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gece kitaplığı

International Research and Evaluations in the Field of Health Sciences

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INTERNATIONAL RESEARCH AND EVALUATIONS IN THE FIELD OF HEALTH SCIENCES

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Chapter 1

LC-MS/MS METHODS FOR THE DETERMINATION OF PACLITAXEL IN BIOLOGICAL FLUIDS: A REVIEW*

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INTRODUCTION

Oncology stands out as a dynamic field of science, driven by continuous development and innovative research leading to advances in treatment methods. In this context, paclitaxel is a chemotherapy drug that is effectively used in the treatment of a wide variety of cancer types. The drug's areas of application include breast, ovarian, bladder, lung, prostate, melanoma, oesophageal cancers, Kaposi's sarcoma, and various other solid tumours. This review details paclitaxel's therapeutic indications, its mechanism of action at the cellular level, its role in suppressing tumour cell proliferation, as well as dosage adjustments, infusion protocols, routes of administration, and possible contraindications; it also emphasises the clinical importance of monitoring patients undergoing treatment. Paclitaxel, initially known as "taxol" when it was first discovered, is a natural diterpenoid compound derived from the Pacific yew tree (Taxus brevifolia). The drug's discovery was the result of natural product screening programmes conducted by the National Cancer Institute (NCI) in the United States in the late 1960s and early 1970s. During this process, researchers examined various plant extracts in an effort to identify compounds with anticancer potential, and paclitaxel's pronounced cytotoxic effects attracted attention. In particular, its capacity to halt the cell cycle and induce apoptosis by inhibiting microtubule depolymerisation has made paclitaxel a priority agent in anticancer research (1).

Liquid chromatography tandem spectrometry (LC-MS/MS) a technique combining liquid chromatography with tandem mass spectrometry, is an effective analytical method that integrates chromatographic systems providing high resolution in the separation of analytes with mass spectrometric detection offering high selectivity and sensitivity. Thanks to its mass spectrometry component in particular, this technique offers advanced sensitivity and separation capacity, thereby gaining significant momentum in analytical applications. Today, it is recognised as one of the most effective and reliable techniques in the field of pharmaceutical analysis (2).

In this review, the pharmacological properties of paclitaxel are examined, and LC-MS/MS analyses of paclitaxel in biological fluids are provided.

*GENERAL SECTIONS

1. Taxane Class Compounds and Paclitaxel

Taxanes constitute a group of chemotherapeutic agents widely employed in cancer management. Chemotherapy involves the systemic administration of cytotoxic drugs designed to destroy malignant cells and suppress tumour proliferation. Each category of chemotherapeutic agents acts through distinct biological mechanisms to accomplish this goal. Taxanes exhibit their antineoplastic properties by interfering with the cellular machinery responsible for cell division and replication in cancer cells. Since uncontrolled proliferation is essential for tumour expansion, the inhibition of this process by taxanes effectively contributes to limiting cancer progression. These compounds specifically interrupt mitosis — the stage of the cell cycle in which cells divide — and therefore are classified as mitotic inhibitors. Taxanes are naturally sourced from yew trees. Paclitaxel, the first compound identified within this class, was originally isolated from the bark of the Pacific yew (Taxus brevifolia). As a plant-derived anticancer drug, paclitaxel represents one of the two major plant-based chemotherapy classes, the other being the vinca alkaloids, which are obtained from periwinkle plants. (3).

Paclitaxel is an anticancer agent with mitotic inhibitor activity and hydrophobic properties that inhibits tumour growth by stopping cell division. This compound, together with docetaxel, belongs to a group of cytotoxic diterpene compounds derived from yew trees called taxanes. It is particularly noteworthy for its high efficacy against certain malignant tumour types known to be resistant to conventional chemotherapy agents. Paclitaxel was first identified in 1962 as part of the National Cancer Institute's research into naturally occurring anticancer compounds. During these studies, thousands of plant extracts were screened to identify substances with therapeutic potential, and it was determined that the crude extract obtained from the bark of the slow-growing, rare Pacific yew tree (Taxus brevifolia) exhibited significant antitumour activity in various tumour models (4).

2. Therapeutic Indications of Taxane Class Compounds

In ovarian cancer treatment, paclitaxel is used in combination with a platinum-derived agent as first-line therapy in advanced or metastatic cases; it is also recommended as a second- line treatment option in the same patient group. In breast cancer cases, it is included in treatment following anthracycline and cyclophosphamide administration for adjuvant thera-

py in early-stage, node-positive patients. In metastatic or advanced breast cancer cases, it is combined with anthracycline if its use is appropriate; if not appropriate, it can be used alone or in combination with trastuzumab in patients with immunohistochemically detected HER2 positivity. It is used as second-line therapy in cases where combination chemotherapy has failed. Nevertheless, in the absence of clinical contraindications, anthracyclines are generally incorporated into first-line chemotherapy protocols. For patients with non-small cell lung cancer (NSCLC) who are unsuitable for surgical intervention or radiotherapy, paclitaxel is typically administered as part of a first-line regimen in combination with a platinum-based compound. Moreover, in the management of AIDS-related Kaposi's sarcoma, paclitaxel serves as an effective chemotherapeutic option, particularly when used as a second-line treatment. (5).

3. Side Effects of Taxanes

Taxanes, like other chemotherapy drugs, target cancer cells with rapid division characteristics, inhibiting their proliferation and thus exhibiting anticancer effects. However, they can also damage rapidly dividing healthy cells and cause side effects. The group of rapidly dividing cells includes skin cells, hair follicle cells, epithelial cells in the gastrointestinal system, and haematopoietic blood cells. The interaction of taxanes with rapidly dividing cells during chemotherapy often results in the development of certain adverse effects. Among these, neutropenia is one of the most frequently observed toxicities, characterized by a reduction in white blood cell count that increases the patient's vulnerability to infections. Peripheral neuropathy is another notable complication, manifesting as a "glove-and-stocking" pattern of numbness, tingling, or weakness in the hands and feet. Additional adverse reactions commonly associated with taxane-based regimens include myalgia, arthralgia, injection-site rash, nausea, vomiting, fluctuations in blood pressure, thrombocytopenia, anaemia, and alopecia. The intensity and incidence of these side effects can vary depending on the specific taxane used and the dosage administered. (3).

4. FDA-Proven Effect of Taxanes

Paclitaxel was approved by the FDA as a chemotherapeutic agent for the treatment of ovarian cancer in December 1992. In order to meet the growing demand for the drug, a research group led by Robert Holton developed a method for the semi-synthetic production of paclitaxel. In sub-

sequent studies, the drug's efficacy against metastatic breast cancer was evaluated, and clinical trials yielded positive results. Following these findings, in 1994, the FDA also approved paclitaxel for use in the treatment of breast cancer. Paclitaxel is used effectively in combination therapy (6).

5. Chemical Formula and Molecular Information of Paclitaxel

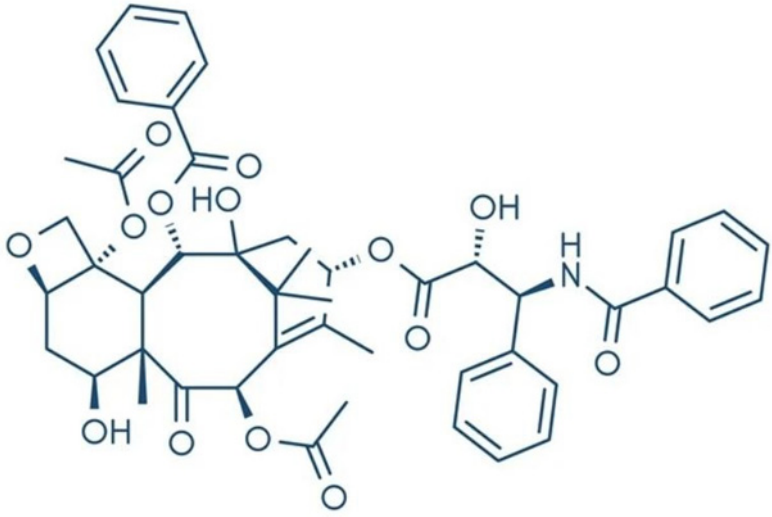

Figure 1. *Chemical formula of paclitaxel (4)*

Molecular formula: C47H51NO14, molecular weight: 853.9 g/mol, melting point: 216–217 °C, solubility: 5.56×10^{-3} g/L (7).

6. Pharmacological Aspects of Paclitaxel

Paclitaxel possesses a narrow therapeutic margin and exhibits strong lipophilic properties, rendering it almost insoluble in aqueous environments. Currently, cancer chemotherapy with paclitaxel often causes hypersensitivity reactions. One of the main challenges in achieving clinical success with paclitaxel is the availability of the active ingredient and limitations in its pharmaceutical delivery. Various problems encountered in the treatment process today clearly demonstrate the need for a more effective and safer delivery system for this drug. Therefore, current approaches have primarily focused on: developing formulations without Cremophor® EL, the possibility of large-scale preparation, and stability over longer periods. Identifying new molecules with more effective therapeutic activity will continue to be an integral part of healthcare systems (8).

It has rapid distribution, exhibits distribution in large volumes, and binds significantly to plasma proteins. Paclitaxel is metabolised in the

body primarily via the cytochrome P450 enzymes CYP2C8 and CYP3A isoenzymes. When administered intravenously, the most common toxic effects include neutropenia, hypersensitivity reactions, peripheral neurotoxicity, and hair loss (alopecia). Several new formulations are in development; albumin-bound paclitaxel (Abraxane) has recently been approved. Development studies are being conducted on oral formulations of taxane group drugs, and most of these formulations are still in Phase I clinical trials. These new dosage forms are expected to increase both treatment efficacy and safety, as well as provide ease of administration (9).

Paclitaxel and its semi-synthetic analogue docetaxel exert their antitumour effects by promoting the polymerisation of microtubule structures and inhibiting the disassembly of these structures. Both agents halt cell division by increasing intracellular microtubule stability. Although these compounds bind similarly to the β-tubulin subunit, the microtubule structures resulting from their effects differ. For example, the microtubules formed by docetaxel contain an average of 13.4 tubulin subunits, while those formed by paclitaxel are limited to approximately 12 subunits. Docetaxel penetrates cells more rapidly than paclitaxel and remains active in the cell for a longer period. In vitro and in vivo studies conducted in line with these pharmacokinetic advantages have demonstrated that docetaxel exhibits 2 to 4 times higher antitumour efficacy than paclitaxel. Furthermore, numerous studies have shown that prolonged exposure to paclitaxel significantly increases treatment efficacy (10). The antitumour efficacy of paclitaxel is largely dependent on the presence of the C13 side chain, A ring, oxetane ring, and the benzoil group at the C2 position. Paclitaxel is highly lipophilic in its chemical structure and therefore exists as a white crystalline powder with low solubility in water (11).

7. Mechanism of Action of Paclitaxel

Unlike traditional cancer drugs, paclitaxel does not affect DNA and RNA synthesis in cancer cells or damage DNA molecules. Its mechanism of action is primarily based on microtubules, which form spindle fibres during the prophase stage to transport chromosomes towards the cell poles. In the subsequent stages of cell division, these structures disintegrate and dissolve. Under normal conditions, microtubules lose their structure through depolymerisation when exposed to cold environments or calcium ions. However, paclitaxel interferes with this process; it binds to microtubules, increasing their stability. Thanks to this binding, microtubules maintain their structure without degrading despite cold or calcium effects and gain resistance to depolymerisation. Therefore, paclitaxel

treatment supports tubulin polymerisation and inhibits the progression of mitosis (12).

8. Discovery and Development of Paclitaxel

The discovery of paclitaxel and its journey to clinical use is based on a long and systematic research history. In 1964, as part of a joint project between the US National Cancer Institute (NCI) and the Department of Agriculture (USDA), Taxus brevifolia (Pacific yew) samples were found to possess cytotoxic properties. Following this discovery, in 1967, the Wall laboratory identified the active compound isolated from the plant and named it "taxol". In 1971, the chemical structure of the compound was published scientifically, and in 1978, its antitumour effects were observed in mouse tumour models. In 1979, studies conducted by the Horwitz laboratory revealed paclitaxel's effect on microtubule stabilisation. Following these scientific developments, the drug was included in phase I clinical trials in 1984 and phase II clinical trials in 1985. In 1991, the NCI transferred the commercial rights to taxol to Bristol-Myers Squibb (BMS), and this transfer of was debated in the US Congress. In 1992, BMS registered the name "Taxol," and in the same year, the FDA approved the drug for use in the treatment of ovarian cancer. Additionally, the Pacific Yew Act was enacted to protect the Taxus brevifolia species. In 1993, a second congressional hearing was held regarding this transfer process and in 1994, the FDA also approved Taxol for use in the treatment of breast cancer. In the same year, a semi-synthetic production method for the drug was also approved by the FDA. By 1995, the legal protection period for T. brevifolia had expired. Finally, in 1999, the United States Food and Drug Administration (FDA) officially approved the use of paclitaxel for the treatment of non-small cell lung cancer (13).

REVIEW OF ANALYTICAL METHODS

MA Fernández-Peralbo and colleagues conducted a quantitative investigation of paclitaxel and its principal metabolites in the serum, plasma, and tissues of ovarian cancer patients following intraperitoneal chemotherapy, employing an LC–MS/MS approach. They proposed an analytical protocol capable of detecting paclitaxel, 6α-hydroxypaclitaxel, and p-3′ -hydroxypaclitaxel at sub-nanogram per millilitre concentrations. The sample preparation involved a liquid–liquid extraction step to purify and concentrate the analytes before chromatographic analysis. Quantification was achieved using LC–MS/MS in selected reaction monitoring

(SRM) mode, which allowed for highly selective identification and precise quantitation in biological matrices. Detection limits were established at 0.03–0.15 ng/mL for serum and 0.07–0.62 ng/g for tissue samples, while relative standard deviation values between 0.5% and 2.7% confirmed the intra-day precision of the method. The analytical approach was successfully applied to samples from 13 women diagnosed with ovarian peritoneal carcinomatosis undergoing hyperthermic intraperitoneal chemotherapy (HIPEC). The results demonstrated that this method is suitable for post-treatment monitoring of therapeutic effectiveness and potential toxicity.

Similarly, Bianna Posocco et al. developed a novel LC–MS/MS method for determining paclitaxel and its main metabolite, 6α-hydroxypaclitaxel, in human plasma, which was subsequently utilized in a clinical pharmacokinetic study. The method enables sensitive and specific quantification across all clinically relevant paclitaxel dosage ranges, relying on rapid protein precipitation using minimal plasma volumes. Chromatographic separation was achieved on a SunFire™ C18 column (2.1 × 150 mm, 3.5 µm particle size, 92 Å pore size) with a mobile phase composed of bidistilled water and acetonitrile, both containing 0.1% formic acid. Detection was carried out via electrospray ionization (ESI) in positive ion mode using SRM acquisition, providing a robust and reproducible approach for pharmacokinetic evaluation. The developed bioanalytical method was successfully validated in accordance with the bioanalytical method validation guidelines published by the FDA and EMA. Calibration curves yielded linear results ($R^2 \geq 0.9948$) in the concentration ranges of 1–10,000 ng/mL for paclitaxel and 1–1,000 ng/mL for 6α-hydroxy-paclitaxel, demonstrating high accuracy and precision of the method. Intra- and inter-day precision and accuracy assessments were carried out at three concentration levels for paclitaxel and its major metabolite, 6α-hydroxy-paclitaxel. The obtained values remained within acceptable analytical ranges, with precision below 9.9% and accuracy between approximately 91% and 115%. The validated method demonstrated limits of detection within 0.03–0.15 ng/mL for serum and 0.07–0.62 ng/g for tissue matrices. Repeatability, expressed as relative standard deviation (RSD), was maintained between 0.5% and 2.7%. These findings confirm that the LC–MS/MS approach provides reliable quantification of paclitaxel and its metabolite in plasma samples, supporting its application in optimizing dosage regimens and monitoring therapy-related toxicities in pharmacokinetic investigations.

Tarek Baati and co-workers developed an ultra-sensitive LC–MS/MS method to quantify paclitaxel released from nanocarriers in vitro, using a liquid-phase extraction step for sample purification. The technique involved methanol and a mild acid (acetic acid) during sample preparation

to prevent drug degradation and to achieve recoveries exceeding 80% using an internal standard system with both paclitaxel and docetaxel. This rapid and selective approach enabled quantification of paclitaxel in cell culture media and lysates over linear ranges of approximately 1–250 nM and 5–250 nM, respectively, with limits of quantification at sub-picomole levels. The method was effectively applied to A549 human non-small cell lung carcinoma cells to evaluate the amount of paclitaxel remaining in the medium and intracellular compartment following incubation at various concentrations. Owing to its sensitivity, the method offers a valuable tool for studying the kinetic behaviour of paclitaxel release from nanocarrier systems, a crucial factor in validating drug delivery platforms for cancer therapy.

In another investigation, Pavan K. Yadav et al. examined the combined pharmacokinetic behaviour of paclitaxel (PTX) and bortezomib (BTZ) for potential co-therapy in breast cancer treatment, utilizing a validated LC–MS/MS method. Both analytes were separated using a C18 reversed-phase column under an isocratic mobile phase containing formic acid in methanol and ammonium acetate buffer. The analytical method achieved a lower limit of quantification of 1 ng/mL with a total run time of six minutes per analyte, and demonstrated linearity between 1 and 600 ng/mL. The established LC–MS/MS protocol was applied to evaluate the oral pharmacokinetic profile of a nanoformulation co-loaded with PTX and BTZ in female Sprague-Dawley rats. The method exhibited excellent reproducibility, sensitivity, and accuracy, fulfilling U.S. FDA bioanalytical validation criteria for parameters such as linearity, stability, and precision.(17).

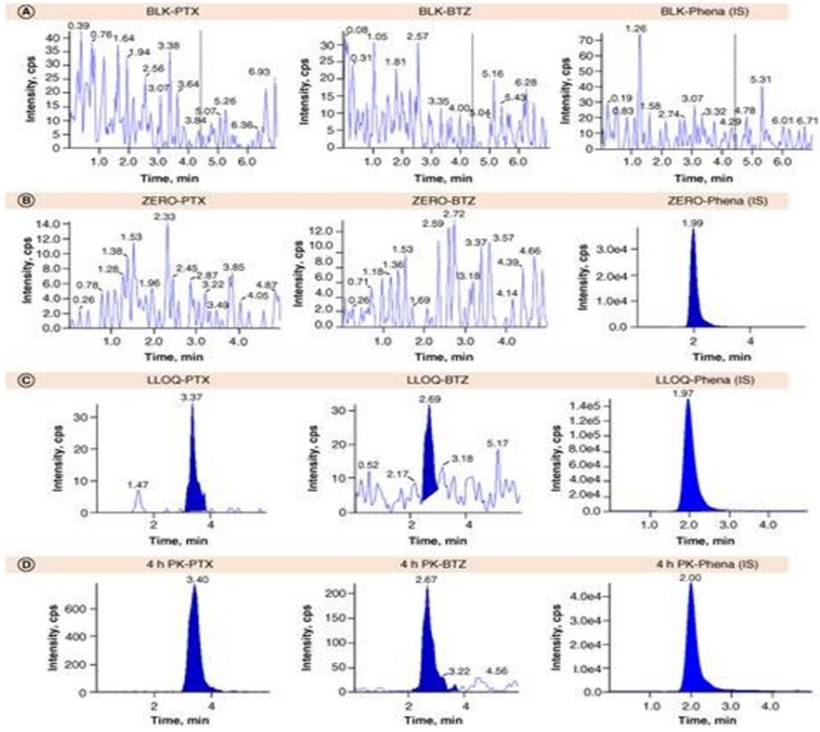

Figure 2. *(A) female blank plasma, (B) female SD-rat plasma (zero sample), (C) female SD rat plasma spiked with PTX and BTZ at LLOQ, and (D) MS/MS chromatograms of the PTX- BTZ pharmacokinetic sample at 4 hours. Chromatograms of phenacetin (IS) were used with each BTZ and PTX plasma sample (17).*

Susan M. Christner et al. quantitatively evaluated paclitaxel and its 6-alpha-OH and 3-para-OH metabolites in human plasma using LC-MS/MS (Figure 3). A high-performance liquid chromatography-mass spectrometry method was developed to quantitatively determine paclitaxel and its 6-alpha-OH and 3-para-OH metabolites in 0.1 mL of human plasma. Following liquid-liquid extraction with MTBE, chromatographic separation was achieved using a Phenomenex Synergy Polar Reverse Phase column (4 µm, 2 mm × 50 mm) and a gradient of acetonitrile and 0.1% formic acid in water over an 8-minute run time. Mass spectrometric analysis was performed on an ABI SCIEX 4000Q instrument operating in positive mode using an electrospray ionisation (ESI) source. The method yielded linear results for paclitaxel in the range of 10–10,000 ng/mL and for both major metabolites in the range of 1–1,000 ng/mL; accuracy values ranged from 94.3% to 110.4%, and the coefficient of variation was measured to be below 11.3%, demonstrating that the method is both accurate and precise. The recovery rate from plasma samples was found to

be between 59.3% and 91.3%, while the matrix effect was determined to be between -3.5% and +6.2% and negligible. In sample stability tests, the freeze- thaw stability was 90.2%–107.0%, the stability of samples stored at -80°C for 37 months was 89.4–112.6%, and the stability of samples kept at room temperature for 4 hours was 87.7– 100.0%, all of which were within acceptable limits. This method allows for detailed examination of the pharmacokinetic and pharmacodynamic behaviour of paclitaxel and its metabolites in a clinical setting; it also has potential for use in therapeutic drug monitoring and in the phenotypic assessment of patients' CYP2C8 and CYP3A4 enzyme activities (18).

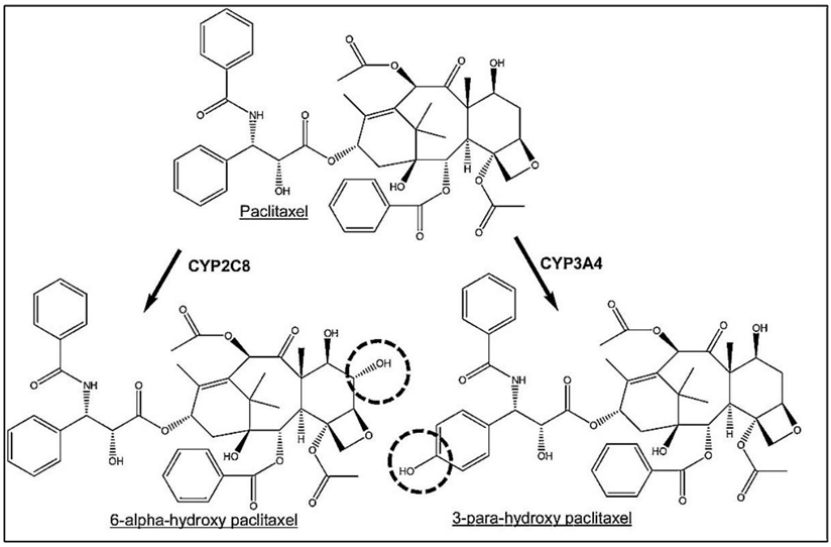

Figure 3. *Paclitaxel and its metabolites, 6-alpha-hydroxy paclitaxel and 3-para-hydroxy paclitaxel (18).*

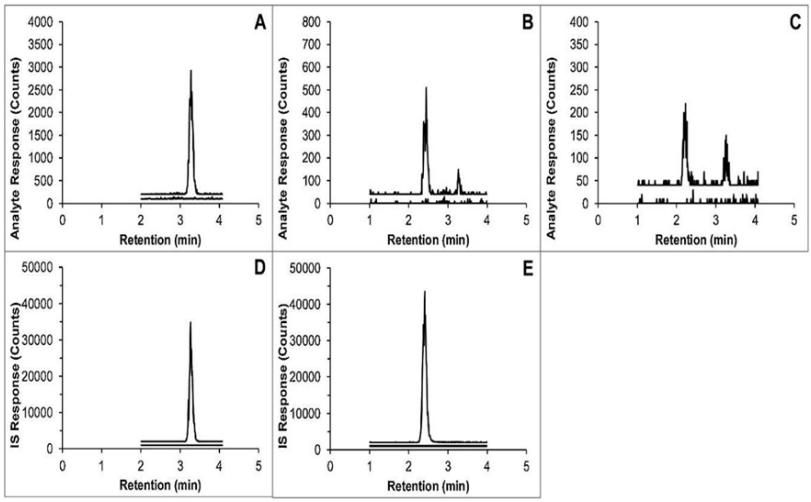

Figure 4. *The ion signals related to the detection of paclitaxel (PTX) and its metabolites at different concentrations in human plasma and control plasma (18).*

In Figure 4, Figure A shows the data obtained by adding PTX (m/z 854.5 → 286.0; 3.3 min) at a concentration of 10 ng/mL LLOQ to control plasma with an offset of 200 counts and to human plasma with an offset of 100 counts. Similarly, Figures B and C present the detection of 6-α–OH-PTX (m/z 870.5 → 286.0; 2.5 min) and 3-p–OH-PTX (m/z 870.5 → 569.5; 2.3 min) at the 1 ng/mL LLOQ level are presented. The internal standards [13C6]-PTX (m/z 860.5 → 292.0; 3.3 min) and [D5]-6-α–OH- PTX (m/z 875.5 → 291.0; 2.5 min) were analysed at a concentration of 500 ng/mL with different offset values. These methods enable the quantitative analysis of PTX and its metabolites (18).

Xinran Chen and co-workers established a validated LC–MS/MS protocol capable of simultaneously quantifying vancomycin, norvancomycin, methotrexate, paclitaxel, and imatinib in human plasma. The method was developed in accordance with international bioanalytical validation guidelines and successfully implemented in a clinical setting. The calibration ranges for these analytes were 0.5–100 μg/mL for vancomycin and norvancomycin, 5–1000 ng/mL for methotrexate, 10–2000 ng/mL for paclitaxel, and 5–500 ng/mL for imatinib. Method validation demonstrated that both accuracy (bias) and precision values for all compounds were within ±15%, fulfilling regulatory requirements. The recovery efficiency, normalized against an internal standard, was approximately 45% for vancomycin and norvancomycin, whereas near-complete recovery (≈100%) was achieved for methotrexate, paclitaxel, and imatinib. No significant carry-over was detected in the analytical sequence. Sample stability was

confirmed for at least 24 hours in the autosampler, up to 72 hours under refrigerated storage (4°C), and for one week at −80°C. Comparable drug concentrations were observed between plasma and serum matrices.

Correlation analyses indicated that methotrexate and vancomycin plasma levels were positively associated with serum creatinine concentrations, and imatinib exposure increased with patient age. For paclitaxel, systemic exposure was positively correlated with both therapeutic response and adverse event frequency. Considerable interindividual and intraindividual variability in plasma drug concentrations was reported. Nonlinear pharmacokinetic evaluation suggested that maintaining paclitaxel plasma levels above approximately 0.05 μmol/L could serve as a predictive marker for both clinical efficacy and potential toxicity. (19).

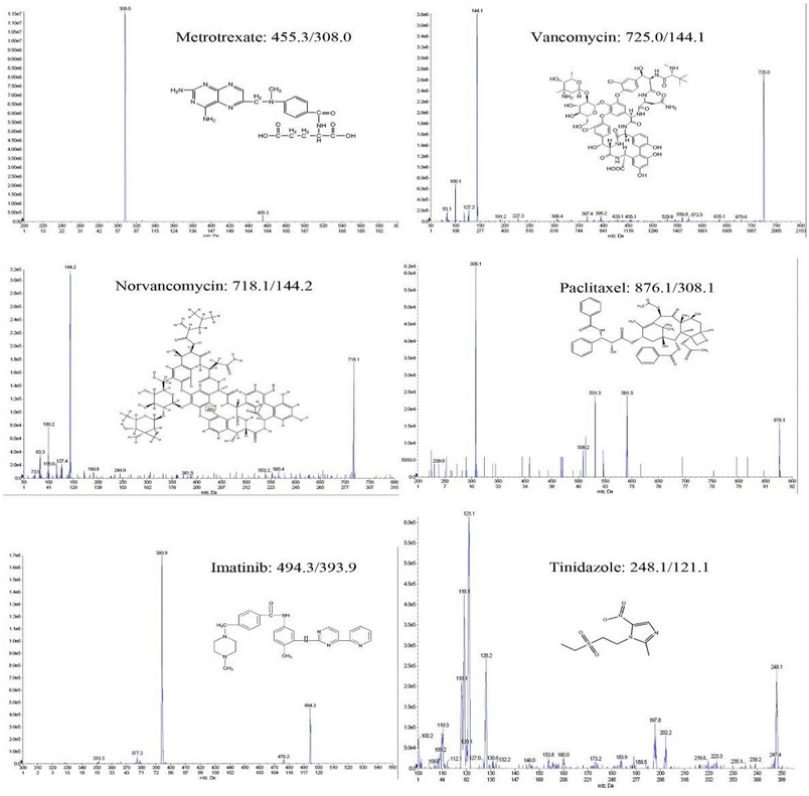

Figure 5. *MS/MS conditions for vancomycin, norvancomycin, methotrexate, paclitaxel, imatinib, and tinidazole (19).*

Lin Hou and colleagues reported, for the first time, the development and validation of an LC–MS/MS method enabling the simultaneous quantification of curcumin (CUR) and paclitaxel (PTX). Methanol was employed for analyte extraction, with docetaxel serving as the internal stan-

dard. Chromatographic separation was achieved using a C18 column (4.6 × 50 mm, 3.5 µm) under an isocratic mobile phase composed of methanol and an aqueous solution containing 0.1% formic acid (80:20, v/v), at a flow rate of 0.5 mL/min. The validated procedure was subsequently applied to assess the pharmacokinetic behaviour of CUR and PTX in rat plasma. Calibration curves exhibited strong linearity across concentration ranges of 2–1000 ng/mL for paclitaxel and 5–500 ng/mL for curcumin. Extraction recovery and matrix effect values for both compounds, as well as the internal standard, were within acceptable analytical limits. The method demonstrated high sensitivity, reliability, and ease of operation for simultaneous analysis. Interestingly, when paclitaxel was co-administered with curcumin, a notable increase in its apparent volume of distribution was observed, indicating that curcumin may modulate the pharmacokinetic profile of paclitaxel. (20).

CONCLUSION

Paclitaxel is used as a chemotherapeutic agent in oncology. Paclitaxel has a unique mechanism of action that causes microtubule stabilisation, thereby arresting cell division and inducing apoptosis in cancer cells. It treats cancer by its ability to inhibit microtubule depolymerisation. This agent, which binds to microtubules and inhibits cell division, is particularly effective in breast and ovarian cancer. LC-MS/MS is a powerful analytical technique that combines high-resolution chromatographic separation with extremely sensitive and specific mass spectrometric detection. It offers advantages such as high sensitivity, high selectivity, the ability to analyse complex matrices, short analysis time, provision of quantitative (numerical) and qualitative (descriptive) information, high resolution, and accuracy. It has a wide range of applications in many fields such as pharmaceutical analysis, clinical diagnosis, toxicology, food safety, and environmental analysis. It was considered that simple, accurate, selective, and sensitive results could be obtained using the liquid chromatography method for paclitaxel determination. Research in the literature has shown that LC-MS/MS method provides high reliability and accuracy in paclitaxel analysis. Understanding the pharmacokinetic profile of paclitaxel and monitoring the therapeutic dose range are critical for effective and safe treatment. At this point, the LC-MS/MS method stands out as one of the most widely used and reliable analytical techniques today, thanks to both its analytical performance and biological compatibility. This method is effectively used in pharmaceutical analysis and clinical applications due to its advantages, such as low limit of quantification (LLOQ), high selectivity, repeatability, and short analysis time. Studies conducted using

LC-MS/MS have enabled the accurate identification of paclitaxel and its metabolites in plasma, thereby contributing significantly to the generation of pharmacokinetic data for the individualisation of treatment.

Consequently, the LC-MS/MS technique is a highly suitable method for analysing drugs such as paclitaxel, which have a narrow therapeutic range and exhibit complex pharmacokinetic behaviour. It is anticipated that this method will continue to be widely used not only in pharmaceutical analysis but also in clinical biochemistry, toxicology, and pharmacogenetics studies. These methods developed for the analysis of paclitaxel will be further optimised in the future and will play a pioneering role in areas such as monitoring treatment response, implementing personalised treatment approaches, and evaluating the efficacy of new carrier systems. The combined use of advanced analytical techniques such as LC-MS/MS with nanotechnology-based drug delivery systems has the potential to further enhance the therapeutic efficacy and safety of paclitaxel. In this context, new studies will pave the way for the more effective and safer use not only of paclitaxel but also of other anticancer agents with similar pharmacological properties.

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