].

Table 1 CYP2D6 genotyping data.

Sample	*Area*	*CYP2D6 genotype*	*Predicted phenotype*
1	Nottingham	*1/*3	EM
2	Preston	*1/*1	EM
3	Preston	*1/*1	EM
4	Blackpool	*1/1*	EM
5	Ayr	*1/*1	EM
6	Ayr	*1/*1	EM
7	Ayr	*1/*1	EM
8	Sheffield	*1/*1	EM
9	Sheffield	*1/*1	EM
10	Sheffield	*1/*1	EM
11	Sheffield	*1/*4	EM
12	Sheffield	*1/*4	EM
13	Sheffield	*1/*4	EM
14	Sheffield	*1/*4	EM

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