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Review article

Analytical methods for quantification of tranexamic acid in biological fluids: A review

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ABSTRACT

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine with antifibrinolytic properties. There is still a lack of pharmacokinetic and pharmacodynamic data concerning variable age groups undergoing surgeries with high blood loss. The optimum dose and administration schedules of TXA are still subject of research, aiming at a safe inhibition of fibrinolysis in the perioperative period. Hence, effective methods for determination of TXA in biological samples are needed. The aim of this review is to discuss the required sample treatment procedures and the analytical methods applied for quantification of TXA, focusing on selected derivatisation agents and internal standards. Methods comprising a separative step (GC, LC or CZE) coupled to spectrophotometric, fluorimetric and mass spectrometry detection were considered, showing a tendency for implementation of MS/MS methods in more recent reports. Detection limits ranging from 0.01 to 0.5 μg mL^{-1} in blood plasma were so far attained using LC-MS/MS.

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Contents

Abbreviations: ACA, ε-aminocaproic acid; ACN, acetonitrile; BEH, ethylene bridged hybrid; BTB, bromothymol blue; CE, capillary electrophoresis; CPB, cardiopulmonary bypass; CZE, capillary zone electrophoresis; DLLME, dispersive liquid-liquid microextraction; DNS-Cl, dansyl chloride or 5-(dimethylamino)naphthalene-1-sulfonyl chloride; L-DOPA, 3,4-dihydroxy-L-phenylalanine; EDTA, ethylenediaminetetraacetic acid; EC, electron capture; EI, electron ionization; FA, fluorescamine; FL, fluorescence; GC, gas chromatography; HaCaT, human keratinocyte cells; HPLC, high performance liquid chromatography; IS, internal standard; LC, liquid chromatography; LOD, limit of detection; LOQ, limit of quantification; MS, mass spectrometry; MS/MS, tandem mass spectrometry; MRM, multiple reaction monitoring; MW, microwave; NDA, naphthalene-2,3-dicarboxaldehyde; OAC, ofloxacin acyl chloride; OPA, *o*-phthalaldehyde; PE, paper electrophoresis; PITC, phenyl isothiocyanate; RP, reversed phase; RSD, relative standard deviation; SIM, selected ion monitoring; SPME, solid-phase microextraction; TXA, tranexamic acid; UPLC, ultra-high performance liquid chromatography; UV, ultraviolet; UV–Vis, ultraviolet-visible.

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1. Introduction

Tranexamic acid [*trans*-4-(aminomethyl)cyclohexane-1-carboxylic acid] (TXA, Fig. 1, **1**) is a synthetic derivative of the amino acid lysine developed in 1960's and introduced into clinical practice >40 years ago. TXA is a biologically active compound with antifibrinolytic effect. It reversibly blocks the lysine binding sites on plasminogen through formation of a reversible complex of the drug with plasminogen molecules disrupting the action of plasmin and preventing the dissolution of the fibrin clot [1–4]. As a result, TXA is associated with reduction of bleeding due to its inhibitory effect on clot breakdown.

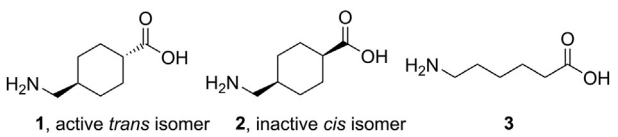
TXA was recently included in the World Health Organization (WHO) core list of essential medicines for use in adult trauma patients with ongoing significant haemorrhage, or at risk of significant haemorrhage within 8 h of injury [5]. This list contains minimum medicine needs for a basic health-care system which gives the most efficacious, safe and cost-effective medicines for priority conditions. Its usefulness has been reported in a wide range of clinical conditions to manage abnormal bleeding or bleeding tendencies in which local or systemic hyperfibrinolysis is considered to be involved [4,6–8]. TXA is employed to treat women suffering from menorrhagia, bleeding during pregnancy and for prevention and treatment of postpartum haemorrhage, in upper gastrointestinal bleeding, bleeding after cardiac surgery, to reduce blood loss and transfusion in trauma patients, etc. [9–12]. The therapeutic value of TXA has been also considered in the prevention of human ovarian carcinoma cell growth [13,14]. Other potential clinical and cosmetic applications have been proposed for TXA namely treatment of ultraviolet radiation-induced pigmentation and suppression of ultraviolet B eye irradiation-induced melanocyte activation [15–20].

The interest on TXA overwhelmingly grew after withdraw, in 2008, of the antifibrinolytic agent aprotinin, a serine protease inhibitor [21,22]. TXA has been associated, however, with an increased incidence of postoperative seizures and has led to adverse neurological outcomes, longer hospital stays, and increased in-hospital mortality [23]. The lack of pharmacokinetic and pharmacodynamic data, in different age groups undergoing different surgeries, reinforce the difficulties to define the optimum therapeutic plasma concentration of TXA needed to safely inhibit fibrinolysis in the perioperative period. Some dosing schedules were based on doses previously determined to inhibit plasma fibrinolytic activity in different settings; while others were developed empirically. Clinical trials performed so far suggest a wide variability in response to TXA. Thus, a renewed attention to TXA has emerged in the literature as the pharmacokinetic, optimum dose and administrations schedules of this drug are still subject of research.

The present paper aims to provide an updated review of the analytical methods reported for the determination of this compound in biological material such as plasma, serum and urine. The review covers and critically addresses an extensive selection of instrumental analytical techniques ranging from liquid and gas chromatography to electrophoresis, automated and electroanalytical approaches. Attention is also paid on sample preparation protocols focusing on biological material.

2. Determination of TXA in biological fluids

In what concerns biological matrices, TXA has been mainly determined in human plasma and serum as summarized in Tables 1, 2 and 3. Because of the complexity of the biological matrices, most of the techniques require a careful and extensive sample pre-treatment, to remove potential interferences, namely proteins and branched-chain amino acids. As TXA has a structural resemblance to amino acids, the concomitant presence of these molecules in biological samples can interfere upon separative procedures prior to analysis.



1, active *trans* isomer **2**, inactive *cis* isomer **3**

Fig. 1. Chemical structures of tranexamic acid (**1** and **2**) and ε-aminocaproic acid (**3**).

The most commonly used methods associate reversed-phase HPLC to fluorescence [24–29] or UV [30–32] detection, as depicted in Fig. 2. Considering that TXA does not possess in its chemical structure a chromophore or fluorophore, exhibiting therefore a poor absorption at 220 nm, a derivatisation step is, in most cases, needed to increase the methods' sensitivity. More recently, several methods have been developed based on chromatographic techniques coupled to mass spectrometry [33–41]. MS detection enables straightforward analyte identification and quantification eliminating the need of any derivatisation procedure, which may introduce large assay variations, namely the stability of the newly formed derivative. Less common applications reporting the determination of TXA include techniques such as capillary electrophoresis and paper electrophoresis coupled to UV–Vis detection [42,43].

2.1. Sample preparation

Generally, the determination of TXA concentration in plasma or serum obtained from collected human blood requires firstly the deproteinization of the samples, after addition of the chosen internal standard (IS) if used (Tables 1, 2 and 3). A fluxogram of method analysis focused on sample treatment strategies used for TXA is presented in Fig. 3.

Several protein precipitation reagents have been applied to achieve this goal, specifically picric acid [42,44], heptafluorobutyric acid [33], perchloric acid [25,34,35,43], methanol [37,41], ethanol [26,30], and acetonitrile [24,28,31,39,45,46], which is in fact the most commonly used. Fiechtner et al. [28] reported the pre-treatment of plasma samples with leucine dehydrogenase prior to deproteinization by acetonitrile. This enzyme was used to minimize interferences by branched-chain amino acids since it is highly specific for these compounds [47].

Depending on the precipitation reagent used and if a derivatisation procedure is followed, pH adjustment might be necessary [24,26,30,31,35,44]. If one chooses to use a mass spectrometer as detection system, the supernatant can, at this stage, be transferred into an auto-sampler vial and subsequently injected into, for example, the LC-MS or LC-MS/MS system [34,39]. In other cases, the supernatant is dried, the residue retaken in the mobile phase and injected [37].

Solid phase microextraction (SPME) has also been applied to the determination of TXA concentration in human plasma [36,38,40,48]. The viability of this technique in clinical use for the analysis of polar drugs such as TXA was first established by Bojko et al. [36] by analysing plasma samples from patients who underwent heart surgery with the use of cardiopulmonary bypass (CPB). For this, commercial thin-film microextraction (TFME) fibers coated with octadecyl carbon chains (C_{18}) were used after preconditioning overnight in a methanol:water (1:1, v/v) solution. Based on studies performed to evaluate the extraction time profile and to improve the method sensitivity, 300 μL of sample were exposed to the fiber for 90 min with vortex agitation at 1200 rpm, followed by rinsing with purified water for 30 s. The fiber was then placed, for desorption, in a mixture of ACN:water (4:1, v/v) with 0.1% (v/v) formic acid using the same type of agitation. The efficiency of this method was compared with standard techniques such as protein precipitation and ultrafiltration and the results revealed that the accuracy and precision obtained were equivalent. The linear ranges of TXA concentration in plasma samples obtained for this SPME procedure was 1.56–25 and 25–300 μg mL^{-1} [36].

Bojko et al. [40] latter developed an automated TFME procedure, where a polyacrylonitrile-C_{18} 60 μm thin-film was applied to cover miniaturized stainless steel blades. The amount of analyte extracted in this modified format was 12 times higher when compared to conventional fibers [36]. However, both procedures required an extensive time for extraction and desorption, around 2 h for each step. Considering the

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