

INTRODUCTION:

Etizolam [4-(2-chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine] is a benzodiazepine analogue. The benzene ring is replaced with a thiophene ring making the drug a 'thienodiazepine'. This poster reviews four post-mortem cases, submitted to Imperial College Toxicology Unit, in which etizolam was detected in the post-mortem, femoral blood.

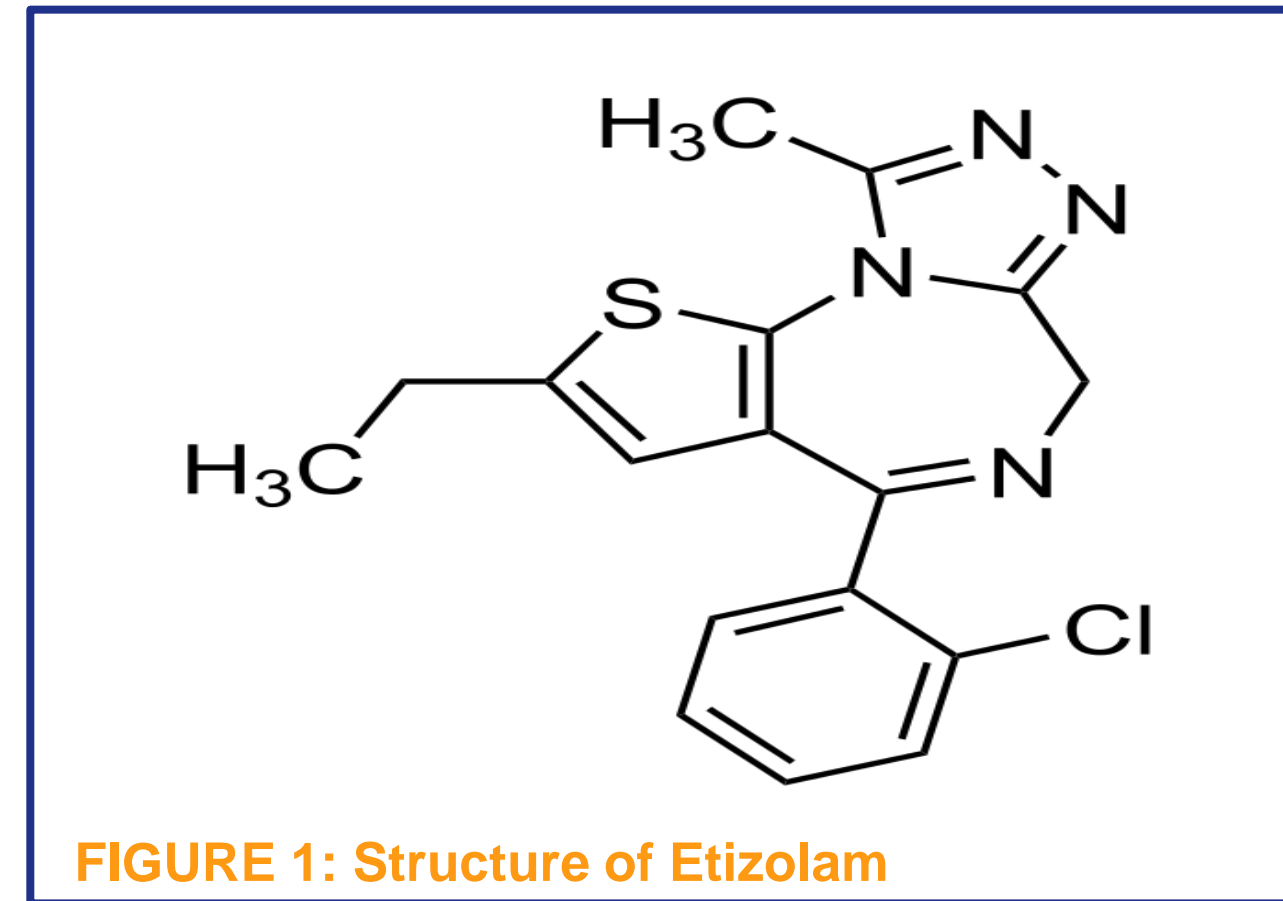


FIGURE 1: Structure of Etizolam

Medicinal use:

- Widely available in Japan (*Depas, Sedekopan*) and India (*Etilaam, Etizola*).
- Adult daily doses range from 0.5 – 3.0 milligrams.
- Used in short-term treatment of insomnia or anxiety. ¹
- Acts as a full agonist at the benzodiazepine receptor. ²
- Has potent hypnotic properties comparable with other short-acting benzodiazepines.
- (Etizolam has anxiolytic effects six times greater than diazepam). ³
- Thought to have reduced tolerance/dependence than classical benzodiazepines. ⁴
- However, long-term use may produce similar side-effects to benzodiazepines: addiction, hostile behaviour, memory loss and severe withdrawal. ⁵

Illicit use:



- Etizolam is not licenced as a medicine in the UK.
- It is offered via the internet and in 'head shops' as a 'legal' alternative to benzodiazepines.
- Reports on drug forums suggest it is abused for its euphoric effects or to 'comedown' after taking stimulant drugs:⁶⁺⁷
 - ❖ *"Made me feel happy (in a scattered, muddled, giddy sort of way)"*
 - ❖ *"Just a bit of heaviness in my body, slight euphoria and just a bit more feeling of well being. Nothing too strong, just a relaxed body and calm mental state"*
 - ❖ *"Etizolam is certainly not a party drug but more of a lifestyle enhancer"*
 - ❖ *"Etizolam are perfect for Comedowns... Gives you a nice smooth landing"*
 - ❖ *"Fun, helpful for anxiety, but 'more-ish', and potentially dangerous for those with poor judgement about use"*

Pharmacology:

- Etizolam is absorbed fairly rapidly with peak plasma levels achieved within 0.5 – 2 hours. ⁸
- Average peak plasma concentrations range from 0.008 – 0.02 µg/ml following therapeutic doses. ⁹⁺¹⁰
- Average elimination half-life (t_{1/2}) ranged from 3.4 – 15 hours. ⁶
- Volume of distribution: 0.7 – 1.1 L/Kg (minimal concentration increase after death). ⁶

ANALYSIS:

Identification:

Etizolam was detected during routine screening using Gas Chromatography-Mass Spectrometry (GC-MS) after liquid-liquid back extraction.¹

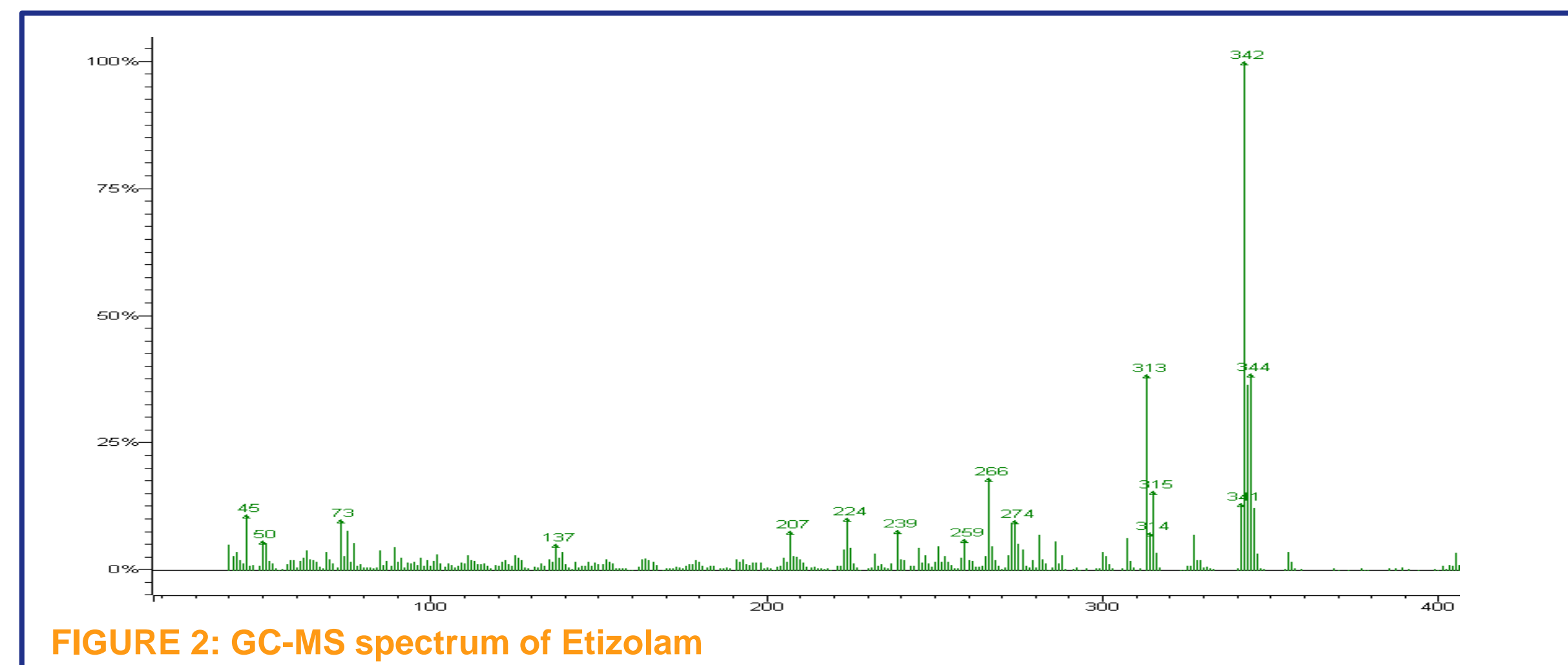


FIGURE 2: GC-MS spectrum of Etizolam

Quantitation:

Etizolam was quantitated using High Performance Liquid Chromatography with Diode Array detection (LC-DAD) after basic liquid-liquid extraction.

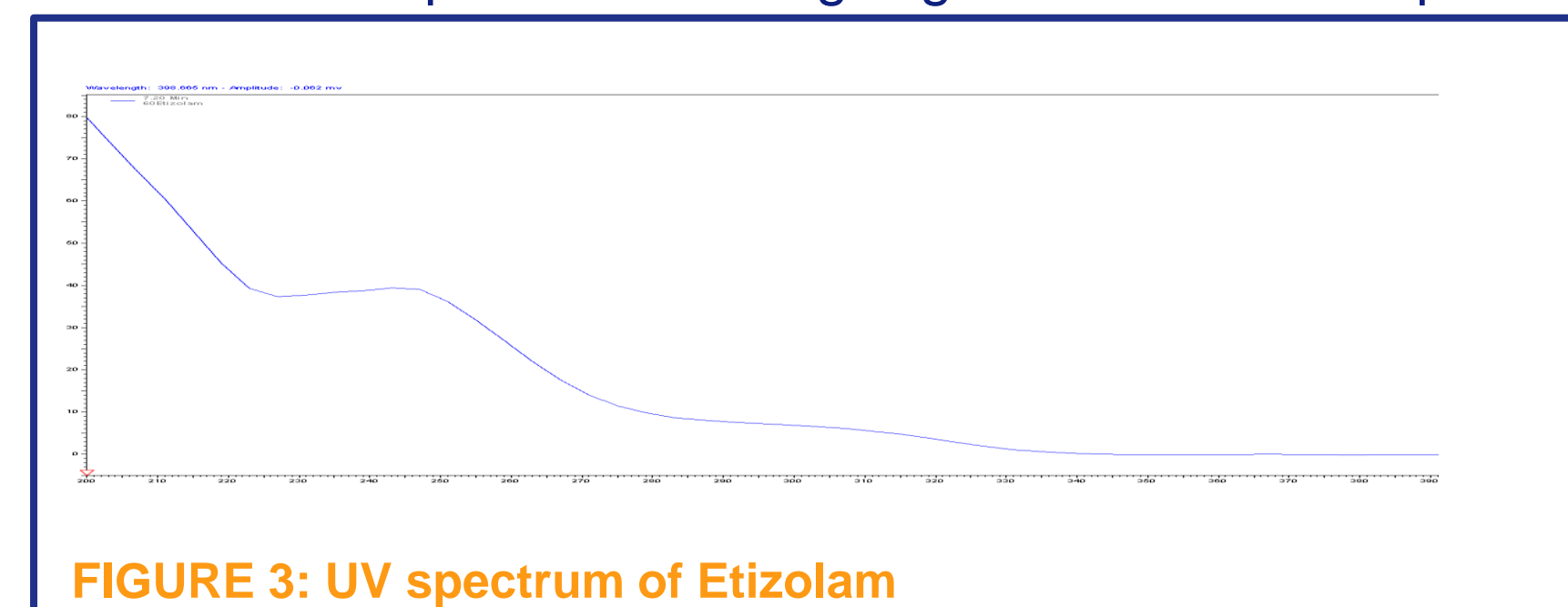


FIGURE 3: UV spectrum of Etizolam

- Column: C18 (Hi-chromTM)
- Mobile phase: phosphate buffer (pH6): methanol (60:40% v/v)
- Internal standard: mirtazapine
- Optimum wavelength: 245nm.

RESULTS: The findings are summarised in the tables below.

CASE 1:

- 52 year old female
- Found dead in church yard surrounded by empty medication packets

Drug	Blood Concentration
ETIZOLAM	0.09 µg/ml
Diphenhydramine	High therapeutic
Amitriptyline	High therapeutic
Ethanol	<10 mg/dL

CASE 2:

- 47 year old male
- History of alcohol abuse and depression
- Found dead in bed surrounded by empty medication packets.

Drug	Blood Concentration
ETIZOLAM	0.46 µg/ml
Venlafaxine	7.10 µg/ml
Mirtazapine	1.41 µg/ml
Citalopram	0.79 µg/ml
Ethanol	<10 mg/dL

CASE 3:

- 25 year old male
- Took 'ecstasy' at a rave
- Took liquid etizolam at home to help him sleep

Drug	Blood Concentration
ETIZOLAM	0.52 µg/ml
MDMA	2.33 µg/ml
MDA	0.08 µg/ml
Methoxetamine	0.19 µg/ml
Ethanol	<10 mg/dL

CASE 4:

- 35 year old male
- Found dead in bed

Drug	Blood Concentration
ETIZOLAM	0.07 µg/ml
Dihydrocodeine	0.44 µg/ml
Codeine	0.61 µg/ml
Morphine	0.10 µg/ml
Ethanol	<10 mg/dL

DISCUSSION:

Post-mortem etizolam concentrations:

- There is only one notable etizolam overdose in literature: a fatal drowning following intentional overdose. A post-mortem blood concentration of 0.264 µg/ml was recorded. ⁶
- In our cases the Etizolam concentration in post-mortem blood ranged from 0.07 – 0.52 µg/ml.
- In all of the cases there was another drug involved.
- Deaths from benzodiazepine-type drugs are rare. The risk of severe respiratory depression and death is greatly increased when the drug is combined with alcohol or other CNS depressants (e.g. opiates).

α-hydroxyetizolam:⁶

- α-hydroxyetizolam is the major metabolite produced with pharmacological activity nearly equal to etizolam
- It accumulates in plasma due to a longer elimination half-life and concentrations of the metabolite can be around twice that of the parent drug.
- It would be important in post-mortem cases to measure the metabolite to establish overdose.
- Unfortunately, there is currently no reference standard readily available.

REFERENCES

1. T. Nakamae et al. **Case report: Etizolam and its major metabolites in two unnatural death cases**, *Forensic Sci Int.*, 2008; 182: e1-e6
2. S. Paterson et al. **Screening and semi-quantitative analysis of post mortem blood for basic drugs using gas chromatography/ion trap mass spectrometry**, *J. Chromatogr. B*, 2004; 813(1-2): 323-330