Pharmacy Education (2024) 24(3) 197 - 203
https://doi.org/10.46542/pe.2024.243.197203

IGSCPS SPECIAL EDITION

REVIEW

Vancomycin bioanalysis for TDM services by using immunoassay and HPLC: A scoping review

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Keywords
High-performance liquid chromatography
Immunoassay
Therapeutic drug monitoring
Vancomycin

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Abstract

Background: Administration of vancomycin in treating infections caused by Methicillin-resistant *Staphylococcus aureus* (MRSA) requires therapeutic drug monitoring (TDM). The immunoassay method and high-performance liquid chromatography (HPLC) are the two methods of choice for examining vancomycin levels, with their respective advantages. **Objective:** This study aims to review the validity of immunoassay and HPLC methods, as well as consider which method is appropriate, effective, and efficient for TDM in the clinical setting. **Method:** Related articles were searched for using the keywords "*immunoassay*", "*vancomycin*", "*HPLC*", "*bioanalysis*", and "*human*" in the PubMed, Google Scholar, and Science Direct databases. **Result:** A total of 20 publications examined immunoassays, whereas 23 articles covered HPLC. Both the immunoassay and HPLC methods provided acceptable bioanalytical validation values. **Conclusion:** The immunoassay method is an option for routine sample analysis that requires fast results, but this method is not recommended for patients with high immunoglobulin levels. The HPLC method is a choice because it offers better selectivity and sensitivity.

Introduction

Vancomycin is the first-line treatment for Methicillin-Resistant Staphylococcus aureus (MRSA) (Brozmanová *et al.,* 2017). Vancomycin has a narrow therapeutic index, reaching only 10-15 or 15-20µg/mL for such severe infection as MRSA. A vancomycin concentration exceeding the minimum toxic concentration (MTC) risks nephrotoxicity and ototoxicity. In contrast, a concentration below the Minimum Effective Concentration (MEC) can potentially induce resistance (Van Hal *et al.,* 2013). Furthermore, vancomycin has a substantial interindividual pharmacokinetic variability, necessitating therapeutic drug monitoring (TDM) (Monteiro *et al.,* 2018).

Immunoassay and liquid chromatography are the most developed methods, and they have their respective advantages and disadvantages for TDM applications. This review discussed various studies of immunoassay and HPLC methods and comparisons of the determination of vancomycin concentrations in human biological fluids for TDM service requirements. The findings could be considered when determining and selecting an appropriate, effective, and efficient bioanalysis technique for vancomycin, particularly in clinical settings and for newly established healthcare facilities when implementing the TDM application.

Methods

The keywords–immunoassay, vancomycin, HPLC, bioanalysis, and human were used for a reference search in PubMed, Google Scholar, and ScienceDirect databases. Articles published in English that studied vancomycin bioanalysis utilising immunoassay or HPLC, experimental study, used human biological fluid samples and demonstrated validation parameters met the inclusion criteria. A total of 97 studies were found, and 64 were excluded. Articles without full text, no validation parameters, and irrelevant discussion, such as the pharmacokinetics of vancomycin in various patient conditions, were excluded. A total of 33 articles were selected for review: 20 discussed the

immunoassay, 23 related to HPLC, and 14 compared the immunoassay with HPLC.

Results

Vancomycin analysis using the immunoassay method

Table I below summarises a number of immunoassay approaches for determining vancomycin concentrations in human fluids that have been substantially investigated and developed. The RIA method uses radioactive marker compounds that are very harmful to the environment and health, and such method has proved to experience cross-reactivity with degradation products and needs more time and costs than other types of immunoassay (Darwish, 2006). Not only RIA but also FPIA are subject to cross-reactivity, which leads to biased results in patients with renal impairment. However, this method is efficient, and it is the fastest, affordable immunoassay technique.

Table I: Vancomycin measurement using immunoassay in human biological fluids

Method	Matrix	Conc. range (ppm)	Recovery (%)	CV (%)	Sensitivity (ppm)	References
PETINIA	Plasma	2-50	-	-	2	(Usman & Hempel, 2016)
ELISA	Serum Wound exudate	0.02-5	91.6-108.8 107	-	0.02	(Odekerken *et al.,* 2015)
FPIA	Plasma	3-100	-	3.1-6.2	3	(Oyaert *et al.,* 2015)
HI		1.7-80	-	2.4-4.4	1.7	
HI		5-100	-	5.1-6.1	5	
PETINIA		0.8-50	-	2.7-3.9	0.8	
RIA	Plasma, BAL	0-80		2.4-4.4	1.7	(Hagihara *et al.,* 2013)
PETINIA	Serum	3-35	-	-	3	(Berthoin *et al.,* 2009)
FPIA	Serum	-	-	-	2	(Sym *et al.,* 2001)
EMIT		-	-	-	5	
FPIA TDx	Plasma	-	8.4-8.8 (accuracy)	8.2-10.4	-	(Farin *et al.,* 1998)
FPIA TDx	Plasma, serum	-	-	1.1-4.15	-	(Li *et al.,* 1995)
FPIA TDx	Plasma, tissue, bone	-	-	2.3-8.2	0.1 µg/g	(Martin *et al.,* 1994)
FPIA TDx	Bone	-	-	5.5-10	1 µg/g	(Massias *et al.,* 1992)
FPIA	Serum	-	-	-	-	(Hu *et al.,* 1990)
EMIT		-	-	-	-	
EMIT	Serum	<30	95	5.7-8.5	-	(Yeo *et al.,* 1989)
FPIA TDx		-	-	-	-	
FPIA TDx	Bone	0.6-100	-	<5	0.6	(Graziani *et al.,* 1988)
FPIA TDx	Serum	0.6-100	-	2-4.6	0.6	(Morse *et al.,* 1987)
RIA	Serum	1-32	-	-	-	(Jehl *et al.,* 1985)
FPIA TDx	Serum	-	-	1.34-5.36	-	(Ristuccia *et al.,* 1984)
RIA	Serum	1-32	-	4.7-11	-	(Pfaller *et al.,* 1984)
FIA		0-128	-	8.9-16.2	-	
FPIA		0-100	-	0.9-8.1	-	
RIA	Serum	0-64	-	1.5-4.1	-	(Ackerman *et al.,* 1983)
FPIA TDx		0-100	-	9.5-12.2	-	
RIA	Serum	-	-	-	-	(Schwenzer *et al.,* 1983)
FPIA TDx		0.6-100	103.2	1.55-4.6	0.6	
FPIA TDx	Serum	5-100	103-126	0.88-2.25	-	(Filburn *et al.,* 1983)

Note: Particle-Enhanced Turbidimetric Inhibition Immunoassay (PETINIA); Enzyme-Linked Immunosorbent Assay (ELISA); Fluorescence Polarisation Immunoassay (FPIA); Homogeneous immunoassay (HI); Radioimmunoassay (RIA); Enzyme-mediated Immunoassay Technique (EMIT); Fluorescence Immunoassay (FIA).

Vancomycin analysis using the HPLC method

The chromatography method and system in some previous studies for the quantification of vancomycin in human biological fluids are summarised in Table II. The particle size in the HPLC column has a significant influence on the retention time (tR) and peak spacing. A study by Abu Shandi and colleagues increased the particle size of the column to improve the separation performance (Abu-Shandi *et al.*, 2009). However, it is different from another research that used a smaller particle size for the column to accelerate the tR of vancomycin (Lima *et al.,* 2018). In addition, vancomycin normally precipitates at a pH of 7, a condition that is absolutely harmful for the column because it will be very challenging to obtain a stable peak (Ghassempour *et al.,* 2001). However, there were no reports of any problems associated with vancomycin peaks in the another studies with a buffer pH of 7 and 6.8 (Das *et al.,* 2011; Kees *et al.,* 2014).

Accuracy and precision

Previous research has demonstrated in Tables I and II that the accuracy of HPLC and immunoassay approaches is not significantly different. Meanwhile, the CV value suggests that HPLC is not the most precise approach, whereas Immunoassay is (Farin *et al.,* 1998; Usman & Hempel, 2016). Table III summarises the results of studies comparing immunoassay and HPLC.

Table II: HPLC technique for determining vancomycin in human biological fluids

Column	Detector	Matrix	Recovery (%)	CV (%)	LoD (ppm)	LoQ (ppm)	References
C_{18} (150×4.6 mm, 2.7 µm)	DAD 240 nm	Plasma	95.4-109.5	<11.5	-	1	(Lima *et al.,* 2018)
C_{18} (125×4.6 mm, 5 µm)	UV 205 nm	Plasma	91.5 and 115	≤ 17.8	-	0.25 (LloQ)	(Usman & Hempel, 2016)
C_{18} (150×4.6mm, 5µm)	UV 230 nm	Plasma, urine	87.1 (plasma) and 92.8 (urine)	1.6-2.1	0.003	0.01	(Khalilian *et al.,* 2015)
C_{18} (100 × 3 mm, 2.6 µm)	-	Serum, plasma	97.4	5	-	0.4 (LloQ)	(Kees *et al.,* 2014)
C_{18} (50×2 mm, 5 µm)	MS	Plasma, bone, fat	±100	<10	-	0.05	(M. Zhang, 2014)
C_{18} (150×4.6 mm, 5 µm)	UV 240 nm	Plasma, BAL	90.8	1.68-2.43	-	1 (LloQ)	(Hagihara *et al.,* 2013)
C_{18} (150×4.6 mm, 4 µm)	UV 229 nm	Plasma	99.3-101.1	-	-	-	(Das *et al.,* 2011)
C_{18} (300×4 mm, 10 µm)	FLD 225 nm; 258 nm	Plasma	96.22-98.78	0.736-6.557	0.002	0.005	(Abu-Shandi, 2009)
C_{18} (150×4,6 mm)	DAD 280 nm	Serum	98.2-103.9	-	-	-	(Berthoin *et al.,* 2009)
C_{18} (150×4 mm, 5 µm)	UV 220 nm	APF	99.38-101.43	0.62-7	-	0.1	(Jesús Valle *et al.,* 2008)
C_{18} (50×3 mm, 3 µm)	MS	Serum	95.5-100.4	0.7-7.2	0.001	0.005	(T. Zhang *et al.,* 2007)
C_{18} (124×4 mm, 5 µm)	UV 240 nm	Plasma	86.7	≤10.9	-	0.4 (LloQ)	(Plock *et al.,* 2005)
C_{18}	DAD 205 nm	Serum	-	5.2	1	-	(Ghassempour *et al.,* 2001)
C_{18} (100×4.6 mm, 3 µm)	UV 282 nm	Plasma, tissue	>92.1-97.5	8-20.6	-	0.5 (LloQ)	(Farin *et al.,* 1998)
C_{18} (250×4.6 mm, 5 µm)	UV 225 nm	Plasma, serum	100.6-103.6	0.97-5.83	0.32	-	(Li *et al.,* 1995)
C_{18} (150×4.6 mm, 5 µm)	UV 229 nm	Plasma	98.1-116.4	0.3-27.3	0.2	1	(Lukša & Marušič, 1995)
C_{18} (300×3.9 mm, 10 µm)	UV 228 nm	Serum	95.6-95.74	0.44-4.13	1	-	(Demotes-Mainard *et al.,* 1994)
C_{18} (220×4.6 mm)	UV 235 nm	Serum	94	3.4-4.9	-	-	(Hu *et al.,* 1990)
C_{18}	UV 210 nm	Serum	70	<7	-	-	(Morse *et al.,* 1987)
C_{18} (150×4 mm, 5 µm)	AUFS 214 nm	Serum	115	5.8-11.4	0.1	-	(Jehl *et al.,* 1985)
C_{18}	AUFS 210 nm	Serum	-	3.1-3.3	-	-	(Ristuccia *et al.,* 1984)
C_{18} (300 × 3.9 mm, 10 µm)	UV 210 nm	Serum	-	2.4-6.4	-	-	(Pfaller *et al.,* 1984)

Note: Bronco alveolar Lavage Fluid (BAL); Artificial perfusion fluid (APF)

Table III: Correlation of vancomycin concentrations between immunoassay and HPLC methods

Matrix	Method	Regression Equation	R	Ref
Plasma	PETINIA vs. HPLC	HPLC=0.949(PETINIA)+0.554	0.947	(Usman & Hempel, 2016)
Plasma	FPIA vs. HPLC	HPLC=1.04 FPIA+0.15	0.97	(Oyaert *et al.,* 2015)
	HPLC vs. HI	HPLC=1.22(immunoassay)-0.27	0.98	
	HPLC vs. HI	HPLC=0.93(immunoassay)+1.37	0.98	
	PETINIA vs. HPLC	HPLC=0.99(PETINIA)+0.45	0.97	
Plasma	RIA vs. HPLC	HPLC=0.651(RIA)+3.98	0.916	(Hagihara *et al.,* 2013)
		HPLC=0.859(RIA)+0.766	0.973	
Serum	HPLC vs. FPIA	HPLC=0.82(PETINIA)-1.61 (total vancomycin)	0.955	(Berthoin *et al.,* 2009)
	HPLC vs. PETINIA	HPLC=0.78(PETINIA)+1.35 (free vancomycin)	0.960	
Blood	HPLC vs. FPIA TDx	FPIA=-0.84(HPLC)+1.04	0.964	(Farin *et al.,* 1998)
Serum	HPLC vs. FPIA	FPIA=1.025(HPLC)+2.438	0.94 (research lab)	(Li *et al.,* 1995)
		FPIA =1.046(HPLC)+1.236	0.943 (private lab)	
Serum	EMIT vs. HPLC	EMIT=0.51+(HPLC)	0.963	(Demotes-Mainard *et al.,* 1994)
Serum	FPI vs. HPLC	FPIA=1.148(HPLC)+0.507	0.939	(Hu *et al.,* 1990)
	EMIT vs. HPLC	EMIT=0.958(HPLC)+1.924	0.933	
Serum	FPIA vs. HPLC	-	-	(Morse *et al.,* 1987)
Serum	HPLC vs. RIA	RIA=1.13(HPLC)+2.32	0.945	(Jehl *et al.,* 1985)
	HPLC vs. FPIA	FPIA=1.11(HPLC)+2.06	0.967	
Serum	HPLC vs. FPIA	FPIA=1.0489(HPLC)-0.737	0.9996	(Ristuccia *et al.,* 1984)
Serum	HPLC vs. FIA	EMIT=0.51+(HPLC)	0.919	(Pfaller *et al.,* 1984)
	HPLC vs. FPIA	FPIA=0.877(HPLC)+0.819	0.977	
	HPLC vs. RIA	FIA=0.899(HPLC)+0.539	0.964	
Serum	FPIA vs. HPLC	FPIA=0.84557(HPLC)+3.3205	0.97	(Filburn *et al.,* 1983)
Serum	FPIA vs. HPLC	FPIA=1.09(HPLC)+3.04	0.98	(Schwenzer *et al.,* 1983)

Selectivity and sensitivity

The method used in TDM applications must be selective, able to differentiate analytes from metabolites or other substances. There was a case report of vancomycin TDM in PETINIA in two patients with elevated IgM that led to a falsely low result (Simons *et al.,* 2009; Gunther *et al.,* 2013). Immunoassay with polyclonal antibodies, such as FPIA and RIA, have proved to be able to recognise the presence of crystalline degradation product (CDP-1) which commonly accumulates in patients whose kidneys are damaged, thus yielding biased results, whereas EMIT with monoclonal antibodies shows cross-reactivity (Anne *et al.,* 1989; Hu *et al.*, 1990;). Different from previous studies, two case reports proved that EMIT had cross-reactivity (Singer *et al.,* 2019; Tsoi *et al.*, 2019). Such cross-reactivity indicates that immunoassays have lower selectivity than HPLC. Furthermore, nearly all studies show that HPLC is a more sensitive method than immunoassay, and the sensitivity parameter of the method used in TDM applications provides an advantage for patients whose vancomycin concentrations are below the MEC range.

Discussion

Tables I and II show the determination of vancomycin levels using several types of biological fluid matrices, although serum and plasma are still the main choices. The obtained method validation parameters indicate that other biological fluids are suitable for use in TDM procedures. Furthermore, Tables I and II present information related to the efficiency of the vancomycin separation process from the biological matrix is also included, in the form of recovery and precision parameters (CV). The sensitivity of each method can be observed from the values of sensitivity, LOD, and LOQ. Table III summarises the results of studies comparing immunoassay and HPLC. However, in addition to the r parameter, the mean difference in the obtained concentrations should be considered because it is significant.

HPLC requires a long analysis time while immunoassay works more quickly, easily, and simpler procedure. The rapidity of immunoassay is supported by the fact that different steps are performed automatically, therefore the instrument reads numerous samples in a single analysis (Pfaller *et al.,* 1984; Hazarika, 2015). Therefore, it offers an advantage in the clinical application of vancomycin TDM in providing fast results to enable immediate interventions for patients. On the other hand, in practice, HPLC requires a long series of procedures, this has led to possible variability at each stage (Filburn *et al.,* 1983). However, speed is not the only factor needed in TDM as accuracy is also required to achieve more accurate data interpretation and follow-ups to patient therapy.

In terms of costs, the initial investment for HPLC is higher compared to immunoassay, especially HPLC using MS detector. This instrument is less suitable for healthcare facilities that are just starting clinical TDM services, such as in Indonesia. In addition, the operational process of complex HPLC instruments requires skilled technicians. However, the reagents or kits in immunoassay have a short term of use after opening, making it necessary to adjust their use to TDM needs considering that TDM implementation in Indonesia remains minimal and rare (Setiabudy, 2011). Another study also showed that the cost of equipment and materials for HPLC with the isocratic elution technique was lower than that for immunoassay (Hagihara *et al.,* 2013). These studies indicate that HPLC requires a higher initial investment cost, but the cost of HPLC analysis is lower in the following stages. The higher the cost of analysis incurred, the higher the price that patients should pay. However, the costs incurred by patients are reduced when the need for analysis or TDM in patients is higher (Setiabudy, 2011).

Conclusion

In the clinical practice of vancomycin TDM, the two methods reviewed in this article demonstrate a remarkable ability in analysis and consistent correlations in describing vancomycin concentrations although with different precision, levels of selectivity, and sensitivity. This study does not aim to determine the best method; instead, it recommends that some factors should be considered when one method is selected for determining vancomycin concentrations in a patient. The immunoassay method become a preferred recommendation in conditions that require rapid analysis and routine use. However, in varied clinical conditions, the HPLC method is recommended for high levels of sensitivity and selectivity, although this method is neither fast nor easy.

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