



Full length article

Stratification of cephalosporins based on physicochemical and pharmacokinetic variables using multivariate statistical tools

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HIGHLIGHTS

- Need for more objective drug selection: The article emphasises the importance of moving beyond arbitrary drug selection, especially in the case of cephalosporins.
- Importance of physicochemical and pharmacokinetic variables: It is emphasised that the physicochemical and pharmacokinetic variables of cephalosporins significantly influence their behaviour in the body and thus their therapeutic efficacy.
- Stratification of cephalosporins: The study has succeeded in stratifying cephalosporins into different groups based on their common characteristics. This stratification allows the identification of the most appropriate cephalosporins for each clinical situation.
- Optimising treatment: Selecting the most appropriate cephalosporin can improve treatment efficacy, reduce the risk of bacterial resistance and minimise adverse effects.
- Personalisation of therapy: By considering the individual characteristics of each patient, further personalisation of antibiotic therapy can be achieved.

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ABSTRACT

Introduction: Cephalosporins, a class of beta-lactam antibiotics, are commonly used in medical practice. However, their potential advantages, based on physicochemical and pharmacokinetic variables, are often overlooked. This research, proposing strategies based on multivariate statistics to stratify different cephalosporins, is a significant step towards providing the prescribing team with more rational and effective options. The potential benefits of this research are promising, as it has the potential to significantly improve the efficacy and safety of cephalosporin therapy.

Method: Exploratory study and review of pharmacokinetic parameters of cephalosporins. Data were extracted from DrugBank go.drugbank.com, and multivariate statistical techniques such as Pearson correlation and cluster analysis were applied. This approach allowed the identification of groupings of cephalosporins with similar characteristics, thus facilitating their rational selection in clinical practice.

Results: The results reveal that cefazolin, cefotetan, cefoperazone, and ceftriaxone form the conglomerate with the most favorable properties for reaching effective concentrations at the site of action due to their high solubility, high percentage of binding to plasma proteins, and adequate residence times in the organism. Solubility, protein binding, half-life, MRT, molecular weight, volume of distribution, number of interactions, and pKa are all critical factors that influence the efficacy and safety of cephalosporin therapy.

Conclusions: It is relevant to highlight the use of multivariate statistics as a tool for drug selection and rational use. In the present study, cefazolin, cefotetan, cefoperazone, and ceftriaxone were highlighted as the best therapeutic alternatives according to the variables selected for the study.

1. Introduction

Prescription is one of the most important strategies for the treatment of patients, with the objective of managing symptoms and, on occasion,

preventing future conditions. *Prescribing* is a complex exercise that requires diagnostic skills, knowledge of common medications, understanding of the principles of clinical pharmacology, communication skills, and the ability to make decisions based on judgments of potential

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benefits and risks based on available evidence and specific factors related to the patient being treated. The progressive accumulation of clinical trial data on commonly used drugs would allow the possibility of providing sufficient evidence to support most prescribing decisions. However, physicians generally prescribe under varying circumstances and often in the absence of directly related evidence. Rational prescribing decisions are often based on evidence that must be interpreted in the context of many other factors not found in any clinical trial.^{1–4} (Table 1).

Considering that the most widely used therapeutic technology is the drug, but in some circumstances, its use can be inefficient, which affects the quality of healthcare, jeopardizes patient safety, and wastes resources. Clinicians are confronted with an ever-increasing supply of drugs that exceeds their knowledge of how to use them; therefore, it is necessary to select drugs rationally, based on evidence of efficacy and safety, while seeking the greatest benefit for patients at the lowest possible cost. Medicines can be selected at different levels: health systems, organizations, health centers, and professionals, but they always follow the same criteria. As the drug and its knowledge are constantly changing, drug evaluation and selection must be a continuous and multidisciplinary process. Due to those above, it is pertinent to propose strategies based on multivariate statistical tools, taking into account the capacity of this type of statistics to stratify the different pharmacological alternatives in order to provide less subjective options to the prescribing team.^{5,6}

A group of drugs frequently used in clinical practice are cephalosporins, which correspond to a type of beta-lactam antibiotics frequently used in medicine due to their high activity against bacteria, proven efficacy, and good safety. These antimicrobials are used as first-choice treatments in various clinical conditions, such as skin and soft tissue infections, intra-abdominal sepsis, diabetic foot infections, acute meningitis, pneumonia, endocarditis, and as prophylaxis in cardiothoracic, orthopedic, abdominal and pelvic surgery. However, they can be used indistinctly without taking into account some possible advantages derived from their physicochemical and pharmacokinetic variables, a situation that, at a given moment, may allow better diffusion to infected tissues. The objective was to look for options to interpret and take advantage of the information related to the physicochemical nature of drugs in order to facilitate decision-making on the choice of pharmacological therapies, trying to select the appropriate alternatives for each case based on their possible kinetics and distribution on the basis of the inherent properties of each substance.⁷

2. Methodology

Study design: An exploratory and descriptive cross-sectional study was performed.

Study population: The study population, which encompasses all cephalosporins available in the Colombian market, provides a comprehensive view of the pharmacokinetics of these drugs.

Sample selection: The selection of the most commonly used cephalosporins in clinical practice, based on drug consumption data, was a carefully considered process that underlines the methodological rigor of this study.

Data Collection: Data on pharmacokinetic parameters of cephalosporins were obtained from the DrugBank database (go.drugbank.com). The pharmacokinetic parameters included in the study were:

Table 1

Final partitioning of clusters obtained with the variables discriminated by principal component analysis.

	Variables
Conglomerate 1	Solubility (mg/mL)
Conglomerate 2	% Protein binding
Conglomerate 3	Half-life time (h) MRT
Conglomerate 4	Molecular weight

- Solubility
- Percentage of binding to plasma proteins
- Half-life time
- Mean Residence Time
- Molecular weight
- Volume of distribution
- Number of reported drug interactions

The possible correlation between variables was determined using Minitab software (Pearson correlation) to establish the possibility of using multivariate statistics for data analysis.

Statistical analysis: To establish the dimension of the variables in the principal components, a principal component analysis with subsequent cluster analysis (using Minitab software) was performed for variables. Based on the results of the previous analyses, the variables were selected to perform a cluster analysis by observations (Minitab software) to stratify the cephalosporins according to their best characteristics.

3. Results

Table 2 shows the pharmacokinetic parameters of several cephalosporins, with values obtained from the DrugBank database. The parameters include solubility (expressed in mg/mL), percentage protein binding, half-life (in hours), mean residence time (MRT, in hours), molecular weight, volume of distribution (expressed in L/kg), number of interactions, and pKa (acidity constant).

The solubility parameter (mg/mL) of cephalosporins is a fascinating aspect that varies significantly, influencing their absorption and bioavailability. For instance, Cefazolin boasts a relatively high solubility of (0.487 mg/mL), while Ceftazidime presents a much lower solubility of (0.00573 mg/mL).

The percentage of protein binding indicates what proportion of the drug is bound to plasma proteins, which can affect drug distribution. Ceftriaxone has the highest binding (95%), suggesting a lower free fraction available for antibacterial activity, while Ceftazidime has the lowest binding (13.5%). The half-life (h) and MRT (h) are related to the duration of drug action. Ceftriaxone has the longest half-life (7.25 h) and the longest MRT (5.4 h), indicating slower elimination and, therefore, less frequent dosing. The molecular weight may influence the ability of the drug to cross cell membranes. Cefoperazone has the highest molecular weight (645.67), which could affect its pharmacokinetics.

As for the Volume of Distribution (L/kg), this parameter indicates how the drug is distributed in the body.

Ceftazidime has the highest volume of distribution (0.31 L/kg), suggesting a wider distribution in the body.

Finally, the number of potential interactions with other drugs is an important factor in patient safety. All the cephalosporins listed have a similar number of interactions, indicating that they should be used with caution in polymedicated patients.

The pKa is important to understand the drug's ionization at different pHs, which affects its absorption and elimination. Cephalotin has the highest pKa (3.43), which could influence its behavior in varied pH environments.

In general, each cephalosporin has a unique pharmacokinetic profile that should be considered when choosing the appropriate drug for a specific patient. Solubility, protein binding, half-life, MRT, molecular weight, volume of distribution, number of interactions, and pKa are all critical factors that influence the efficacy and safety of cephalosporin therapy.

Table 3 shows the correlation between different pharmacokinetic variables of the cephalosporins we studied. These correlations tell us how two variables are related. A value above 0.5 or below –0.5 means there's a good or strong connection between the variables.

The variables studied include molecular weight, solubility, pKa, protein binding percentage, volume of distribution, half-life, and mean residence time (MRT).

Table 2Characteristics of the cephalosporins studied and values of their respective variables captured from go.drugbank.com.

Cephalosporin	Solubility (mg/mL)	Protein binding percentage (%)	Half-life time (h)	Mean Residence Time MRT (h)	Molecular weight	Distribution Volume (L/kg)	Number of Interactions	pKa
Cefazoline	0.48700	80.0	1.80	2.20	454.507	0.120	747	2.84
Cefalotine	0.05210	72.5	0.50	0.65	396.438	0.070	746	3.43
Cefuroxime	0.28400	50.0	1.70	1.10	424.385	0.150	692	2.96
Cefoxitine	0.19500	70.0	0.90	0.79	427.452	0.170	670	3.39
Cefotetan	0.52100	88.0	3.00	5.20	575.619	0.130	700	3.03
Cefotaxime	0.14600	40.0	1.00	1.20	455.465	0.190	746	2.73
Ceftriaxone	0.10500	95.0	7.25	5.40	554.580	0.084	734	2.70
Ceftizoxime	0.22900	30.0	1.80	1.60	383.403	0.200	746	2.66
Cefoperazone	0.28600	93.0	2.00	2.20	645.670	0.170	701	3.19
Ceftazidime	0.00573	13.5	2.15	2.20	546.576	0.310	700	2.42
Cefepime	0.01730	20.0	2.00	2.10	480.561	0.280	674	2.82
Ceftobiprole	0.15900	16.0	3.00	3.00	534.570	0.270	670	2.89

Table 3

Pearson correlation coefficient values.

	Molecular weight	Solubility (mg/mL)	pKa	Protein binding percentage (%)	Distribution Volume (L/kg)	Half-life time (h)	Mean Residence Time MRT (h)
Solubility (mg/mL)	0.141						
pKa	-0.128	0.184					
Protein binding percentage (%)	0.276	*0.530	0.524				
Distribution Volume (L/kg)	0.161	-0.416	*-0.514	*-0.857			
Half-life time (h)	0.497	-0.024	-0.382	0.284	-0.176		
Mean Residence Time MRT (h)	*0.653	0.285	-0.300	0.348	-0.151	*0.857	
Number of Interactions	-0.314	0.120	-0.186	0.290	*-0.543	0.029	-0.036

* correspond to values above 0.5, which allows inferring the correlation between more than one variable.

Of particular significance are the correlation coefficients, which provide crucial insights into the pharmacokinetic properties of the cephalosporins studied.

- A moderate positive correlation (*0.530) between solubility and percent protein binding, suggesting that the more soluble cephalosporins (Cefazolin, Ceftriaxone, cefoperazone, and cefotetan) tend to have higher protein binding.
- There is a strong negative correlation (*-0.857) between the volume of distribution and mean residence time (MRT), indicating that cephalosporins with a larger volume of distribution (Cefazolin, Ceftriaxone, cefoperazone, and cefotetan) tend to have shorter residence times in the body.
- There is a significant positive correlation (*0.653) between MRT and solubility, suggesting that the more soluble cephalosporins (Cefazolin, Ceftriaxone, cefoperazone, and cefotetan) tend to remain longer in the body.

These results provide important information on the relationships between the different pharmacokinetic properties of the cephalosporins studied, which can be useful to understand their behavior in the body better and optimize their clinical use from the pharmacokinetic and posological perspectives; this means that we can be more certain about the strengths of each drug from the pharmacokinetic point of view in terms of the therapeutic objective proposed. For this reason, of these four cephalosporins, cefazolin, ceftriaxone, cefoperazone, and cefotetan can be found commercially as a powder for reconstitution and for parenteral use, and all can be used in both intermittent and continuous infusion, given their dissolution characteristics, the volume of distribution and

half-life times.

In [Table 4](#), the first principal component (C1) explains most of the variability (36.1%), the second principal component (C2) explains the next significant amount (30.4%), the third principal component (C3) contributes 16.8% of the variability, in total, the first three components explain 83.2% of the variability (cumulative), the following components (C4 to C8) contribute in minor measure to variance. In summary, these eigenvalues and eigenvectors help us understand how the pharmacokinetic properties of the cephalosporins under study are distributed. By considering these components, we can reduce the dimensionality of the data and make informed clinical decisions. It is evident that, with the third component calculated, 83.2% of the behavior of the variables can be explained, and 92.9% with the fourth component calculated.

To analyze [Table 5](#), which contains the eigenvectors of a principal component analysis (PCA), we must first understand that each principal component (PC) represents a direction in the data space where there is the most variability. [Table 6](#) and [Table 7](#) show the eigenvector loadings, which indicate how each variable contributes to each principal component and how it can be grouped respectively.

Here is a brief analysis of each major component based on the values provided:

- **PC1:** It has strong positive contributions of '% protein binding' and 'MRT,' and a strong negative contribution of 'volume of distribution (L/kg),' suggesting that this component could be associated with the pharmacokinetics of the substances.
- **PC2:** It presents a significant negative contribution of 'molecular weight' and 'half-life time (h),' while 'pKa' has a positive

Table 4

Analysis of the eigenvalues and eigenvectors of the correlation matrix.

	C1	C2	C3	C4	C5	C6	C7	C8
Own value	2.8868	2.4284	1.3441	0.7737	0.4063	0.1065	0.0331	0.0211
Proportion	0.3610	0.3040	0.1680	0.0970	0.0510	0.0130	0.0040	0.0030
Cumulative	0.3610	0.6640	0.8320	0.9290	0.9800	0.9930	0.9970	1000

Table 5

Values for the eigenvectors of the different components obtained from the principal component analysis.

Variable	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8
Molecular weight	0.261	-0.419	-0.350	-0.033	0.715	-0.005	0.267	-0.223
Solubility (mg/mL)	0.347	0.148	-0.150	-0.841	-0.219	-0.080	0.256	0.094
pKa	0.131	0.444	-0.518	0.330	-0.039	0.433	0.324	0.338
Protein binding (%)	0.528	0.219	-0.116	0.128	0.195	-0.422	-0.572	0.316
Volume of distribution (L/kg)	-0.445	-0.373	-0.158	-0.221	0.140	0.038	-0.142	0.741
Half-life time (h)	0.347	-0.427	0.196	0.334	-0.351	-0.318	0.477	0.308
Mean Residence Time MRT	0.409	-0.425	0.028	-0.032	-0.247	0.662	-0.387	-0.033
Number of Interactions	0.172	0.235	0.713	-0.072	0.445	0.296	0.181	0.288

Table 6

The table of variables reduced according to the results of the principal component analysis, which were used for the final selection analysis.

Cephalosporin	Solubility (mg/mL)	Protein binding (%)	Half-life time (h)	Mean residence time (MRT)	Molecular weight
Cefazolina	0.48700	80.0	1.80	2.20	454.507
Cefalotina	0.05210	72.5	0.50	0.65	396.438
Cefuroxima	0.28400	50.0	1.70	1.10	424.385
Cefoxitina	0.19500	70.0	0.90	0.79	427.452
Cefotetan	0.52100	88.0	3.00	5.20	575.619
Cefotaxima	0.14600	40.0	1.00	1.20	455.465
Ceftriaxona	0.10500	95.0	7.25	5.40	554.580
Ceftizoxima	0.22900	30.0	1.80	1.60	383.403
Cefoperazona	0.28600	93.0	2.00	2.20	645.670
Ceftazidima	0.00573	13.5	2.15	2.20	546.576
Cefepima	0.01730	20.0	2.00	2.10	480.561
Ceftobiprole	0.15900	16.0	3.00	3.00	534.570

contribution. This could indicate a relationship with the chemical structure and stability of the substances.

- **PC3:** It is highlighted by a high positive charge in 'number of interactions' and a negative charge in 'pKa,' which could reflect the interaction of substances with their environment or with other compounds.
- **PC4:** Solubility (mg/mL)' has a very strong negative contribution, which could indicate that this component is related to the solubility and dispersion of substances in solutions.
- **PC5:** 'Molecular weight' has the highest charge in this component, suggesting that PC5 may be related to the size and mass of the molecules.
- **PC6:** 'MRT' has a strong positive contribution, which could be associated with the time a substance remains in the system.
- **PC7:** It has strong negative contributions of '% protein binding' and 'MRT,' which could indicate a relationship with the substances' elimination or metabolism.
- **PC8:** Volume of Distribution (L/kg)' has a very high loading, suggesting that this component may be related to the distribution of substances in the body.

Each major component helps to understand different aspects of the data and, taken together, can provide a comprehensive view of the pharmacological properties of the cephalosporins studied.

Fig. 1 is a scatter plot showing the relationship between "observation" and "Mahalanobis distance" for different cephalosporins:

The graph has a clear grid with numbers from 0 to 12 on the X-axis

Table 7

Amalgamation steps of the cluster analysis by variables.

Step	Number of clusters	Level of similarity	Distance level	Incorporated conglomerates		New conglomerate	Number of obs. in the new cluster
1	4	92.8452	0.14310	3	4	3	2
2	3	76.4796	0.47041	1	2	1	2
3	2	74.8470	0.50306	3	5	3	3
4	1	48.7904	1.02419	1	3	1	5

labeled 'observation' and 0 to 8 on the Y-axis labeled 'Mahalanobis distance'. Drugs include Cefazoline, Cephalotin, Cefuroxime, Cefoxitin, Cefotetan, and Ceftazidime, among others. The highest point on the graph is associated with Ceftobiprole at an approximate observation of 11 and a distance from Mahalanobis close to 8. The horizontal line represents a threshold for identifying outliers. It's worth noting that our data is of high quality, as none of the points exceed this line.

Fig. 2 shows a descending curve of eigenvalues as a function of component number. This curve is typical in PCA. The above summarises the key points:

Initial fast descent: The first components¹⁻⁴ explain most of the variance in the data. The before is common in PCA, where the initial components capture the most relevant information.

Subsequent stabilization: After the initial decline, the curve stabilizes. This suggests that the subsequent components contribute less to the total variance or have a smaller impact.

This means that we must focus on the first components to stratify cephalosporins. These components will contain the most important information (92.9%) on pharmacokinetic and physicochemical variables.

Fig. 3 shows the score of cephalosporins in a two-dimensional space defined by the first two principal components. The graph axes show that the horizontal axis represents the "first component," and the vertical axis represents the "second component." Each point on the graph corresponds to a specific cephalosporin. The cephalosporins are scattered in space, indicating their variability in terms of measured characteristics. The cephalosporins that are close together in the graph have similar profiles in terms of the variables analyzed. Those that are further apart have significant differences in their properties. This information can be used to stratify cephalosporins according to their characteristics. For example, those grouped close together may share similar pharmacokinetic or physicochemical properties. From the graph, it can be concluded that cefazolin and cefoperazone show the best rankings using the values of all variables for the analysis, taking into account their scores on the axes included.

Fig. 4 is a biplot representing data and vectors for different variables in relation to two principal components; each point on the graph corresponds to a specific cephalosporin. The vectors indicate how each variable contributes to the two principal components. For example, if a vector is close to a cephalosporin, it means that the variable has a significant impact on that cephalosporin. This information is useful for understanding how variables relate to cephalosporins. Patterns and clusters can be identified based on the measured characteristics (see Fig. 5).

Where it is determined that most of the variables are congruently associated in the first two components, with the exception of the volume

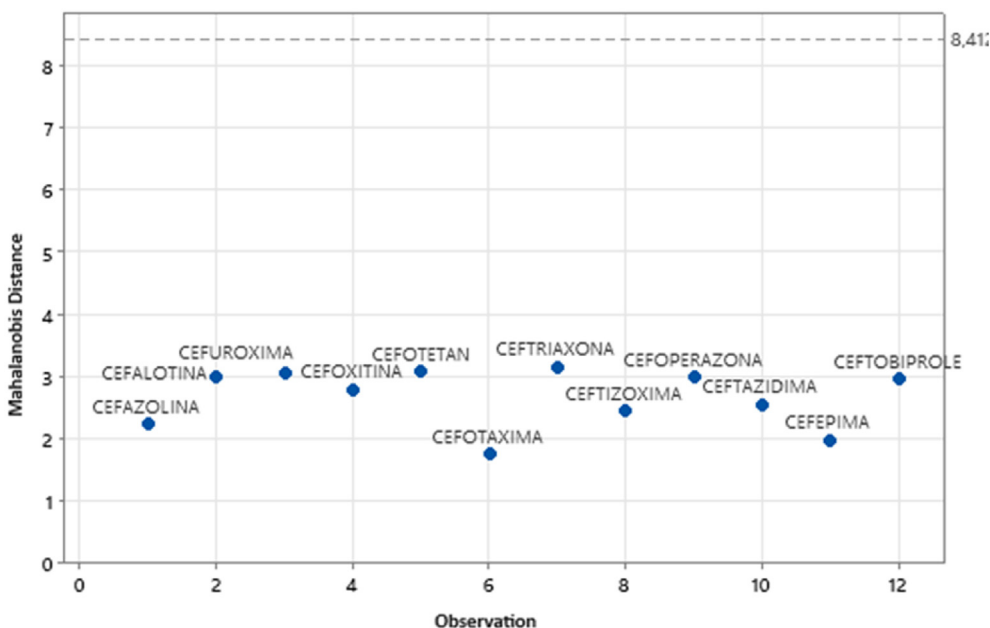


Fig. 1. Visualization of possible outliers in the data subjected to principal component analysis. There were no outliers in any of the variables for the different cephalosporins.

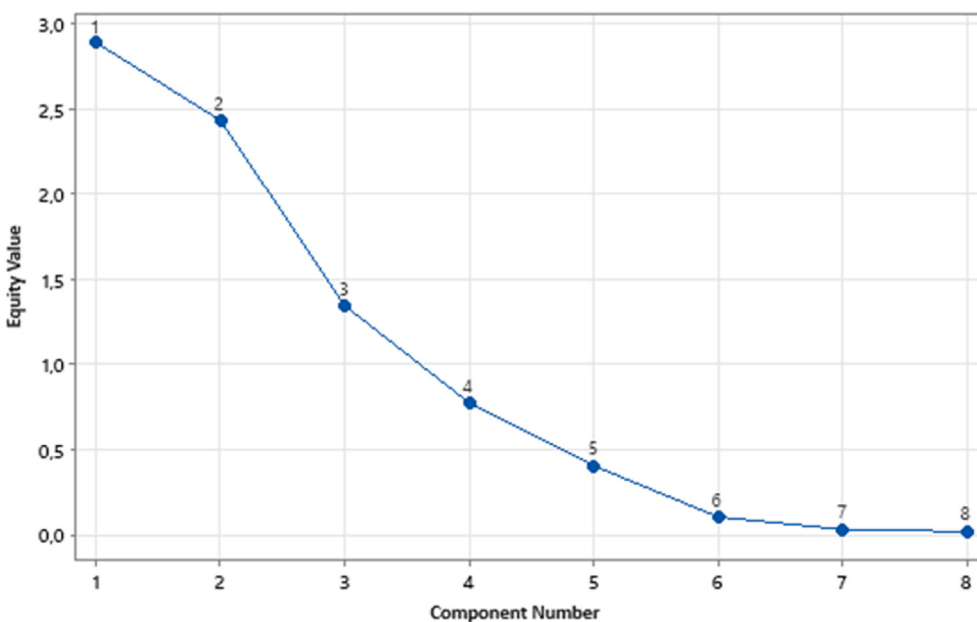


Fig. 2. Sedimentation plot of principal components obtained after analysis. It can be seen that the first four components describe a linear trend which, as can be seen in the values of the components, can be explained by 92.9% with the fourth component calculated.

of distribution, which is in contrast to the rest of the variables.

Cluster analysis is a technique that groups observations or variables into clusters based on their similarities. In cephalosporins and principal component analysis, certain steps are followed to amalgamate the clusters.

Conglomerate merger: In the first step, two clusters merge to form a new cluster. In each subsequent step, another cluster joins an existing cluster, creating a new cluster. In the final step, all observations or variables are combined into a single cluster.

The cephalosporin clusters are formed according to their similarity. In Fig. 6 (dendrogram), the main clusters can be seen:

Blue Group (left): Contains the cephalosporins Cefazolin and

Cefotaxime. **Red Group (right):** Includes Cefuroxime, Ceftazidime, Ceftriaxone, Cefoperazone, Ceftibuten and Cefepime.

The height at which the branches join represents the similarity or dissimilarity between the groups. The lower the height, the more similar the grouped cephalosporins are. In summary, this dendrogram allows us to identify patterns and relationships between cephalosporins according to the variables considered. It is a valuable tool to better understand the stratification of these antibiotics.

In this case, Fig. 6 can help us to show that cefazolin, cefotetan, cefoperazone, ceftriaxone occupy the first four positions based on the analysis of the physicochemical and pharmacokinetic variables analyzed, while ceftazidime, cefepime and cefbiprole occupy the last positions.

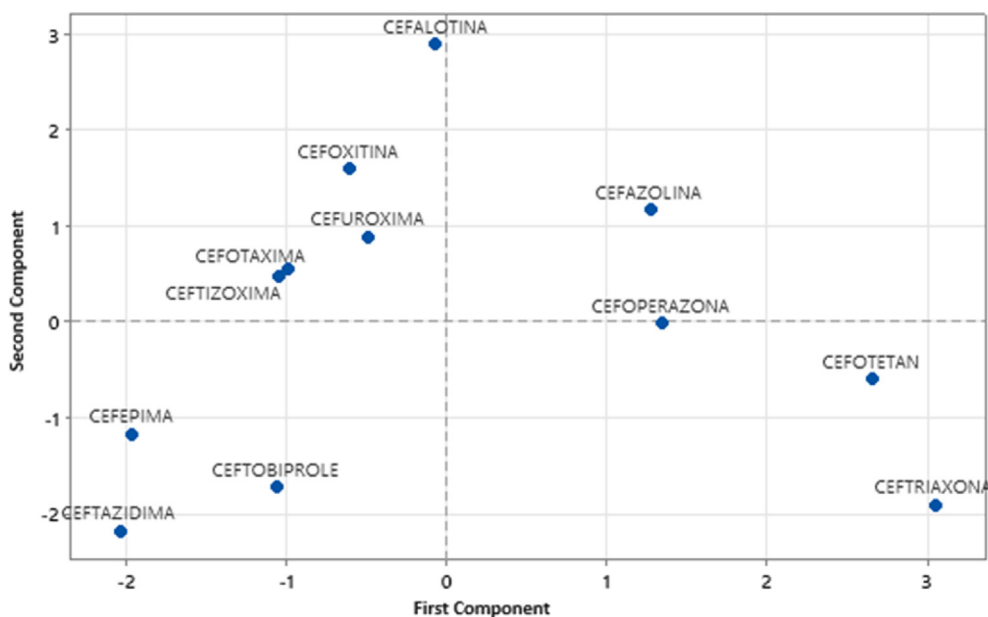


Fig. 3. Score plot of the different cephalosporins subjected to principal component analysis.

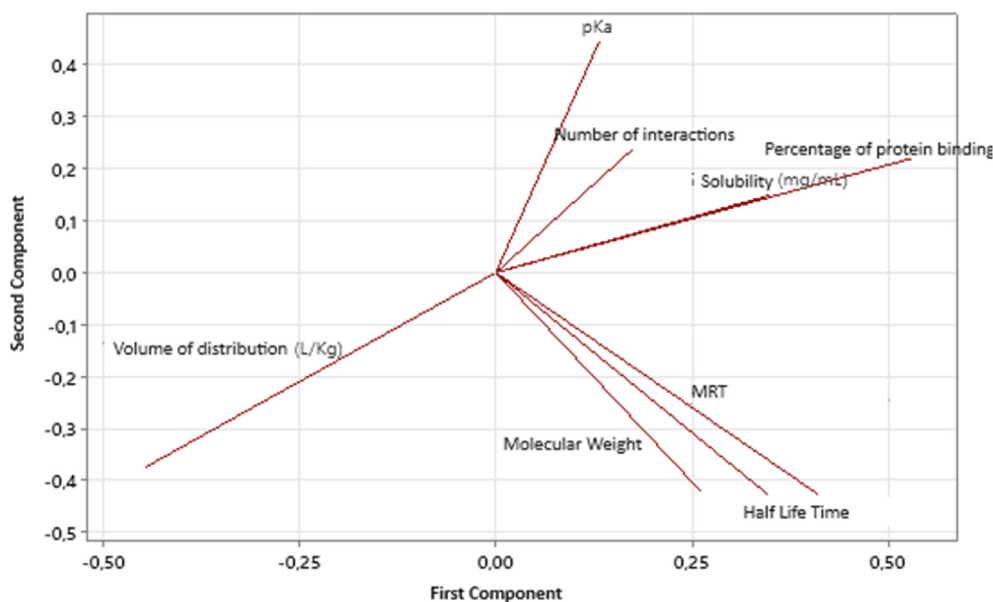


Fig. 4. Plot of the two main components obtained after the analysis (biplot).

4. Discussion

The physicochemical and pharmacokinetic variables of the same group of substances can allow certain analyses to be carried out to determine which are the best alternatives in a group of substances. In this specific case, we proposed the use of principal component analysis and cluster analysis as multivariate statistical tools for the classification of cephalosporins in order to select the best cluster according to certain physicochemical and pharmacokinetic variables of the substances. In the above analysis, it can be seen that not all physicochemical and pharmacokinetic variables contribute in the same way to the principal components constructed since, in the case of the volume of distribution, as occurs in the kinetics of drugs, the greater the volume occupied by a substance, the lower the plasma concentrations of the substances (8), this is a situation that, when trying to integrate with the other variables in the construction of the components, turns out to be counterproductive, as can

be seen in Fig. 4. On the other hand, it was decisive that solubility and the percentage of binding to plasma proteins make up the first group of variables, a situation that is concordant since both are fundamental in the capacity of the drugs to permeate the plasma and the rest of the extracellular liquid, which allows their concentrations in the different body fluids (9), while the residence times of the drugs in the organism, determined by the variables half-life and half-residence time, make up the second group, a situation that is framed within the logic of drug kinetics, since first the dissolution and distribution process takes place, followed by clearance, both of which determine the drug's residence time (10).

Taking under consideration that cephalosporins are a group of bactericidal beta-lactam antibiotics that inhibit enzymes of the cell wall of sensitive bacteria, thus interrupting their synthesis, it is essential to stratify them based on physicochemical and pharmacokinetic variables, which made it possible to show after the analysis that Cefazolin,

reference and explore the application of this methodology in conjunction with clinical studies to evaluate the therapeutic efficacy of stratified cephalosporins.

Recommendations

- Extend the methodology to other antibiotic groups.
- Evaluate the therapeutic efficacy of stratified cephalosporins in clinical studies.

Data availability

The data generated in this article were derived from primary data obtained from previously published literature available in the public domain. The referenced papers that form the empirical basis of this review are appropriately cited in the text of the manuscript. Any additional information needed to support the conclusions of this review can be obtained from the corresponding author.

Data availability

The authors have data available in our excel databases. The primary data were taken for each of the cephalosporins studied from [go.drugbank.com](https://www.go.drugbank.com).

CRediT authorship contribution statement

Carlos Alberto Escobar Angulo: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Antistio Alviz Amador:** Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Julián Javier Martínez Zambrano:** Writing – review & editing, Writing

– original draft, Visualization, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis.

Declaration of competing interest

This research has been conducted independently and has not received any external funding. The authors declare that they have no conflicts of interest that may influence the presentation or interpretation of the data.

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