A simple and fast, yet effective and precise UHPLC method for qualitative determination of an antidepressant medication trazodone in biological samples has been developed. Both UV (DAD, 254 nm) and fluorescence (Ex. 320, Em. 440 nm) detection modes are determined applicable. Excellent linearity ($r > 0.9999$) over sufficiently wide concentration range (from 0.15 up to 15 µg mL$^{-1}$) covering therapeutic, toxic, and comatose blood levels has been demonstrated. High precision (RSD < 1.6%), good recovery (85%) and low detection limits (LOQ 150 ng mL$^{-1}$) make this relatively rapid method (ca. 30 min for a single run) a suitable asset in identification of acute intoxications, diagnosis refinement and treatment monitoring. The applicability and importance of newly developed method are demonstrated by a clinical case of Trittico self-poisoning and a corresponding treatment course.

Keywords: Trittico, Desyrel, trazodone, overdose, self-poisoning, acute intoxication

Introduction

Trazodone (under the trade name Trittico® in Europe and Desyrel® in USA, among many others worldwide) is a second-generation SARI-class antidepressant of phenylpiperazine type. Chemically, it is 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-1, 2, 4-triazolo[4, 3-apyridin-3(2H)-one (Fig. 1). Commonly, trazodone is used in treatment of major depressive disorder [1, 2], anxiety disorder [3] and insomnia [4], although there are positive reports for its application in cases of schizophrenia [5], OCD [6] and alcohol dependence [7, 8]. For analytical toxicology, some important reference blood trazodone concentrations are as follows: therapeutic – 0.8-1.6 µg mL$^{-1}$; toxic – above 4.0 µg mL$^{-1}$, and comatose (fatal) – 12.0 µg mL$^{-1}$ and higher [9]. An in-depth review on trazodone’s pharmacology can be found elsewhere [10].

Although trazodone is considered safer than TCAs and MAOIs [11] and over dosage is reported to be with good prognosis and low lethality in controlled conditions, combined acute intoxications with other psychotherapeutic agents (usually in cases of suicide attempts) are potentially fatal [12, 13]. Thus, availability of a rapid and precise method for blood trazodone level determination is important in evaluation of detoxification procedures (in cases of acute intoxications) as well as in therapeutic drug monitoring (during the course of treatment).

A modern approach to determination trazodone in biological samples is represented mostly by chromatographic techniques. Identification is usually done by GC-MS for major metabolite 1-(3-chlorophenyl) piperazine (mCPP) [14]. Quantitation adopts HPLC separation combined with UV [15], fluorescence [16], or electrochemical [17] detection, or in tandem with mass-spectrometry [18]. As for clinical use we praise swiftness and reliability over sensitivity and precision, we needed to combine advantages of known techniques and optimize performance for requirements of our Department of Analytical toxicology.

Fig 1: Chemical structure of trazodone – a phenylpiperazine type antidepressant
Dynamically analyzing analytical toxicology data (trazodone concentration profile on Fig. 2) it became obvious that initial gastric lavage did not bring the desired efficiency, as trazodone concentration continued its growth. Within 24 hours blood trazodone concentration fell below the toxic level, and, consequently, on the 3rd day – below the therapeutic zone. The patient was discharged from the hospital on the 5th day, without having any toxicological problems.
Conclusion
Acute intoxications, caused by combination of trazodone and other psychoactive drugs, may lead to unexpectedly severe ongoing and, although with a good prognosis, are potentially fatal. A HPLC technique for trazodone identification and determination has been proposed and validated. The method has been applied for diagnosis refinement and treatment monitoring. It is shown that in some cases an initial gastric lavage may not guarantee a successful stomach purge.

Acknowledgement
We would like to thank the team of Analytical toxicology Lab, Military Medical Academy, Sofia, for valuable support and scientific guidance.

References